JMIR Research Protocols

Impact Factor (2022): 1.7
Volume 5 (2016), Issue 2 ISSN 1929-0748 Editor in Chief: Xiaomeng (Simone) Ma, PhDc, MS, BS

Contents

Protocols

Original Papers

Proposals

Short Paper

Corrigenda and Addenda

Protocol

Comparing Brief Internet-Based Compassionate Mind Training and Cognitive Behavioral Therapy for Perinatal Women: Study Protocol for a Randomized Controlled Trial

Alex R Kelman[1], M Sc; Meagan L Stanley[1], M Sc; Alinne Z Barrera[1,2], PhD; Michelle Cree[3,4], M Sc; Yotam Heineberg[1,5], PsyD; Paul Gilbert[3,4], PhD

[1]Palo Alto University, Palo Alto, CA, United States

[2]i4health, Palo Alto, CA, CA, United States

[3]Derbyshire Healthcare NHS Foundation Trust, Derby, United Kingdom

[4]Compassionate Mind Foundation, Derby, United Kingdom

[5]Stanford University, Center for Compassion and Altruism Research and Education, Palo Alto, CA, United States

Corresponding Author:
Alex R Kelman, M Sc
Palo Alto University
1791 Arastradero Road
Palo Alto, CA, 94304
United States
Phone: 1 650 396 9349
Fax: 1 650 433 3888
Email: akelman@paloaltou.edu

Abstract

Background: Depression that occurs during the perinatal period has substantial costs for both the mother and her baby. Since in-person care often falls short of meeting the global need of perinatal women, Internet interventions may function as an alternate to help women who currently lack adequate access to face-to-face psychological resources. However, at present there are insufficient empirically supported Internet-based resources for perinatal women.

Objective: The aim of this study is to compare the relative efficacy of Internet-based cognitive behavioral therapy (CBT) to a novel Internet-based compassionate mind training approach (CMT) across measures of affect, self-reassurance, self-criticizing, self-attacking, self-compassion, depression, and anxiety. While CBT has been tested and has some support as an Internet tool for perinatal women, this is the first trial to look at CMT for perinatal women over the Internet.

Methods: Participants were recruited through Amazon Mechanical Turk (MTurk) and professional networks. Following completion of demographic items, participants were randomly assigned to either the CBT or CMT condition. Each condition consisted of 45-minute interactive didactic and follow-up exercises to be completed over the course of two weeks.

Results: Post course data was gathered at two weeks. A 2x2 repeated measures analysis of variance will be conducted to analyze differences between conditions at post course.

Conclusions: The implications of the trial will be discussed as well as the strengths and limitations of MTurk as a tool for recruitment. We will also briefly introduce the future directions along this same line of research.

Trial Registration: ClinicalTrials.gov NCT02469324; https://clinicaltrials.gov/ct2/show/NCT02469324 (Archived by WebCite at http://www.webcitation.org/6fkSG3yuW)

(JMIR Res Protoc 2016;5(2):e65) doi:10.2196/resprot.5332

KEYWORDS

perinatal depression; comparative trial; Internet intervention; Amazon Mechanical Turk

Introduction

Mood changes during and after pregnancy are common although they do not always result in clinically significant depressive episodes. However, both severe and the moderate/milder forms of depression during the perinatal period and postnatal can be a source of major problems to mothers, their babies, and even other family members. Symptoms of postpartum depression (PPD) include, but are not limited to, concentration difficulties, poor sleep, heightened anxiety, feelings of inadequacy, ruminative fears and compulsive thoughts, loss of attachment sentiments, and guilt feelings [1]. The physiological effects of prenatal depression such as elevated cortisol can adversely affect the baby's development and result in negative consequences that remain undetected into adulthood [2].

The costs of PPD, both for the mother and her child, are concerning, especially since the incidence of PPD reaches 7.1% in the United States (US) and is as high as 19.2% when minor depressive episodes are included [3]. It is estimated that the global incidence of PPD is even higher than within the United States [4], suggesting a pressing global health concern for women and their children. Additionally, there is research that demonstrates a relationship between lower income areas and higher PPD prevalence [5], demonstrating that communities who already lack access to adequate health and mental health resources are further affected by untreated PPD in their communities.

Even though the human and financial costs of untreated PPD are well-established, adequate resources to address the global need of women suffering from PPD or who are at risk of developing PPD do not yet exist. Presently, the first line of psychological treatment for PPD is cognitive behavioral therapy (CBT). However, in a review of five randomized controlled trials (RCTs) comparing CBT with standard postpartum care, only two trials demonstrated better outcomes in the CBT group [6]. While preliminary Interpersonal Therapy (IPT), with a focus on handling the interpersonal disputes that occur during childbirth and childcare, has shown some promise in addressing this pressing need [7]. The first line of treatment for PPD continues to be medication [8], particularly selective serotonin reuptake inhibitors (SSRIs), which show some level of efficacy and perform equal to psychotherapy in randomized trials [8,9]. However, there are concerns regarding the safety of antidepressants for pregnant and nursing women [10].

There are many practical limitations to treatment seeking, not least being the availability of appropriately qualified therapists. In addition, issues such as stigma, childcare difficulties, lack of knowledge, and financial constraints can inhibit help seeking [11]. As such, psychological resources that do not require women to leave their homes may allow for more women to participate in psychological interventions. In general, Internet interventions can be private and used anonymously, accessed repeatedly at any time, and from any location, and Internet interventions may provide a much-needed service to users who feel marginalized or stigmatized [12]. Clatworthy's [13] meta-analysis did not find a relationship between the length of an in-person preventative intervention and its effectiveness, suggesting that increasing the length of psychological interventions is not an important factor in enhancing benefit. However, there is research to show that interventions based on psychological models tend to be more effective than interventions that are not based on these models [13], meaning that researchers seeking to create new resources for women should maintain fidelity to empirically supported psychological models.

As a result of the limitations that preclude many women from seeking in-person resources, Internet interventions offer promise in providing care with less financial and practical barriers. Additionally, Internet interventions can be used as adjuncts to in-person treatments or replacements in other cases [14], and perhaps offer even more promise for reducing health disparities. Nonconsumable interventions, or those that can be reused with minimal cost for each additional participant, can help to close the gap in services through offering assistance without needing the support of a clinician or operator on the other end [15]. Currently, there is a dearth of research on Internet interventions for perinatal women or to address PPD [16].

Importantly, over the last 20 years different psychotherapies have been developed that are increasingly rooted in the scientific understanding of psychological processes, including those associated with attachment. For example, compassion focused therapy (CFT) is based on evolutionary insights of brain function, particularly the importance of building and developing affiliative and prosocial relationships with self and other [17,18]. This model in particular articulates the role of affiliative emotion and motivation in threat regulation and how these can be cultivated through (1) addressing issues of self-criticism and shame and (2) with affiliation building exercises (compassion cultivation). This is important because at the heart of many depression difficulties is a harshly self-critical relationship with the self and at times nonaffiliative relations with self and with others. In addition, helping to build affiliative relationships between mothers and their babies is obviously important. There is now considerable evidence that compassion cultivation has an impact on a range of physiological systems including the immune system, frontal cortex, and cardiovascular systems [19]. It also promotes prosocial and empathic behavior [20]. This makes compassion cultivation an especially important focus for intervention for this population.

The present study therefore seeks to assess the efficacy of an Internet-based Compassionate Mind Training (CMT) program, the intervention component of CFT, compared to a standard CBT program in a sample of childbearing and perinatal women. As there is currently a lack of Internet interventions for maternal mental health, the research team intends to assess the relative efficacy of CMT as a resource for women during this period.

It is expected that participants randomized to both Internet-based CMT and CBT will demonstrate improved affect as well as reduced depression and anxiety at similar, if not better, levels which are the secondary outcome measures of this trial. However, in terms of the primary outcome measures, we expect that Internet-based CMT will provide unique benefit above and beyond CBT in the constructs of self-reassurance,

self-criticizing, self-attacking, and self-compassion, as CMT is specifically targeted towards these constructs.

Methods

Participants and Procedures

Participants were recruited through two primary sources: online through Amazon Mechanical Turk (MTurk) and through professional networks. Recruitment for the present study occurred between April 2015 to September 2015.

Upon navigating to the landing page, participants were asked to review and agree to informed consent (IC) before beginning the study. For a copy of the IC for the present study, see Multimedia Appendix 1. Participants who met criteria for inclusion were then randomized to either the CBT (n=60) or CMT (n=60) condition. As the trial was designed to assess the efficacy among perinatal women of an Internet-based CMT relative to an Internet-based CBT intervention, a control group was not employed. To ensure equivalent numbers of participants were randomized to both conditions, an embedded algorithm was used.

Each condition was divided into equal parts (a) and (b) with condition-specific content reflective of the theoretical orientation of the intervention. In part (a), participants completed a didactic, which included written materials and brief experiential exercises. The didactic portion of the course provided an introduction to the approach and was created to take approximately 45 minutes to complete. Following completion of part (a), participants received an automatically generated email based on their assigned condition. The email included follow-up exercises for the CBT condition and audio meditations for the CMT condition. At this point, participants were informed that they would receive additional emails at Day 4, Day 7, and Day 14 of the course.

Based on a power analysis to detect an effect of .4 at alpha .05 with 80% power, this study needed to include a minimum of 23 participants for each condition who complete the post course assessment at two weeks. The standardized effect size was estimated using [21] and the meaning of this size is .25 for small, .5 for medium and 1.00 for large. The designated medium effect size is consistent with what is universally agreed upon in published mindfulness research [22]. However, the research team tried to recruit 60 participants for each condition in order to account for attrition that is inherent in clinical trial, especially ones conducted over the Internet.

Inclusion Criteria

In order to be included in the present study, participants needed to be proficient in English, over the age of 18 years, currently pregnant, pregnant within the last year, or intending to become pregnant in the future. Interested women who met eligibility criteria were included in the present study regardless of depression status at study entry.

Exclusion Criteria

Participants were excluded from participation in the present study if they were male, under the age of 18 years, not intending to become pregnant in the future, not pregnant, and not pregnant within the last year.

Treatment Conditions

For the present trial, participants were randomly assigned to either the Internet-based CBT or CMT condition. The CBT condition, which did not have pregnancy-specific information within the course, included lessons on (1) thoughts, (2) activities, (3) assertiveness, and (4) sleep. Ricardo Muñoz and the Institute for International Internet Interventions (i4health) team developed the materials for this condition, which is based on standard CBT constructs [23]. The CMT condition, which had a limited amount of pregnancy-specific content only in module three, included (1) finding ourselves here in the flow of life, (2) old brain, new brain, (3) the three circles of affect regulation and pregnancy, and (4) cultivating the compassionate self.

Outcome Measures

Self-criticizing, self-attacking, and self-reassurance were assessed through the Forms of Self-Criticizing/Attacking and Self-Reassurance Scale (FSCRS; [24]). This measure identifies levels of self-criticizing and attacking and capacity for one to engage in self-reassurance [24]. In a sample of female college students, Cronbach alpha for inadequate self was at .90 and .86, for hated self and reassured self-subscales, respectively [24]. The FSCRS was administered to participants before and after the didactic portion of the course.

A Likert-scale affect item (“how would you rate your mood currently?” from 0-very bad to 7-very good) was employed to assess current affective state of participants at two time points during the course. The affect item was presented to participants at baseline and following the didactic portion of the course.

Depression and anxiety were assessed through the Patient Health Questionnaire-4 (PHQ-4; [25]. The PHQ-4 is a self-report measure that has two items to assess depression through the PHQ-2 and two items to assess anxiety through the Generalized Anxiety Disorder scale-2 (GAD-2) [26]. Based on a sample from the general population, Cronbach alpha was .78 for PHQ-2 and .75 for GAD-2 [25]. When compared to the Structured Clinical Interview for DSM-IV Disorders (SCID-4), a scaled score of 3 on the PHQ-2 scale demonstrated sensitivity of 87% and specificity of 78% for Major Depressive Disorder (MDD), and it demonstrated comparable diagnostic performance relative to longer measures [27]. The PHQ-4 was administered before the didactic portion of the course and following completion of post course measures at two weeks.

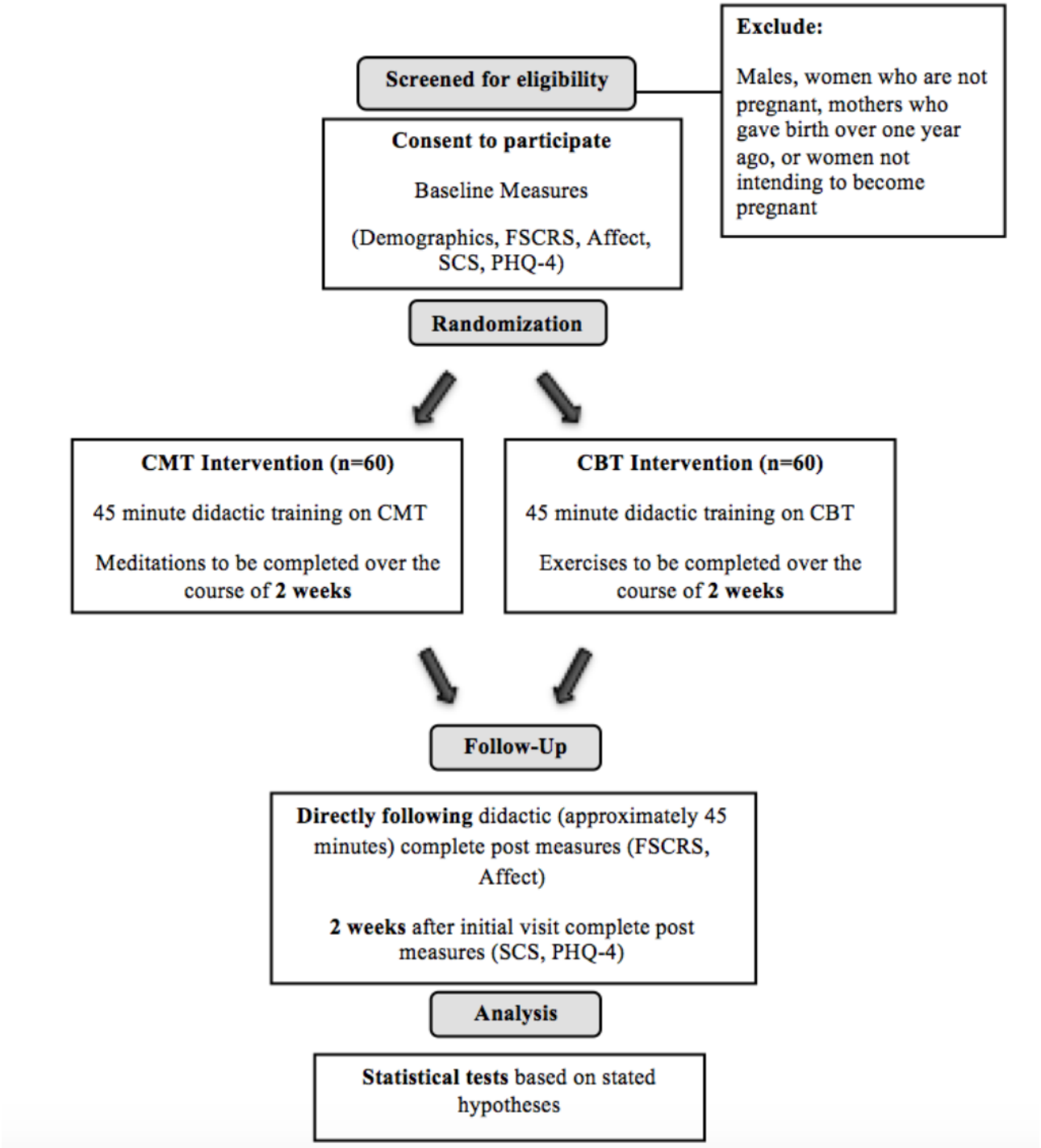
Self-compassion shifts were measured through the short form of the Self-Compassion Scale (SCS-SF; [28]). The SCS-SF measures how individuals respond to themselves during times of stress in order to assess level of self-compassion [28]. The SCS-SF has a near perfect correlation with the longer version of the measure at .97. It has a Cronbach alpha of .86 in the general population in the United States [28]. The SCS-SF was given to participants before the didactic portion of the course and after completion of post course measures at two weeks.

Participant feedback items were asked at post course to elicit information on use (ie, the number of times materials were practiced during each week, overall perceived helpfulness of the materials). While no formalized measure was given to elicit feedback, the information on perceived helpfulness and

utilization was gathered in order to provide participant-directed guidance for updating the CMT condition materials.

For a visual representation of the study design, refer to Figure 1.

Figure 1. Design of the study.



Ethics

The present study received approval by the Palo Alto University Institutional Review Board and is being conducted under the supervision of Alinne Barrera, PhD.

Analysis

The present study seeks to compare the efficacy of two theoretical approaches using a randomized conditional approach with outcome comparisons at baseline, throughout the course period, and at the post course two weeks following randomization. Pre course equivalence between participants in each condition will follow analytical procedures recommended by the CONSORT 2010 Statement [29]. A 2x2 mixed analysis of variance (ANOVA) will be run for each measure at baseline and follow-up. The between subjects factor in the ANOVA will be condition and the within subjects factor will be the outcome measure. A main effect of time and a main effect of condition will be analyzed to determine if there is a difference between CBT and CMT on each of the outcome measures.

Results

The present study has the aim to assess relative efficacy of Internet-based CMT compared to CBT for perinatal women through conducting a randomized controlled trial. While there is currently some research to support Internet-based CBT for perinatal women [30-32], there is still a clear need for additional Internet-based psychological resources for this vulnerable population. As such, research into additional Internet-based psychological programs for perinatal women is important to meet this need.

Trial status: as of April 2015, participants were being enrolled in the study. Participants were recruited continuously throughout the enrollment period. Recruitment ended in September 2015.

Discussion

The current study is a two condition randomized controlled trial comparing brief Internet-based CBT and CMT in enhancing the well-being of perinatal women and women with future intentions of pregnancy. As far as the research team is aware, this is the first trial to assess the relative efficacy of an automated compassion meditation program to a CBT program for working with current and future perinatal women over the Internet. The results are expected to impact the future direction of Internet interventions for perinatal women. It is important to note that the trial is not recruiting women based on depression status, but rather a sample of general population perinatal women. As such, the research team will be unable to make decisive conclusions about the treatment effectiveness of the CMT course based on results from this trial. However, upon completion of this preliminary study, future studies will employ a prevention model approach in order to assess the preventative effectiveness of CMT with respect to PPD development among women in their second and third trimesters. Participant feedback from the current study will allow the research team to update the CMT course material in order to better meet the needs of the target population in phase two of the trial. Finally, and with the intention to make the resources widely available to a global population of women, the research team hopes to translate the study materials into additional languages in order to better serve a more diverse group of perinatal women.

The more that is known about differential effects of Internet interventions, the more researchers can start to tailor certain Internet interventions towards the population that is likely to show benefit from that particular content. To this end, in addition to examining the primary and secondary outcomes of this current pilot study, the research team aims to explore several additional questions. For example, perhaps some groups within the included sample of this study will benefit more from utilizing one condition relative to the other. Alternatively, perhaps the data may indicate that women from certain parts of the world respond better to one condition of the intervention relative to the other. Finally, perhaps the effectiveness of each condition of the intervention will be moderated by the levels of depression the woman are currently experiencing at study entry or the demographics of those women. These are all possible avenues for exploration that the research team will aim to examine once all data have been collected for this pilot trial. The long-term goal for this line of research will be to contribute to the psychological community's understanding of how best to create and disseminate Internet interventions that are targeted towards women who may benefit from them the most.

In addition to the important implications that exist, there are also several limitations to the current study. First, since the majority of recruitment is being conducted using the MTurk system, we lack the capacity to verify the demographics of the individuals who take part in the study. While this is a known issue for MTurk [33], there is evidence to support that running research with an MTurk sample tends to produce near equivalent results as trials conducted in a laboratory setting [34]. Additionally, MTurk workers tend to be more demographically diverse than standard Internet samples and college students that comprise samples of many trials [34], which is a strength to using MTurk as a recruitment tool.

MTurk workers received compensation when they completed post course data at two weeks. There is an inherent limitation with a highly motivated sample of women who will receive compensation for completing post course data in order to receive payment for their participation. Internet-based research has a high level of attrition [35], and thus the completion rates witnessed with an MTurk sample are unlikely to be generalizable to a broader group of international perinatal women. As such, it is impossible to know what actual attrition rates would be in a non-MTurk group of women if the majority of recruitments comes from this source.

Perhaps the most important and glaring limitation of the current trial is the lack of a more distal time point for measurement of outcome variables. The limited follow-up with participants, only occurring at two weeks post course, does not allow the team to make inferences about the longer-term maintenance of improvements in either condition. As the ultimate goal of psychological Internet interventions is to decrease suffering on a global scale, knowledge of longer-term utility of these resources is crucial. In order to account for this limitation during future research along this same line, we will add another follow-up after pregnancy, which can be up to six months after providing baseline data.

Acknowledgments

The PI would like to acknowledge the continued support of his research advisor, Alinne Barrera, whose dedicated and kind guidance has been instrumental in getting this project off the ground. Furthermore, the PI would like to acknowledge the financial support provided by both the Campus Research Board at Palo Alto University and the Elton C and Joan R Waelde Meditation Fellowship, which have allowed for international recruitment to the trial through the MTurk system.

Authors' Contributions

Paul Gilbert, PhD, the founder of Compassion-Focused Therapy and CMT, and Michelle Cree, MS developed the structure and audiomeditations for the CMT condition [36,37]. Alex Kelman, MS, PI on the present study, built the CMT condition under the direction of Dr Gilbert and Ms Cree.

Conflicts of Interest

CMT was created by one of the collaborators on the study, Paul Gilbert, PhD. As such, Dr Gilbert will not be directly involved in the IC process or statistical analyses in order to avoid any conflicts of interest. Additionally, Ricardo Muñoz, PhD developed the CBT condition based on his previous written work and will not be directly involved in the IC process or statistical analyses.

Multimedia Appendix 1

Informed Consent document for the study.

[PDF File (Adobe PDF File), 36KB - resprot_v5i2e65_app1.pdf]

References

1. Goodman JH. Postpartum Depression Beyond the Early Postpartum Period. Journal of Obstetric, Gynecologic, and Neonatal Nursing 2004 Jul 01;33(4):410-420. [doi: 10.1177/0884217504266915]
2. Perry BD. The Neurodevelopmental Costs of Adverse Childhood Events. 2000. The Neuroarcheology of Childhood Maltreatment URL: http://www.juconicomparte.org/recursos/Neuroarcheology%20of%20childhood%20maltreatment_zmH8.pdf [accessed 2016-03-03] [WebCite Cache ID 6fjpmrGTm]
3. Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, Swinson T. Perinatal depression: a systematic review of prevalence and incidence. Obstet Gynecol 2005 Nov;106(5 Pt 1):1071-1083. [doi: 10.1097/01.AOG.0000183597.31630.db] [Medline: 16260528]
4. Almond P. Postnatal depression: A global public health perspective. Perspectives in Public Health 2009 Sep 15;129(5):221-227. [doi: 10.1177/1757913909343882]
5. Yonkers KA, Ramin SM, Rush AJ, Navarrete CA, Carmody T, March D, et al. Onset and Persistence of Postpartum Depression in an Inner-City Maternal Health Clinic System. AJP 2001 Nov;158(11):1856-1863. [doi: 10.1176/appi.ajp.158.11.1856]
6. Perveen T, Mahmood S, Gosadi I, Mehraj J, Sheikh S. Long Term Effectiveness of Cognitive Behavior Therapy for Treatment of Postpartum Depression: A Systematic Review and Meta-analysis. J Pioneer Med Sci Oct-Dec 2013;3(4):198-204.
7. O'Hara MW. Postpartum depression: what we know. J Clin Psychol 2009 Dec;65(12):1258-1269. [doi: 10.1002/jclp.20644] [Medline: 19827112]
8. Misri S, Reebye P, Corral M, Milis L. The use of paroxetine and cognitive-behavioral therapy in postpartum depression and anxiety: a randomized controlled trial. J Clin Psychiatry 2004 Sep;65(9):1236-1241. [Medline: 15367052]
9. O'Hara MW, McCabe JE. Postpartum depression: current status and future directions. Annu Rev Clin Psychol 2013;9:379-407. [doi: 10.1146/annurev-clinpsy-050212-185612] [Medline: 23394227]
10. Yonkers KA, Blackwell KA, Glover J, Forray A. Antidepressant use in pregnant and postpartum women. Annu Rev Clin Psychol 2014;10:369-392 [FREE Full text] [doi: 10.1146/annurev-clinpsy-032813-153626] [Medline: 24313569]
11. O'Mahen H, Himle JA, Fedock G, Henshaw E, Flynn H. A pilot randomized controlled trial of cognitive behavioral therapy for perinatal depression adapted for women with low incomes. Depress Anxiety 2013 Jul;30(7):679-687. [doi: 10.1002/da.22050] [Medline: 23319454]
12. Berger M, Wagner TH, Baker LC. Internet use and stigmatized illness. Soc Sci Med 2005 Oct;61(8):1821-1827. [doi: 10.1016/j.socscimed.2005.03.025] [Medline: 16029778]
13. Clatworthy J. The effectiveness of antenatal interventions to prevent postnatal depression in high-risk women. J Affect Disord 2012 Mar;137(1-3):25-34. [doi: 10.1016/j.jad.2011.02.029] [Medline: 21514960]
14. Ritterband LM, Tate DF. The science of internet interventions. Introduction. Ann Behav Med 2009 Aug;38(1):1-3. [doi: 10.1007/s12160-009-9132-5] [Medline: 19816750]
15. Muñoz RF. Using evidence-based internet interventions to reduce health disparities worldwide. J Med Internet Res 2010;12(5):e60 [FREE Full text] [doi: 10.2196/jmir.1463] [Medline: 21169162]
16. Barrera AZ, Kelman AR, Muñoz RF. Keywords to recruit Spanish- and English-speaking participants: evidence from an online postpartum depression randomized controlled trial. J Med Internet Res 2014 Jan;16(1):e6 [FREE Full text] [doi: 10.2196/jmir.2999] [Medline: 24407163]
17. The Compassionate Mind: A New Approach to Life's Challenges 1st edition. Oakland, Ca: New Harbinger Publications; 2010.
18. Gilbert P. Compassion focused therapy: distinctive features. London: Routledge; 2010.
19. Singer T, Bolz M. Compassion: Bridging practice and science. Leipzig: Max Planck Institute for Human Cognitive and Brain Sciences; 2013.

20. Weng HY, Fox AS, Shackman AJ, Stodola DE, Caldwell Jessica Z K, Olson MC, et al. Compassion training alters altruism and neural responses to suffering. Psychol Sci 2013 Jul 1;24(7):1171-1180 [FREE Full text] [doi: 10.1177/0956797612469537] [Medline: 23696200]
21. Cohen J. Statistical power analysis for the behavioral sciences. Hillsdale, N.J: L. Erlbaum Associates; 1988.
22. Eberth J, Sedlmeier P. The Effects of Mindfulness Meditation: A Meta-Analysis. Mindfulness 2012 May 2;3(3):174-189. [doi: 10.1007/s12671-012-0101-x]
23. Muñoz R. Preventing major depression by promoting emotion regulation: A conceptual framework and some practical tools. Int J Ment Health Promot Sept 1998;1(1):23-40.
24. Gilbert P, Clarke M, Hempel S, Miles J N V, Irons C. Criticizing and reassuring oneself: An exploration of forms, styles and reasons in female students. Br J Clin Psychol 2004 Mar;43(Pt 1):31-50. [doi: 10.1348/014466504772812959] [Medline: 15005905]
25. Löwe B, Wahl I, Rose M, Spitzer C, Glaesmer H, Wingenfeld K, et al. A 4-item measure of depression and anxiety: validation and standardization of the Patient Health Questionnaire-4 (PHQ-4) in the general population. J Affect Disord 2010 Apr;122(1-2):86-95. [doi: 10.1016/j.jad.2009.06.019] [Medline: 19616305]
26. Kroenke K, Spitzer RL, Williams Janet B W, Löwe B. An ultra-brief screening scale for anxiety and depression: the PHQ-4. Psychosomatics 2009 Dec;50(6):613-621. [doi: 10.1176/appi.psy.50.6.613] [Medline: 19996233]
27. Löwe B, Kroenke K, Gräfe K. Detecting and monitoring depression with a two-item questionnaire (PHQ-2). J Psychosom Res 2005 Feb;58(2):163-171. [doi: 10.1016/j.jpsychores.2004.09.006] [Medline: 15820844]
28. Raes F, Pommier E, Neff KD, Van GD. Construction and factorial validation of a short form of the Self-Compassion Scale. Clin Psychol Psychother 2011 Jun;18(3):250-255. [doi: 10.1002/cpp.702] [Medline: 21584907]
29. Authors?. www.consort-statement.org/. 2007. CONSORT statement 2007 URL: http://www.consort-statement.org/ [accessed 2016-03-05] [WebCite Cache ID 6fm4lEG6y]
30. O'Mahen HA, Woodford J, McGinley J, Warren FC, Richards DA, Lynch TR, et al. Internet-based behavioral activation--treatment for postnatal depression (Netmums): a randomized controlled trial. J Affect Disord 2013 Sep 25;150(3):814-822. [doi: 10.1016/j.jad.2013.03.005] [Medline: 23602514]
31. O'Mahen HA, Richards DA, Woodford J, Wilkinson E, McGinley J, Taylor RS, et al. Netmums: a phase II randomized controlled trial of a guided Internet behavioural activation treatment for postpartum depression. Psychol Med 2014 Jun;44(8):1675-1689 [FREE Full text] [doi: 10.1017/S0033291713002092] [Medline: 24148703]
32. Barrera AZ, Wickham RE, Muñoz RF. Online prevention of postpartum depression for Spanish- and English-speaking pregnant women: A pilot randomized controlled trial. Internet Interv 2015 Sep 1;2(3):257-265. [doi: 10.1016/j.invent.2015.06.002] [Medline: 26273567]
33. Crump Matthew J C, McDonnell JV, Gureckis TM. Evaluating Amazon's Mechanical Turk as a tool for experimental behavioral research. PLoS One 2013;8(3):e57410 [FREE Full text] [doi: 10.1371/journal.pone.0057410] [Medline: 23516406]
34. Buhrmester M, Kwang T, Gosling SD. Amazon's Mechanical Turk: A New Source of Inexpensive, Yet High-Quality, Data? Perspectives on Psychological Science 2011 Feb 03;6(1):3-5. [doi: 10.1177/1745691610393980]
35. Donkin L, Christensen H, Naismith SL, Neal B, Hickie IB, Glozier N. A systematic review of the impact of adherence on the effectiveness of e-therapies. J Med Internet Res 2011;13(3):e52 [FREE Full text] [doi: 10.2196/jmir.1772] [Medline: 21821503]
36. Gilbert P, Procter S. Compassionate mind training for people with high shame and self-criticism: overview and pilot study of a group therapy approach. Clin. Psychol. Psychother 2006 Nov;13(6):353-379. [doi: 10.1002/cpp.507]
37. Family Nurse Partnership Learning Pack. Compassionate Mind Training For Family Nurses. In: National Health Service: United Kingdom. United Kingdom: Crown Copyright; 2011.

Abbreviations

ANOVA: analysis of variance
CBT: cognitive behavioral therapy
CFT: compassion focused therapy
CMT: compassionate mind training
FSCRS: Forms of Self-Criticizing/Attacking and Self-Reassurance Scale
IC: informed consent
IPT: interpersonal psychotherapy
MDD: major depressive disorder
MTurk: Amazon Mechanical Turk
PHQ-4: Patient Health Questionnaire-4
PPD: postpartum depression
RCT: randomized controlled trial
SCS-SF: Self-Compassion Scale-Short Form
SSRI: selective serotonin reuptake inhibitor

Edited by G Eysenbach; submitted 09.11.15; peer-reviewed by A Gemmill, A Lara; comments to author 20.12.15; revised version received 02.01.16; accepted 03.01.16; published 15.04.16.

Please cite as:
Kelman AR, Stanley ML, Barrera AZ, Cree M, Heineberg Y, Gilbert P
Comparing Brief Internet-Based Compassionate Mind Training and Cognitive Behavioral Therapy for Perinatal Women: Study Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2016;5(2):e65
URL: http://www.researchprotocols.org/2016/2/e65/
doi:10.2196/resprot.5332
PMID:27084301

Original Paper

Design and Methods of a Synchronous Online Motivational Interviewing Intervention for Weight Management

Rebecca Anne Krukowski[1], PhD; Vicki DiLillo[2], PhD; Krista Ingle[3], PhD; Jean Ruth Harvey[4], RD, PhD; Delia Smith West[5], PhD

[1]Center for Population Sciences, Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis, TN, United States
[2]Ohio Wesleyan University, Department of Psychology, Delaware, OH, United States
[3]Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, United States
[4]Department of Nutrition and Food Sciences, University of Vermont, Burlington, VT, United States
[5]Department of Exercise Science, Arnold School of Public Health, University of South Carolina, Columbia, SC, United States

Corresponding Author:
Rebecca Anne Krukowski, PhD
Center for Population Sciences
Department of Preventive Medicine
University of Tennessee Health Science Center
66 N Pauline St.
Memphis, TN, 38163
United States
Phone: 1 9014482426
Fax: 1 9014487041
Email: rkrukows@uthsc.edu

Abstract

Background: While Internet-based weight management programs can facilitate access to and engagement in evidence-based lifestyle weight loss programs, the results have generally not been as effective as in-person programs. Furthermore, motivational interviewing (MI) has shown promise as a technique for enhancing weight loss outcomes within face-to-face programs.

Objective: This paper describes the design, intervention development, and analysis of a therapist-delivered online MI intervention for weight loss in the context of an online weight loss program.

Methods: The MI intervention is delivered within the context of a randomized controlled trial examining the efficacy of an 18-month, group-based, online behavioral weight control program plus individually administered, synchronous online MI sessions relative to the group-based program alone. Six individual 30-minute MI sessions are conducted in private chat rooms over 18 months by doctoral-level psychologists. Sessions use a semistructured interview format for content and session flow and incorporate core MI components (eg, collaborative agenda setting, open-ended questions, reflective listening and summary statements, objective data, and a focus on evoking and amplifying change talk).

Results: The project was funded in 2010 and enrollment was completed in 2012. Data analysis is currently under way and the first results are expected in 2016.

Conclusions: This is the first trial to test the efficacy of a synchronous online, one-on-one MI intervention designed to augment an online group behavioral weight loss program. If the addition of MI sessions proves to be successful, this intervention could be disseminated to enhance other distance-based weight loss interventions.

Trial Registration: Clinicaltrials.gov NCT01232699; https://clinicaltrials.gov/ct2/show/NCT01232699

(JMIR Res Protoc 2016;5(2):e69) doi:10.2196/resprot.5382

KEYWORDS

technology; weight loss; motivational interviewing; methodology

Introduction

Obesity is one of the most pressing public health problems currently facing the United States, with about two-thirds of the adult population categorized as overweight or obese [1]. Fortunately, evidence-based lifestyle weight control programs have been shown to produce clinically significant weight losses, with studies reporting average weight losses of 7%-9% [2,3], a magnitude of weight reduction that confers substantial health benefits [4]. However, access to and engagement in these beneficial programs may be challenging for some individuals because they lack geographic proximity to evidence-based weight management programs and/or they have time constraints associated with travel to the treatment center. Internet-based weight management programs have emerged as a method that may reduce some of these barriers [5-11]. Indeed, the superior incremental cost-effectiveness of one Internet-delivered behavioral weight control program reflected savings in participant travel time [12].

However, while the weight losses achieved in synchronous online interventions are quite promising (approximately 5% of baseline weight), they are not as substantial as those achieved with the identical program delivered in-person (approximately 8% of baseline weight) [11]. Motivational interviewing (MI) has recently been shown to offer significant increases in weight losses achieved by standard face-to-face behavioral weight management programs [13-17] and thus represents a potent technique for exploration to enhance online behavioral weight management programs.

MI is a client-centered counseling approach to promoting behavior change by exploring personal reasons for engaging in change in a nonjudgmental, supportive yet directive fashion [18]. Key elements of MI are reflective listening, objective feedback, eliciting and amplifying expressions of willingness to change, affirming confidence in one's ability to make changes, and supporting perceived importance for making changes. This paper offers a detailed description of an MI intervention implemented online within the context of a group-based behavioral weight loss program delivered totally online. To our knowledge, this is the first description of a therapist-delivered individual online MI treatment for weight management.

Methods

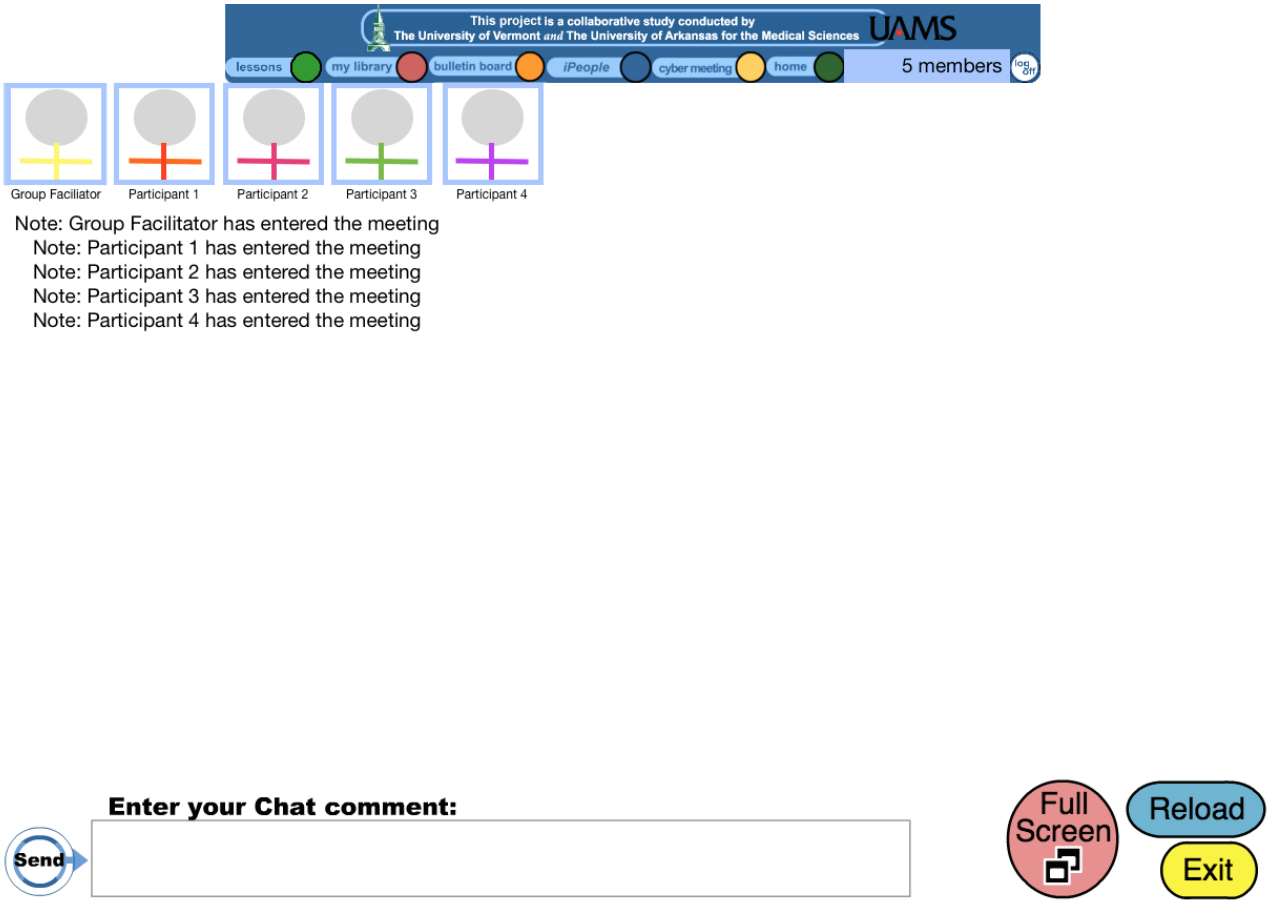
Study Overview

The MI intervention described here is delivered within the context of a randomized controlled trial (NCT01232699) examining the efficacy of an 18-month long, group-based online behavioral weight control program plus individually administered online MI chat (ie, text-based) sessions relative to the group-based program alone. In total, 398 participants (89.7% (357/398) female, 24.1% (96/398) African American, mean age: 48.4±10.1 years, mean BMI 36.6±6.0 kg/m2) were randomized to the 2 conditions. Participants indicated availability for predetermined meeting times; these intact groups were stratified by their baseline BMI percentile value and then were randomized using a biased coin approach.

The online group program utilizes an evidence-based program that achieved an average of 5.5% weight loss in previous research [11] and extends this earlier study to determine whether the addition of MI enhances weight losses over and above the evidence-based group program alone. Briefly, the group program is a manualized comprehensive behavioral weight loss program that features 1-hour-long synchronous group chats weekly for 6 months and then monthly for 12 months. The group chat room can be seen in Figure 1 where, in order to illustrate the format of the chat room while preserving participant confidentiality, stick figures and pseudonyms (eg, participant 1) are used instead of participant/facilitator photos and names. The group program focuses on the modification of eating and exercise habits by using behavioral strategies (eg, dietary, weight, and physical activity self-monitoring, stimulus control, problem solving, goal setting, relapse prevention, and assertiveness training) and self-management skills (eg, calorie and fat goals, graded exercise goals). The password-protected website includes written lesson materials for each session topic; the lessons include opportunities for the participants to apply the topic of the lesson as "homework." The website also includes an online self-monitoring tool, a bulletin board for participants to post comments or questions for one another, and helpful hints (eg, recipes, weight loss tips, and updates on local physical activity opportunities). This online group program has been previously described in detail [11,19]; therefore, this paper focuses on the novel online MI intervention, rather than the full study protocol.

The current report is intended to offer an overview of the MI intervention protocol and of the empirical foundation that guided its development. The MI intervention methods described are based on evidence, where available, and on clinical judgment, in the absence of such data. The study is approved by the Committee on Human Research in the Behavioral Sciences at the University of Vermont and the Institutional Review Board at the University of Arkansas for Medical Sciences.

Figure 1. A screenshot of the group chat room utilized in the program.



Measures

The primary outcomes are change in body weight at 6 and 18 months post randomization, measured in-person by a digital scale. Demographic data are obtained by online questionnaire, and process data (eg, self-monitoring of dietary intake and physical activity, group session attendance, emoticon utilization, program evaluation) are collected throughout intervention delivery. The treatment self-regulation questionnaire [20] is used to measure autonomous and controlled motivation.

We will use the Motivational Interviewing Skills Code version 2.1 (MISC) [21] both to establish treatment fidelity [22] and to examine whether participant language mediates weight loss outcomes [23]. The MISC software was developed to rate counselor adherence to MI within a session by coding global dimensions and specific therapist behaviors. It has been widely used in a range of research settings [24] and offers the advantage of allowing examination of client language as a predictor of treatment outcome [23]. This will be crucial because of the modality of the MI sessions; counselors and participants are not able to gauge one another's nonverbal and auditory cues, such as inflection, tone, or facial expression. In addition, it could be difficult for a participant to determine whether a counselor's comment is a reflective statement or a question, absent inflection and tone. Similarly, it is unclear whether a participant's reading of a counselor's reflective statement or summary will evoke the same response as hearing a counselor's reflection. It is possible that without nonverbal cues, the written version of a reflection may lack the impact and empathy that a spoken MI reflection or affirmation can provide. For this reason, the intervention emphasizes amplified reflections, double-sided reflections, and summaries, while avoiding simple reflections that could be perceived as very redundant. Although there are several potential disadvantages to a text-based MI interaction, we have the advantage that all MI sessions will have a transcript generated from the chat, which will facilitate these analyses.

Analysis Plan

First, we will examine the impact of the addition of individual MI counseling to the group-based online weight control program on weight loss (ie, the main outcome), dietary and physical activity self-monitoring, and group session attendance. We hypothesize that the participants who receive MI sessions will self-monitor their diet and physical activity more frequently and attend more group chat sessions, which will lead to greater weight loss among these participants. Second, we will examine the uptake of MI sessions, autonomous and controlled motivation, and qualitative and quantitative evaluation of the MI sessions by participants to inform future delivery of MI online. Previous research [25-27] has reported favorable responses of participants to online motivational interventions for increasing physical activity, although MI in these settings was delivered in a largely automated intervention. The current study will also allow us to explore participant characteristics that may be associated with engagement in the MI sessions. For example, some preliminary evidence suggests that African

Americans may find MI less helpful than Caucasian Americans [17,28]. Finally, we will examine utilization of particular features of these MI chat sessions (eg, emoticons, importance/confidence ruler).

Motivational Interviewing Intervention

Participants randomized to the MI condition receive 6 MI sessions at regularly scheduled intervals throughout the 18-month program. Participants are assigned to an MI counselor separate from their group weight loss facilitator; the assignment is made when participants select a convenient appointment time for their first MI session. Prior to this, the MI counselors post available appointment times on the online scheduler and then send an email inviting those randomized to the MI condition to schedule their first MI chat. The MI counselor posting the time slot that the participant selects then becomes her MI counselor for the duration of the program, in order to foster rapport and permit continuity. (Note: We decided to use feminine pronouns throughout this article to refer to our participants, as the majority of participants in this study are female, as is the case in most weight loss programs [29].) To facilitate trust, all conversations between the participant and the MI counselor are kept private, with no information shared with the group facilitator, and participants are aware of this separation from the onset of the MI chats.

The MI sessions are conducted using an interactive, synchronous format of a private chat, integrated within the same website as the weight loss program website. We decided to use text-based chat because many of our study participants live in rural areas without consistent access to high speed Internet, which is required for other types of chat sessions (eg, video chat). Individual MI sessions are conducted, as there is greater evidence supporting 1-on-1 MI compared to group MI sessions for behavior change [18]. The MI chat sessions are designed to last approximately 30 minutes and follow a semistructured interview format that allows tailoring of the session to participant concerns and issues, as well as flexibility in the sequencing of topics within the session, while standardizing the range of topics and issues covered across participants. MI chat sessions do not introduce new information about weight loss methods or dietary/physical activity strategies, and specific questions raised by participants related to behavioral strategies or diet or exercise are directed back to the group facilitator. The goal of the MI sessions is to clarify and amplify personal reasons to make behavior changes that promote weight loss and sustained weight maintenance.

Timing of the Motivational Interviewing Sessions

There are no empirical data examining different patterns of MI delivery within weight management to guide selection of the timeframe for the individual MI sessions. Specifically, there are no data to inform the question of whether it is most effective to front-load the MI sessions and capitalize on the motivational forces that compelled an individual to seek treatment, increasing and extending their personal reasons to engage in weight loss efforts to strengthen their motivation and resolve. Alternatively, one can consider more of a “rescue” approach, which seeks not so much to build on the strength of initial motivation but offer augmentation later in the program when motivation can be flagging. A “middle ground” approach that offers some MI sessions up-front and some as the weight control program unfolds was selected to provide intervention at both of these important phases of the treatment experience. Further, this approach to distribute MI sessions across the treatment program is consistent with the approach successfully used in a previous study that offered individual MI sessions as an adjunct to group weight management but delivered the MI sessions face-to-face [14]. The choice of 6 sessions for the current study replicates the number of sessions offered in this previous study.

The first MI session is scheduled after randomization and group assignment (Table 1), but before beginning the group sessions. Initiation of MI prior to starting the group program allows assessment of the primary motivators for enrolling in the weight loss program and expectations surrounding behavior changes to promote weight loss before any contact with the program psychoeducational materials or the group leader, and thus allows focus on the personal motivators that brought the participants into the treatment program.

Table 1. Motivational interviewing session timing, content, and motivational focus.

Session	Timing	Content	Motivational Focus
1	After randomization and before group sessions start	Elicit primary motivators for seeking weight loss treatment, expected outcomes from weight loss, and behavior changes the participant is considering	Evoke change talk focused on selected self-monitoring strategy
2	Week 5 of group program (after 5th group session)	Review objective data on the program engagement (ie, attendance at group chat sessions, submission of self-monitoring records) and perceptions about progress toward goals	Evoke change talk focused on weight control strategies that have been helpful in making progress toward goals and strategies that the participant would like to add to improve weight loss
3	Week 18 of group program (6 weeks before transition to monthly group sessions)	Take stock of progress while considering the good and not-so-good aspects of moving to less frequent meetings; explore whether/how motivators for weight loss have shifted and any plans for maximizing remaining weekly group sessions	Evoke change talk surrounding behavioral goals to maximize desired progress prior to transition to monthly group sessions
4	Week 31 of group program (6 weeks after the transition to monthly sessions)	Reflect on the impact of transition on weight management behaviors, by identifying self-management successes and challenges during this phase and refocusing, if necessary	Evoke change talk about weight control strategies using and/or considering to get back on track toward personal goals
5	Week 44 of group program	Address weight maintenance by focusing on strategies used or considering to maintain commitment to goals and/or to lifestyle behaviors, with focus on the long term after program structure ends	Evoke change talk regarding strategies for sustaining weight loss, re-engaging in weight loss efforts, and/or to reverse weight regain
6	Week 57 of group program	Review accomplishments of which the participant is most proud and identify goals for the final months of program	Evoke change talk regarding strategies for weight maintenance

The second MI session is scheduled after the fifth weekly group session. This point in the treatment program was selected because emerging evidence from our research group indicates that engagement in the initial 4 weeks of a behavioral weight control intervention is predictive of longer-term success [19]. Those who self-monitor relevant weight loss behaviors during this first month of treatment achieve greater weight losses than those who are less engaged. Work of others echoes and extends this emphasis on early engagement [30,31], with weight losses in the first or second month significantly associated with long-term weight losses. Collectively, this research dramatically reinforces the importance of getting involved and engaged in the treatment process during the first few weeks of the weight control program and served as the impetus to include an MI session at this influential juncture.

The transition to a less frequent intervention contact schedule is another point that may be critical in the treatment process. Typically, behavioral weight management programs start with weekly group contact and shift to biweekly or monthly groups after 4 to 6 months, and studies suggest that weight loss can be attenuated when group meetings become less frequent, although this is an understudied area [32]. Further, clinically, participants can express anxiety or apprehension about leaving the structure of the weekly accountability provided by the group sessions; therefore, in hopes of buffering the impact of the transition from weekly to monthly group meetings at 6 months, the third MI session is scheduled approximately 6 weeks before that change in hopes of offering a motivational boost entering into the transition. The fourth MI session is scheduled approximately 6 weeks after the transition (ie, week 31) to allow the participant to reflect on the experiences associated with the transition and the impact that it has had on their engagement in weight management behaviors and outcomes, offering an opportunity for refocusing if necessary. The fifth and sixth MI sessions are offered at weeks 44 and 57, respectively, when there is time to make some changes before the end of the program, to re-engage in weight loss efforts, and/or to reverse weight regain that might have occurred, should the participant elect to focus on behavior change. These MI sessions are designed to prompt self-reflection on current goals and motivations in contrast with those expressed when starting the program. The goal of these 2 final MI sessions is to facilitate increased self-efficacy and autonomous motivation [33] for behavior change and/or to revitalize motivation and purpose, if that is necessary and desired.

Content of Motivational Interviewing Chat Sessions

All of the sessions use a semistructured interview format that guides the content and suggests the session flow. The content and motivational focus for each session is detailed in Table 1. Each session also provides an opportunity for the participant to add items to the agenda for discussion. In this way, standardization across participants can be balanced with personalization of the sessions based on individual needs and issues.

The first MI session focuses on the participant's primary motivators for seeking weight loss treatment, expected outcomes from weight loss, and the behavior changes the participant considers most efficacious for her personal weight loss efforts. Specifically, the counselor queries the participant about the reasons that led her to enroll in a weight control program at this point in her life and the behaviors that she is considering changing to achieve weight loss. The counselor also explores with the participant how she thinks her life will be different if she is as successful as possible with her planned behavior changes. With permission from the participant, the counselor provides information on the strong associations between

self-monitoring of dietary intake and physical activity early in the program (ie, in the first 4 weeks) and weight loss success. A collaborative discussion about how self-monitoring might figure in the participant's thoughts about her own personal engagement in the program follows. Among those participants who express interest in using self-monitoring to maximize her personal success, a discussion about the self-monitoring approach (eg, logging foods before consuming them, logging foods at the end of the day) she thinks would be most effective for her is then initiated. The MI counselor utilizes the importance/confidence rulers (with amplification) to evoke change talk regarding the self-monitoring strategy identified. Change talk is at the heart of MI counseling and refers to a participant's stated desire, ability, reason, and/or need to change behavior, as well as her commitment to changing [18]. As in all subsequent MI sessions, the initial session ends with a summary of what has been discussed during the chat followed by a query about the completeness of the summary and a request for the participant to provide annotations of any missing critical elements.

The second MI session includes objective data on the participant's engagement thus far in the program (ie, her attendance at group chat sessions, her submission of self-monitoring records—not the content of the records or her reported calorie levels but the act of completing the records). In addition, the counselor asks about the participant's perceptions of her progress toward her goals and the role, if any, that thinking about her primary motivators for weight loss has played in her behavior change efforts thus far. Because the nature of the queries in this MI session can be quite different depending on how the participant is feeling about her progress thus far (ie, is she pleased/excited vs disappointed/frustrated?), the counselors have 2 versions of the semistructured interview to allow tailoring to participant's self-evaluation; the counselor selects the semistructured interview with the more positive or the more negative self-evaluation based on the participant's response to the initial question querying about progress thus far. Notably, the initial question does not specify progress about what (ie, progress with weight loss, performance of behavior changes, or any other concrete outcome) but instead offers an open-ended question that allows the participant to focus on whatever dimension she finds most relevant in her self-evaluation.

The third MI session allows the participant a chance to take stock of her progress once again and make plans for how she wants to proceed as she moves into the transition period and has fewer group sessions each month. The format of the session offers deliberation of the good things about transitioning to less frequent meetings and the less-good things to allow participants to explore both aspects of the upcoming change. The content of this session is focused on exploring whether/how the motivators for weight loss have shifted, her perspective on her engagement and progress thus far, and eliciting emotional reactions to the prospect of transitioning to monthly sessions (eg, concerned, excited). Exploration of the steps that she is considering taking to maximize her satisfaction with her progress is also part of this chat. The counselor then utilizes the importance/confidence rulers (with amplification) to evoke change talk regarding the steps that the participant identifies as likely to maximize her satisfaction, with an ultimate goal of negotiating a plan of action to make the most of the next few weeks before transitioning to monthly group sessions.

The fourth MI session highlights current status after transitioning to monthly sessions, identifying any successes in self-management during this phase of the program and exploring any challenges or obstacles encountered. Such discussions foster autonomous motivation, build self-efficacy [34], and allow these strengths to be balanced with identification of the changes (if any) that the participant would like to see in her performance and/or her goals for this next phase of the program. Again, the emphasis is on eliciting change talk about weight maintenance related behaviors or about weight loss promoting behaviors. With permission, the counselor provides information from the National Weight Control Registry [35] about strategies that other individuals have used to successfully maintain their weight. After providing this information, the counselor elicits participant self-report about strategies she might already be using and which, if any, she might be considering implementing in the near future. The counselor then utilizes the importance/confidence rulers (with amplification) to evoke change talk regarding these strategies.

The fifth MI session centers on strategies that the participant has used or would like to use to maintain her commitment to her goals and to lifestyle behaviors over the long-term, as she will not have the structure of the group chats and other components of the weight control program to support her in these efforts after the end of the program. With permission, the counselor also uses a menu of options to provide information about strategies that others have found helpful in sustaining weight loss [36,37] and elicits reactions to which strategies appeal to the participant.

The final MI session emphasizes the accomplishments the participant is most proud of over the course of her participation in the program, prompting her to review her experiences over the full program to facilitate a balanced perspective of successes and challenges. This conversation also aims to elicit envisioning about the long-term goals, then moves on to discuss how the final 3 months in the program can support this longer-range vision.

The semistructured interview formats provide a template that will be useful in replicating and disseminating the approach taken to deliver the counseling, should the MI sessions prove effective in enhancing weight loss outcomes. Furthermore, the chat format generates a transcript that is used for constructing clinical notes for the counselor and for supervision.

Motivational Interviewing Techniques and Strategies Employed in Chat Sessions

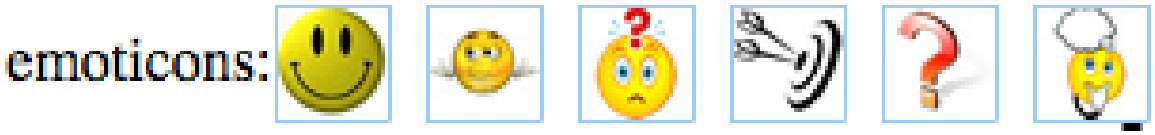
In addition to the specific content areas described above, there are session components that speak to how the MI spirit is embodied in this intervention by the counselor. Present in each chat is an emphasis on collaborative agenda setting and participant-driven goal setting, which is facilitated by counselors who provide a menu of options if participants do not immediately identify their own goals. In addition, open-ended

questions are used, with the counselor attempting to maintain a 2-to-1 ratio of reflective statements to questions. The underlying goal for each chat is to foster a strong collaborative relationship in an environment of empathy and respect with an emphasis on evoking the participant's personal reasons for change and seeking to elaborate and strengthen these reasons. Counselor summaries at the end of the session followed by an invitation to the participant to amend and/or correct as needed are also incorporated into each MI session. Furthermore, counselors use importance and confidence rulers as tools to elicit change talk and fortify self-efficacy, respectively. To facilitate the use of the rulers, a visual representation of a yardstick is graphically displayed in the chat room, and the participant clicks on the location on the ruler which corresponds to where she sees herself. This value is immediately displayed in the chat log (eg, importance=10) to allow the counselor to comment and to guide continued conversation. Finally, in recognition of the lack of nonverbal communication with the online chat format, and the concern that it might be difficult to place text-only comments in an emotional context without voice inflection, we created 6 emoticons that are displayed in the chat room. The 6 emoticons are intended to convey facial expressions or body language that could be seen if the session were face-to-face. Upon selecting an emoticon, the participant's selection is transformed into text for her counselor to see in the chat log (eg, when she selects the smiley face, the counselor sees the text "I'm smiling" in the chat log). The 6 emoticons (and the text equivalent in parentheses) are: (1) a smiley face ("I'm smiling."); (2) a smiling person shrugging ("That's in the ball park but not quite what I mean."); (3) a smiley face with a question mark ("I'm not certain what you're saying. Can you tell me more?"); (4) a bull's-eye with an arrow ("You're on the right track. Keep going."); (5) a question mark ("I have a question."); and (6) a man with bubbles over his head ("I'm giving this some thought.") (Figure 2). The behavioral change techniques [38] used in the MI sessions are detailed in Table 2.

Table 2. Behavior change techniques included in motivational interviewing sessions.

Category	Technique
Goals and planning	Goal setting (behavior)
	Goal setting (outcome)
	Review behavior goal(s)
	Discrepancy between current behavior(s) and goal(s)
	Review outcome goal(s)
Feedback and monitoring	Feedback on behavior
	Self-monitoring of behavior
Comparison of outcomes	Credible source
	Comparative imagining of future outcomes
Self-belief	Focus on past success

Figure 2. The emoticons used in the motivational interviewing weight loss intervention.



Scheduling Motivational Interviewing Sessions

Participants are prompted by email to schedule their MI chat session at the protocol-specified time in the program. An online scheduling system allows participants to schedule the individual chat with her MI counselor at a time that is convenient for her. There is a 2-week window around the protocol-specified week in which the MI session is to occur and during which participants can schedule. An additional week or "grace period" can be added to accommodate rescheduling due to illness, schedule conflicts, etc. If the window closes without an MI session being completed, the participant must wait to chat with her MI counselor until the next window opens. Within each MI chat window, a series of 3 reminder emails are sent (later emails are not sent if the MI session is completed). The first email is sent at the beginning of the 2-week window, the second email is sent 5 business days after the first email, and the third email is sent 7 business days after the first email. We chose to send 3 emails to schedule the MI sessions because we felt that this approach provides an appropriate number of reminders to schedule the session without alienating participants who are not interested in scheduling a session at that point in time.

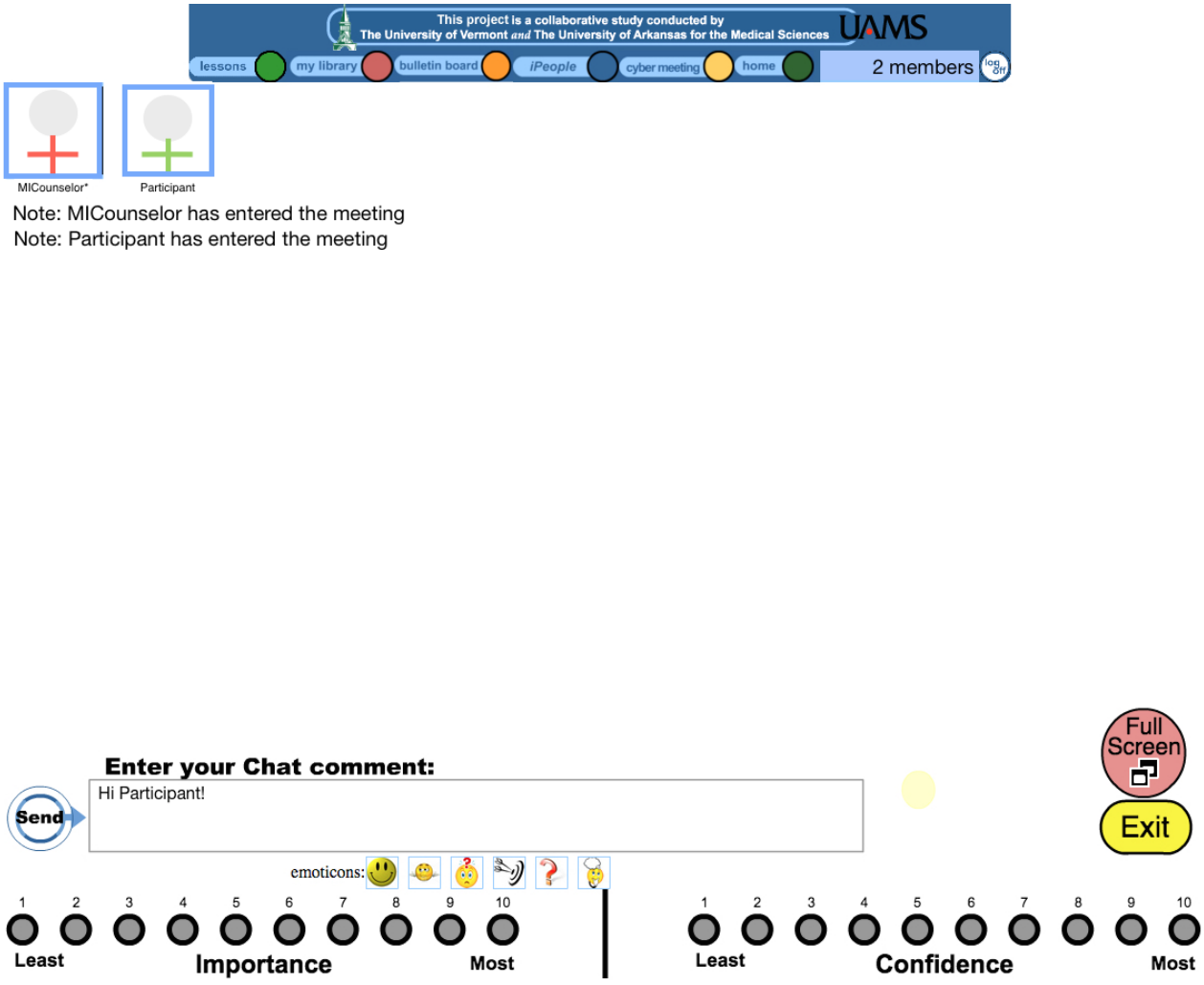
The Motivational Interviewing Chat Room

All MI chats are conducted in a private chat room with only the participant and the MI counselor able to access this chat room. This ensures that the conversations between MI counselor and a particular participant remain private and confidential. When

the MI counselor or the participant "enters" the chat room, her photograph and her name (or a profile substitute if the participant prefers that over a photograph) appears at the top of the screen. These photographs allow the participant and counselor to "see" each other and to establish that no one else entered the chat room. When someone logs off, or experiences technical difficulties, the photograph and name disappears, which alerts the remaining person of a departure from the chat room. If someone is currently typing text, an asterisk appears next to their name. A screenshot of the MI chat room is shown in Figure 3. Multiple MI chats conducted by separate counselors can occur simultaneously on the study website, but they all occur in separate, private chat rooms. Participants are very familiar with the mechanics of this chatting process as it is the same process we use for the group chats during which the behavioral weight control group program is delivered.

The website was created in Adobe ColdFusion and is run using ColdFusion Server software. The chat room was created using Adobe Flash. The website and the chat room were intentionally created using technologies with minimal participant requirements to facilitate program implementation and eventual dissemination.

Figure 3. Screenshot of the chat room utilized in the motivational interviewing sessions.



Motivational Interviewing Counselors

The counselors are 5 PhD-level clinical psychologists with previous training and experience with motivational interviewing in face-to-face counseling. Initial training for this study included 20 hours of didactic review of the core tenets of MI and the approach to MI within weight control, and counselors had required readings focused on distinguishing MI from cognitive behavioral treatment within the context of weight management [39] as well as the most recent thinking on delivery of MI [18]. The senior author (DSW) attended a Motivational Interviewing Network-sponsored training conducted by Dr. William Miller and Dr. Theresa Moyer that focused on training-the-trainer using strategies from the third edition of *Motivational Interviewing* [40]. DSW implemented these exercises with the study's MI counselors. Counselors were required to "test chat" to criterion before being certified to conduct chats with study participants, ensuring that they were comfortable with the features of the chat room and with implementing the semistructured interview format. Online delivery of the MI intervention allows counselors to be geographically distributed, and, indeed, the counselors are located across the country.

Ongoing training and supervision to monitor treatment fidelity and to resolve clinical challenges by consensus is used to enhance standardization. The counselors participate in biweekly supervision-focused conference calls, which identify difficulties

in implementing the protocol that may need to be resolved and provide opportunities to problem solve challenging situations. In this ongoing training, we "role-play" by way of reviewing chat scripts to offer opportunities for modeling and for refining protocol scripts about how to handle specific clinical situations that arise. Supervision calls also focus on strategies for increasing attendance at the MI sessions.

Results

The project was funded in 2010 and enrollment was completed in 2012. Data analysis is currently under way and the first results are expected in 2016.

Discussion

This paper describes the design of a synchronous, online, 1-on-1 MI intervention currently being tested as an adjunct to an online, group behavioral weight control program to determine whether the addition of the MI chats augment weight loss outcomes compared with the group program alone. MI counseling has typically been delivered face-to-face or by telephone, but there is a growing body of literature examining online strategies to deliver MI-based interventions that target a range of behaviors, including smoking [41], substance abuse [42-46], physical activity [25,26], and disordered eating [47].

These online interventions are most often delivered via an automated Web-based platform in which elements of a standardized motivational intervention are tailored to a particular participant based on individual characteristics or responses to questions [25,26,42,43,45]. It is clear to participants in these interventions that they are interacting with a computer rather than an actual counselor. In contrast, a few interventions, including the current intervention, provide a synchronous interaction with an actual counselor [41,48]. Intervention with a counselor should allow for greater responsiveness, more accurate but not reiterating reflections, and more nuanced summaries than possible with an automated approach, however sophisticated it might be. This, in turn, might be hypothesized to have greater influence on behavior change. The earlier studies that delivered MI by online counselor personified as an avatar in a virtual chat room [41] and in a group format [48] have not demonstrated markedly greater effect than the automated-algorithm driven approaches, but this may not be surprising. Group MI has not been shown as robust as individual MI counseling [18] and the use of an avatar may have obscured attributions to the actual counselor.

The current study is the first of which we are aware to provide online, synchronous MI counseling delivered by a clinician (without an avatar) to individuals. We had considered conducting the MI sessions by video chat (eg, using video cameras) to emphasize the presence of the counselor and to more closely mirror the face-to-face MI counseling, which has been shown to be effective. However, many of our study participants live in rural areas without consistent access to high speed Internet and have other technical limitations that might preclude their participation in this format of chatting. Therefore, the substantive limits to generalizability that the lack of consistent high-tech access would impose caused us to elect not to use this approach in this study. Use of Internet-delivered weight management treatment is particularly attractive for rural settings that have high rates of obesity and face geographic challenges in access to care [36]. However, one of the challenges of text-only chatting is that it is difficult to determine how focused the participant is on the MI session during the counseling time. Many people have the habit of multitasking while on the computer, and when attention is divided by multitasking or interruptions, participants may be less immersed in the MI counseling experience and find it less compelling. This is not so problematic with face-to-face or phone-based sessions, during which divided attention may be more apparent. With the increasing proliferation of FaceTime and other visual chatting platforms that may be more broadly accessible, it may be beneficial in the future to examine the efficacy of video-enhanced MI sessions as this would enable counselors and participants to interpret and respond to subtle changes in inflection, tone, and meaning.

Conclusions

The current study will add to the body of evidence regarding the efficacy of MI for weight management [13-17], as well as the growing literature on the use of MI in eHealth and mHealth environments [25-27,41-45,47,48]. Should synchronous online individual MI counseling confer benefits to overall weight loss, there are a range of potential applied benefits that could be readily realized. Many commercial weight loss programs have an online presence for which real-time online MI sessions could augment weight loss outcomes. Further, other group-based lifestyle interventions, whether delivered face-to-face or online, might similarly find it useful to consider an online MI element to enhance their behavior change outcomes.

Acknowledgments

This study was supported by 2R01DK056746 (PIs: Delia Smith West and Jean Harvey).

Conflicts of Interest

None declared.

References

1. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. JAMA 2014 Feb 26;311(8):806-814. [doi: 10.1001/jama.2014.732] [Medline: 24570244]

2. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002 Feb 7;346(6):393-403 [FREE Full text] [doi: 10.1056/NEJMoa012512] [Medline: 11832527]
3. Look AHEAD Research Group, Pi-Sunyer X, Blackburn G, Brancati FL, Bray GA, Bright R, et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. Diabetes Care 2007 Jun;30(6):1374-1383 [FREE Full text] [doi: 10.2337/dc07-0048] [Medline: 17363746]
4. Blackburn G. Effect of degree of weight loss on health benefits. Obes Res 1995 Sep;3 Suppl 2:211s-216s. [Medline: 8581779]
5. Gold BC, Burke S, Pintauro S, Buzzell P, Harvey-Berino J. Weight loss on the web: A pilot study comparing a structured behavioral intervention to a commercial program. Obesity (Silver Spring) 2007 Jan;15(1):155-164. [doi: 10.1038/oby.2007.520] [Medline: 17228043]
6. Micco N, Gold B, Buzzell P, Leonard H, Pintauro S, Harvey-Berino J. Minimal in-person support as an adjunct to internet obesity treatment. Ann Behav Med 2007 Feb;33(1):49-56. [doi: 10.1207/s15324796abm3301_6] [Medline: 17291170]
7. Tate DF, Wing RR, Winett RA. Using Internet technology to deliver a behavioral weight loss program. JAMA 2001 Mar 7;285(9):1172-1177. [Medline: 11231746]
8. Tate DF, Jackvony EH, Wing RR. Effects of Internet behavioral counseling on weight loss in adults at risk for type 2 diabetes: a randomized trial. JAMA 2003 Apr 9;289(14):1833-1836. [doi: 10.1001/jama.289.14.1833] [Medline: 12684363]
9. Tate DF, Jackvony EH, Wing RR. A randomized trial comparing human e-mail counseling, computer-automated tailored counseling, and no counseling in an Internet weight loss program. Arch Intern Med 2006;166(15):1620-1625. [doi: 10.1001/archinte.166.15.1620] [Medline: 16908795]
10. Harvey-Berino J, Pintauro S, Buzzell P, Gold E. Effect of Internet support on the long-term maintenance of weight loss. Obes Res 2004:12-329.
11. Harvey-Berino J, West D, Krukowski R, Prewitt E, VanBiervliet A, Ashikaga T, et al. Internet delivered behavioral obesity treatment. Prev Med 2010 Aug;51(2):123-128 [FREE Full text] [doi: 10.1016/j.ypmed.2010.04.018] [Medline: 20478333]
12. Krukowski RA, Tilford JM, Harvey-Berino J, West DS. Comparing behavioral weight loss modalities: incremental cost-effectiveness of an internet-based versus an in-person condition. Obesity (Silver Spring) 2011 Aug;19(8):1629-1635 [FREE Full text] [doi: 10.1038/oby.2010.341] [Medline: 21253001]
13. Smith DE, Heckemeyer CM, Kratt PP, Mason DA. Motivational interviewing to improve adherence to a behavioral weight-control program for older obese women with NIDDM. A pilot study. Diabetes Care 1997 Jan;20(1):52-54. [Medline: 9028693]
14. West DS, DiLillo V, Bursac Z, Gore SA, Greene PG. Motivational interviewing improves weight loss in women with type 2 diabetes. Diabetes Care 2007 May;30(5):1081-1087. [doi: 10.2337/dc06-1966] [Medline: 17337504]
15. Carels RA, Darby L, Cacciapaglia HM, Konrad K, Coit C, Harper J, et al. Using motivational interviewing as a supplement to obesity treatment: a stepped-care approach. Health Psychol 2007 May;26(3):369-374. [doi: 10.1037/0278-6133.26.3.369] [Medline: 17500624]
16. Rubak S, Sandbaek A, Lauritzen T, Christensen B. Motivational interviewing: a systematic review and meta-analysis. Br J Gen Pract 2005 Apr;55(513):305-312 [FREE Full text] [Medline: 15826439]
17. Armstrong MJ, Mottershead TA, Ronksley PE, Sigal RJ, Campbell TS, Hemmelgarn BR. Motivational interviewing to improve weight loss in overweight and/or obese patients: a systematic review and meta-analysis of randomized controlled trials. Obes Rev 2011 Sep;12(9):709-723. [doi: 10.1111/j.1467-789X.2011.00892.x] [Medline: 21692966]
18. Miller W, Rollnick S. Motivational interviewing: Helping people change. 3rd edition, New York, NY: Guilford Press; ISBN 2012:1609182278.
19. Krukowski RA, Harvey-Berino J, Bursac Z, Ashikaga T, West DS. Patterns of success: online self-monitoring in a web-based behavioral weight control program. Health Psychol 2013 Feb;32(2):164-170. [doi: 10.1037/a0028135] [Medline: 22545978]
20. Williams GC, Grow VM, Freedman ZR, Ryan RM, Deci EL. Motivational predictors of weight loss and weight-loss maintenance. J Pers Soc Psychol 1996 Jan;70(1):115-126. [Medline: 8558405]
21. Miller W, Moyers T, Ernst D, Amrhein P. 1. Manual for the motivational interviewing skills code version 2 URL: http://casaa.unm.edu/download/misc.pdf [accessed 2015-11-25] [WebCite Cache ID 6dJPPVTsb]
22. Moyers TB, Martin T, Manuel JK, Hendrickson Stacey M L, Miller WR. Assessing competence in the use of motivational interviewing. J Subst Abuse Treat 2005 Jan;28(1):19-26. [doi: 10.1016/j.jsat.2004.11.001] [Medline: 15723728]
23. Moyers TB, Martin T, Christopher PJ, Houck JM, Tonigan JS, Amrhein PC. Client language as a mediator of motivational interviewing efficacy: where is the evidence? Alcohol Clin Exp Res 2007 Oct;31(10 Suppl):40s-47s. [doi: 10.1111/j.1530-0277.2007.00492.x] [Medline: 17880345]
24. Madson MB, Campbell TC. Measures of fidelity in motivational enhancement: a systematic review. J Subst Abuse Treat 2006 Jul;31(1):67-73. [doi: 10.1016/j.jsat.2006.03.010] [Medline: 16814012]
25. Friederichs Stijn A H, Oenema A, Bolman C, Guyaux J, Van Keulen Hilde M, Lechner L. Motivational interviewing in a web-based physical activity intervention: questions and reflections. Health Promot Int 2015 Sep;30(3):803-815. [doi: 10.1093/heapro/dat069] [Medline: 24101160]

26. Friederichs S, Bolman C, Oenema A, Guyaux J, Lechner L. Motivational interviewing in a Web-based physical activity intervention with an avatar: randomized controlled trial. J Med Internet Res 2014;16(2):e48 [FREE Full text] [doi: 10.2196/jmir.2974] [Medline: 24550153]
27. Moreau M, Gagnon M, Boudreau F. Development of a fully automated, web-based, tailored intervention promoting regular physical activity among insufficiently active adults with type 2 diabetes: integrating the I-change model, self-determination theory, and motivational interviewing components. JMIR Res Protoc 2015;4(1):e25 [FREE Full text] [doi: 10.2196/resprot.4099] [Medline: 25691346]
28. Befort CA, Nollen N, Ellerbeck EF, Sullivan DK, Thomas JL, Ahluwalia JS. Motivational interviewing fails to improve outcomes of a behavioral weight loss program for obese African American women: a pilot randomized trial. J Behav Med 2008 Oct;31(5):367-377. [doi: 10.1007/s10865-008-9161-8] [Medline: 18587639]
29. Anderson JW, Konz EC, Frederich RC, Wood CL. Long-term weight-loss maintenance: a meta-analysis of US studies. Am J Clin Nutr 2001 Nov;74(5):579-584 [FREE Full text] [Medline: 11684524]
30. Unick JL, Hogan PE, Neiberg RH, Cheskin LJ, Dutton GR, Evans-Hudnall G, Look AHEAD Research Group. Evaluation of early weight loss thresholds for identifying nonresponders to an intensive lifestyle intervention. Obesity (Silver Spring) 2014 Jul;22(7):1608-1616 [FREE Full text] [doi: 10.1002/oby.20777] [Medline: 24771618]
31. Nackers LM, Ross KM, Perri MG. The association between rate of initial weight loss and long-term success in obesity treatment: does slow and steady win the race? Int J Behav Med 2010 Sep;17(3):161-167 [FREE Full text] [doi: 10.1007/s12529-010-9092-y] [Medline: 20443094]
32. Middleton K M Ross, Patidar SM, Perri MG. The impact of extended care on the long-term maintenance of weight loss: a systematic review and meta-analysis. Obes Rev 2012 Jun;13(6):509-517. [doi: 10.1111/j.1467-789X.2011.00972.x] [Medline: 22212682]
33. Deci E, Ryan R. Self-determination theory: A macrotheory of human motivation, development, and health. Can Psychol 2008;49(3):182.
34. Markland D, Ryan R, Tobin V, Rollnick S. Motivational interviewing and self-determination theory. J Soc Clin Psychol 2005;24(6):811-831.
35. Wing RR, Phelan S. Long-term weight loss maintenance. Am J Clin Nutr 2005 Jul;82(1 Suppl):222S-225S [FREE Full text] [Medline: 16002825]
36. West DS, Gorin AA, Subak LL, Foster G, Bragg C, Hecht J, Program to Reduce Incontinence by DietExercise (PRIDE) Research Group. A motivation-focused weight loss maintenance program is an effective alternative to a skill-based approach. Int J Obes (Lond) 2011 Feb;35(2):259-269 [FREE Full text] [doi: 10.1038/ijo.2010.138] [Medline: 20680012]
37. Wing RR, Tate DF, Gorin AA, Raynor HA, Fava JL. A self-regulation program for maintenance of weight loss. N Engl J Med 2006 Oct 12;355(15):1563-1571. [doi: 10.1056/NEJMoa061883] [Medline: 17035649]
38. Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. Ann Behav Med 2013 Aug;46(1):81-95. [doi: 10.1007/s12160-013-9486-6] [Medline: 23512568]
39. DiLillo V, Siegfried N, West D. Incorporating motivational interviewing into behavioral obesity treatment. Cogn Behav Pract 2003;10(2):120-130.
40. Miller WR, Rollnick S. Motivational Interviewing, Third Edition: Helping People Change (Applications of Motivational Interviewing). New York, NY: The Guilford Press; 2012.
41. Woodruff SI, Conway TL, Edwards CC, Elliott SP, Crittenden J. Evaluation of an Internet virtual world chat room for adolescent smoking cessation. Addict Behav 2007 Sep;32(9):1769-1786. [doi: 10.1016/j.addbeh.2006.12.008] [Medline: 17250972]
42. Walters ST, Ondersma SJ, Ingersoll KS, Rodriguez M, Lerch J, Rossheim ME, et al. MAPIT: development of a web-based intervention targeting substance abuse treatment in the criminal justice system. J Subst Abuse Treat 2014 Jan;46(1):60-65 [FREE Full text] [doi: 10.1016/j.jsat.2013.07.003] [Medline: 23954392]
43. Osilla KC, D'Amico EJ, Díaz-Fuentes CM, Lara M, Watkins KE. Multicultural web-based motivational interviewing for clients with a first-time DUI offense. Cultur Divers Ethnic Minor Psychol 2012 Apr;18(2):192-202 [FREE Full text] [doi: 10.1037/a0027751] [Medline: 22506822]
44. Ondersma SJ, Svikis DS, Schuster CR. Computer-based brief intervention a randomized trial with postpartum women. Am J Prev Med 2007 Mar;32(3):231-238 [FREE Full text] [doi: 10.1016/j.amepre.2006.11.003] [Medline: 17236741]
45. Pemberton MR, Williams J, Herman-Stahl M, Calvin SL, Bradshaw MR, Bray RM, et al. Evaluation of two web-based alcohol interventions in the U.S. military. J Stud Alcohol Drugs 2011 May;72(3):480-489. [Medline: 21513685]
46. Schaub MP, Wenger A, Berg O, Beck T, Stark L, Buehler E, et al. A Web-Based Self-Help Intervention With and Without Chat Counseling to Reduce Cannabis Use in Problematic Cannabis Users: Three-Arm Randomized Controlled Trial. J Med Internet Res 2015;17(10):e232 [FREE Full text] [doi: 10.2196/jmir.4860] [Medline: 26462848]
47. Hötzel K, von BR, Schmidt U, Rieger E, Kosfelder J, Hechler T, et al. An Internet-based program to enhance motivation to change in females with symptoms of an eating disorder: a randomized controlled trial. Psychol Med 2014 Jul;44(9):1947-1963. [doi: 10.1017/S0033291713002481] [Medline: 24128818]

48. Webber KH, Tate DF, Quintiliani LM. Motivational interviewing in internet groups: a pilot study for weight loss. J Am Diet Assoc 2008 Jun;108(6):1029-1032. [doi: 10.1016/j.jada.2008.03.005] [Medline: 18502239]

Abbreviations

MI: motivational interviewing
MISC: Motivational Interviewing Skills Code software

Edited by G Eysenbach; submitted 25.11.15; peer-reviewed by M Schaub, M Moreau, K Ross; comments to author 17.12.15; revised version received 11.01.16; accepted 28.01.16; published 19.04.16.

Please cite as:
Krukowski RA, DiLillo V, Ingle K, Harvey JR, West DS
Design and Methods of a Synchronous Online Motivational Interviewing Intervention for Weight Management
JMIR Res Protoc 2016;5(2):e69
URL: http://www.researchprotocols.org/2016/2/e69/
doi:10.2196/resprot.5382
PMID:27095604

Protocol

Improving Rates of Influenza Vaccination Through Electronic Health Record Portal Messages, Interactive Voice Recognition Calls and Patient-Enabled Electronic Health Record Updates: Protocol for a Randomized Controlled Trial

Sarah L Cutrona[1,2], MD, MPH; Meera Sreedhara[2,3], MPH; Sarah L Goff[4], MD; Lloyd D Fisher[5,6], MD; Peggy Preusse[7], R.N.; Madeline Jackson[2,3]; Devi Sundaresan[7], MS; Lawrence D Garber[2,8], MD; Kathleen M Mazor[2,3], EdD

[1]University of Massachusetts School of Medicine, Division of General Medicine/Primary Care, Worcester, MA, United States
[2]Meyers Primary Care Institute, Worcester, MA, United States
[3]University of Massachusetts School of Medicine, Worcester, MA, United States
[4]Baystate Medical Center, Springfield, MA, United States
[5]University of Massachusetts Medical School, Department of Pediatrics, Worcester, MA, United States
[6]Reliant Medical Group, Pediatrics Department, Worcester, MA, United States
[7]Reliant Medical Group, Research Department, Worcester, MA, United States
[8]Reliant Medical Group, Internal Medicine Department, Worcester, MA, United States

Corresponding Author:
Sarah L Cutrona, MD, MPH
University of Massachusetts School of Medicine
Division of General Medicine/Primary Care
55 Lake Street
Worcester, MA, 01605
United States
Phone: 1 5088563085
Fax: 1 5088565024
Email: Sarah.Cutrona@umassmemorial.org

Abstract

Background: Clinical decision support (CDS), including computerized reminders for providers and patients, can improve health outcomes. CDS promoting influenza vaccination, delivered directly to patients via an electronic health record (EHR) patient portal and interactive voice recognition (IVR) calls, offers an innovative approach to improving patient care.

Objective: To test the effectiveness of an EHR patient portal and IVR outreach to improve rates of influenza vaccination in a large multispecialty group practice in central Massachusetts.

Methods: We describe a nonblinded, randomized controlled trial of EHR patient portal messages and IVR calls designed to promote influenza vaccination. In our preparatory phase, we conducted qualitative interviews with patients, providers, and staff to inform development of EHR portal messages with embedded questionnaires and IVR call scripts. We also provided practice-wide education on influenza vaccines to all physicians and staff members, including information on existing vaccine-specific EHR CDS. Outreach will target adult patients who remain unvaccinated for more than 2 months after the start of the influenza season. Using computer-generated randomization and a factorial design, we will assign 20,000 patients who are active users of electronic patient portals to one of the 4 study arms: (1) receipt of a portal message promoting influenza vaccines and offering online appointment scheduling; (2) receipt of an IVR call with similar content but without appointment facilitation; (3) both (1) and (2); or (4) neither (1) nor (2) (usual care). We will randomize patients without electronic portals (10,000 patients) to (1) receipt of IVR call or (2) usual care. Both portal messages and IVR calls promote influenza vaccine completion. Our primary outcome is percentage of eligible patients with influenza vaccines administered at our group practice during the 2014-15 influenza season. Both outreach methods also solicit patient self-report on influenza vaccinations completed outside the clinic or on barriers to influenza vaccination. Self-reported data from both outreach modes will be uploaded into the EHR to increase accuracy of existing provider-directed EHR CDS (vaccine alerts).

Results: With our proposed sample size and using a factorial design, power calculations using baseline vaccination rate estimates indicated that 4286 participants per arm would give 80% power to detect a 3% improvement in influenza vaccination rates between groups (α=.05; 2-sided). Intention-to-treat unadjusted chi-square analyses will be performed to assess the impact of portal messages, either alone or in combination with the IVR call, on influenza vaccination rates. The project was funded in January 2014. Patient enrollment for the project described here completed in December 2014. Data analysis is currently under way and first results are expected to be submitted for publication in 2016.

Conclusions: If successful, this study's intervention may be adapted by other large health care organizations to increase vaccination rates among their eligible patients.

ClinicalTrial: ClinicalTrials.gov NCT02266277; https://clinicaltrials.gov/ct2/show/NCT02266277 (Archived by WebCite at http://www.webcitation.org/6fbLviHLH).

(JMIR Res Protoc 2016;5(2):e56) doi:10.2196/resprot.5478

KEYWORDS

electronic health records; influenza vaccines; clinical decision support; Internet; Telephone; Electronic Mail; Health Records, Personal; Medical Informatics Applications

Introduction

Clinical decision support (CDS), including computerized reminders for providers and patients, can improve health outcomes by supporting the delivery of evidence-based and guideline-concordant medical care [1,2]. Many health systems effectively use provider-directed CDS. These provider-directed prompts frequently take the form of noninterruptive or interruptive "pop-up" alerts, reminding providers of recommended prevention or screening measures. While effective in many situations, provider-directed CDS is subject to important limitations. Instructions contained in alerts are often ignored or overridden due to alert fatigue [3-6]. Providers may also start to mistrust alerts if these are frequently triggered by erroneous or incomplete electronic health record (EHR) data. In light of these challenges, and in the setting of nationwide adoption of electronic patient portals, patient-directed CDS delivered via portal offers an innovative approach to improving patient care.

Electronic patient portals are secure websites that provide patients with 24-hour online access to limited EHR information. A portal provides patients with a personal health record "tethered" to their EHR [7]. Accessible information within a tethered portal varies by health system but may include vaccinations, laboratory results, and information from recent doctor visits or hospitalizations. Patients also use portals in numerous interactive ways including requesting prescription refills, scheduling nonurgent appointments, and seeking educational materials; portals can also provide a valuable link to Internet-based local and public health resources [8,9]. A core function of portals is secure messaging—electronic communication with the physician or health care team. A recent review found portals to have facilitated improved patient-provider communication with 10 of 27 articles reporting a positive association with portal's secure messaging [10,11]. Advantages of tethered portals include enhancement of patient-provider communication, patient empowerment, support for care between visits, and improved patient outcomes [10]. Patient portals have been shown to improve medication adherence, decrease office visits, increase self-management of disease and disease awareness, increase use of preventative medicine, and increase inclusion of patients in medical decision making [12,13]. While studies of portal use show promising results, to date few randomized trials have tested the impact of patient-directed CDS via portal on receiving guideline-concordant care.

Vaccinations are a preventive measure well suited for incorporation into a patient-directed CDS intervention via patient portals. Previous patient outreach interventions have been shown to improve rates of vaccine completion and have been tested using multiple options including mailed letters, post cards, person-to-person phone calls, automated phone messages, and post card and phone combination [14,15]. Few studies have tested the use of patient-directed vaccine reminders sent via patient portals; those that have done so have focused exclusively on untethered (ie, personally controlled) patient health records [16]. Influenza vaccines are a logical target for patient-directed CDS because they are familiar to the general population and are recommended widely but completed at suboptimal rates.

Influenza infections contribute to increased health care costs and loss of productivity, and can lead to serious medical complications and even death [17]. The effect is felt most in high-risk groups such as adults aged 65 years or older and those diagnosed with cancer or diabetes [18]; however, low-risk groups also suffer the consequences. In 2007, it was estimated that influenza infections were responsible for 31.4 million outpatient visits, with reports indicating direct medical expenses amounting up to US $10.4 billion (including inpatient, outpatient and pharmaceutical claims) and lost earnings due to death and illness costing about US $16.3 billion [19,20]. According to CDC estimates, during the 2013-14 influenza season, influenza vaccination resulted in approximately 7.2 million fewer illnesses and 90,068 fewer hospitalizations. Despite numerous reasons to protect against influenza, only 45% of the US population received influenza vaccinations during the 2012-13 influenza season [21].

Our intervention, which will be implemented in a large multispecialty group practice in central Massachusetts, aims to improve rates of influenza vaccination among eligible adult patients by using a patient-directed CDS. We also aim to improve the accuracy of existing provider-directed CDS (influenza vaccine alerts) by capturing information on vaccines

completed outside the clinic and using this self-reported patient information to update EHRs. We herein describe the protocol for a randomized controlled trial using EHR patient portal messages and interactive voice recognition (IVR) calls to (1) deliver messages promoting influenza vaccine completion and (2) solicit patient self-report on vaccines completed outside the clinic and on barriers to vaccination.

Methods

Study Objectives

Our overarching goal is to improve rates of influenza vaccination among eligible adults at Reliant Medical Group (RMG). We are conducting this randomized outreach intervention with the following main objectives that support this goal: (1) to determine whether our outreach increases likelihood of influenza vaccination (and if so, whether one mode of outreach is most effective); (2) to improve documentation of influenza vaccinations administered outside the practice by inviting patient self-report (improving accuracy of existing decision support tools); and (3) to deliver to patients targeted factual vaccine information related to that patient's concerns.

Study Outcomes

The primary study outcome is the percentage of eligible patients receiving influenza vaccines administered at our group practice during the 2014-15 influenza season. We will also study process measures including percentage of message recipients reached (ie, percentage of those who answer the IVR call and percentage of those who open the portal message) and number of intervention patients who self-report influenza vaccines administered in the community.

Study Design

We will conduct a nonblinded, randomized controlled trial directed at patients who, by November 2014, do not have influenza vaccinations for the 2014-15 influenza season recorded in the EHR. Among these patients, those also overdue for pneumococcal vaccination(s) will receive outreach messages with additional language encouraging them to speak with their health care provider as well as a link to access more information about pneumococcal vaccination. Description of the pneumococcal vaccine intervention and analysis will not be a focus of this paper.

Authors designed and will implement the study, and will have full oversight and responsibility for data collection, analysis, and manuscript preparation.

Theoretical Model

The Communication Human Information Processing model [22,23] (Figure 1) provides the overarching framework for the design and implementation of the intervention components. Growing out of extensive research on effective communication of safety information, this model includes the core concepts of communication theory (ie, message source, channel, and receiver) while highlighting the need to enhance effective information processing. Effective information processing requires attention to and comprehension of the message (eg, that a vaccine is needed); these processes are influenced by attitudes and beliefs, and motivation. In the context of vaccination, beliefs about susceptibility, severity, disease likelihood, and vaccine effectiveness are likely to be important [24]. All of these processes in turn influence behavior (ie, vaccination). Our interventions are designed to garner attention, be easily understood, address critical beliefs, and motivate vaccination.

Study Procedures

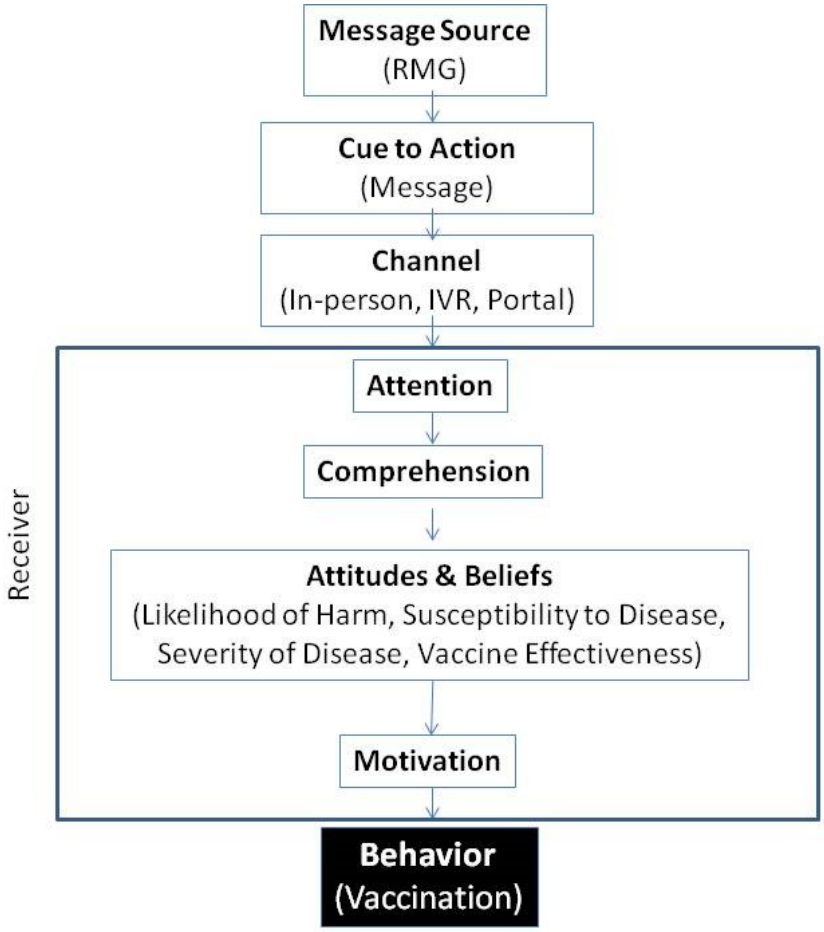
This study consists of two phases, namely, (1) preintervention study components and (2) IVR and portal randomized outreach intervention.

Phase 1: Preintervention

To develop provider, staff, and patient outreach content, we conducted 30 in-depth interviews with patients, providers, and staff. Patient interviews elicited reasons for getting vaccinated, barriers to vaccination, and feedback to inform development of patient outreach materials used for the intervention. Provider and staff perceptions of patient barriers to vaccination helped to further shape patient outreach materials.

Information from interviews also informed our educational outreach; 10-minute in-person presentations were given by physician researchers who were also well-respected members of the group practice. Presentations were incorporated into routine clinical practice meetings attended by both physicians and staff. Based on results from provider and staff interviews, the in-person presentation provided an overview of this study and also provided information on pneumococcal vaccine guidelines. Follow-up emails sent bimonthly to all physicians in the group practice reviewed guidelines for both influenza and pneumococcal vaccines.

Figure 1. The Communication Human Information Processing model [22,23].



Phase 2: Interactive Voice Recognition and Portal Randomized Outreach Intervention

Clinical Setting

This study will be conducted at RMG, a large multispecialty group that employs 217 outpatient physicians at more than 13 clinical locations throughout Central Massachusetts. RMG providers care for approximately 140,000 adults aged 18 years and older. Approximately 113,000 of these adults receive their primary care through RMG via either the internal medicine/geriatric or family medicine departments. Approximately 89.5% of RMG patients are white, 4.3% are African American, and 4.6% Asian.

Electronic Health Record

All RMG providers and staff use an EHR developed by Epic Systems Corporation. Consistent with evidence showing that CDS can improve rates of indicated vaccines [25-27], the RMG EHR is configured to flag a patient's record when they are due or overdue for an immunization based on the patient's age, immunization history, medical, surgical, and social history. When patients call or are seen at RMG, physicians and staff accessing the patient's record are alerted to immunizations that are due or overdue. Using a Microsoft SQL Server database, which is updated nightly with all of the clinical data from the EHR, it is possible to identify patients aged 18 years and older who are eligible and in need of immunizations.

Electronic Patient Portal

All RMG patients are given the option to sign up for MyChart, an electronic patient portal within Epic that is free of cost to patients and provides them with personalized and secure online access to portions of their medical record. Over 30% of RMG patients use MyChart. Patients can view their immunization history as well as alerts for immunizations that are due or overdue. They can securely send messages to and receive messages from RMG providers. The Epic MyChart system has the capacity to survey selected populations of patients.

Current Use of Interactive Voice Recognition Technology

RMG has an ongoing relationship with a company that uses IVR calls to alert patients about upcoming appointments and allows patients to respond to a limited number of scripted questions. Standard operating procedures and methods for transferring patient data existed prior to the intervention and helped guide our protocols.

Participants

Eligibility Criteria

Patients are eligible for the study if they (1) have had an RMG primary care provider during the 1 year prior to randomization; (2) are aged 18 years or older on the date of randomization; (3) have had a recent office visit or telephone encounter with an internal medicine practitioner or family practitioner. The requirement for a recent office visit or telephone encounter was

intended to minimize inclusion of patients who had moved to another practice but whose names were retained in RMG records. Our definition of "recent" depended on patient's age. We defined "recent office visit" based on the age group of the patients; because older RMG patients (aged ≥ 65 years) visit their providers more frequently, we required an office visit or phone encounter within the 18 months prior to randomization for this population. For adults aged 18-64, we required an office visit or phone encounter within the 3 years prior to the intervention. To ensure capture of patients transitioning from pediatric to adult care, the visit or phone call could also be with a pediatrician.

Exclusion Criteria

Patients will be excluded if there is EHR documentation of an allergy to influenza vaccine, or if they were one of 20 patients who participated in preliminary qualitative interviews conducted to inform development of outreach materials. Exclusion criteria also included the presence of any of the following on the date of randomization: (1) EHR documentation of influenza vaccination completion in the 2014-15 influenza season (or documented influenza vaccination after the end of the 2013-14 influenza season but before the start of the 2014-15 season); (2) name listed on the do-not-call list or no listed phone number. A patient is eligible for inclusion in the electronic patient portal (referred to as "portal" herein) portion of the randomized controlled trial if he or she is an active user, which is defined as having an activated portal with a login at least once in the year preceding randomization.

Randomization Approach

Using computer-generated random number assignments, we will randomly select from the eligible population 20,000 portal users and 10,000 nonportal users (total of 30,000 patients). Using a factorial design (Figure 2), we will then use a computerized randomization method to assign 5000 patients to each of the 4 arms (portal users) and, separately, to each of the 2 arms (nonportal users). Thus, we will have a total of 6 arms, each with 5000 patients.

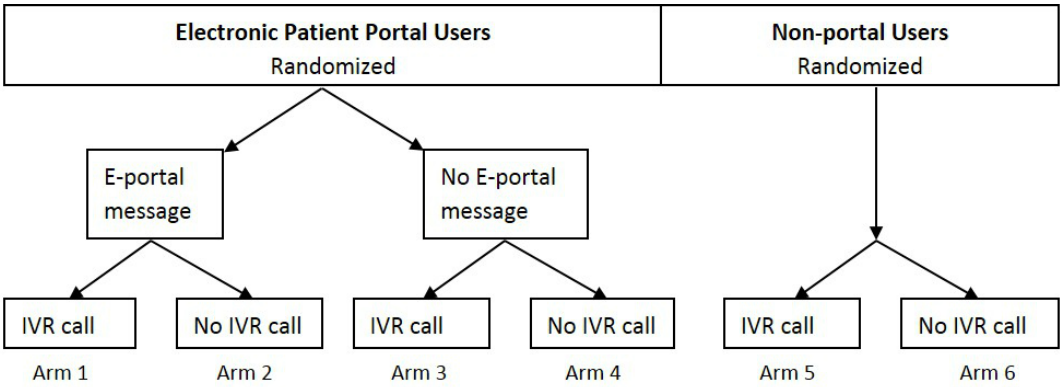
Recruitment and Informed Consent

The study was reviewed and approved in 2014 by the RMG Institutional Review Board (IRB) and subsequently (in 2015) oversight was transferred to the University of Massachusetts IRB. A waiver for informed consent for patient outreach was approved by the IRB.

Intervention

We designed the IVR calls and portal messages to include similar content (Textbox 1)

Figure 2. Outreach design.



Textbox 1. IVR call and portal message content

IVR calls and portal messages included...

- Personalized greeting
- Message seeking to establish influenza vaccines as social norm ("people your age get vaccinated against the flu...") and informing patients what age group vaccines are recommended for
- Information intended to optimize access to vaccines (dates/locations for upcoming Reliant Medical Group (RMG) influenza clinic and list of additional ways to schedule a vaccine appointment)
- Information on accessing the CDC website for vaccine information

IVR calls and portal messages sought to elicit patient responses

- Patients were asked whether they had received influenza vaccines outside of RMG and were offered an opportunity to report date and location of influenza vaccinations received at external sites
- For patients who responded that they had not received any influenza shot for the 2014-15 season, several questions addressing vaccine barriers were presented
- Targeted educational information dispelling myths and misconceptions about the influenza vaccine based on patient responses to barrier questions

Electronic Patient Portal Intervention

We designed an outgoing secure portal message to be sent via MyChart to patients randomized to the portal message arms (see Multimedia Appendix 1). Portal message content will appear in letter format with the signature line reflecting the name of the patient's primary care provider. Portal messages will be delivered through standard channels used for portal-based correspondence between RMG health care providers and patients (ie, generic message that contains no personal health information nor any reference to vaccines is delivered to patient's email account. Message prompts patients to log into secure portal account via hyperlink). Once logged into portal accounts, patients must click on a message labeled "Brief Flu Questionnaire" to view the outreach message.

Characteristics unique to the portal message compared with IVR messages include the ability to offer direct online scheduling of appointments for influenza vaccines. Information about accessing CDC vaccine website(s) appears within the body of the portal message as a hyperlink (and is conveyed verbally in the IVR script). Opportunities to report external influenza vaccinations, vaccine barrier questions, targeted information dispelling misconceptions, and branching logic matched the IVR call content.

Portal Message Delivery

To reach unvaccinated patients, we will intervene 2 months into the influenza season, a practice supported by prior research [28]. Messages will be sent out to 500-1500 patients daily over 9-10 days, beginning 1-week postrandomization.

Interactive Voice Recognition Call Intervention

We designed a script to be delivered via IVR call to patients randomized to the IVR arms. Combining voice recognition with branching logic, calls will elicit patient self-report of influenza vaccinations completed outside of RMG. For patients reporting no influenza vaccine completion, IVR calls will deliver a series of questions on vaccine barriers, providing brief information intended to address the barriers which the patient identifies.

IVR calls will appear on telephone caller ID as "RELIANT MED." This is consistent with current identification of IVR calls used for appointment reminders and is a detail that we consider critical to the success of call answering.

Interactive Voice Recognition Call Delivery

Intervention IVR calls will be placed using standard procedures suggested by the IVR design team, which include identification of optimal times to call based on the patient's age and suggestions for keeping patients engaged to achieve study goals. IVR calls will begin by confirming the patient's identity. If voicemail is encountered or if the person reached identifies himself or herself as someone other than the patient, the IVR system will leave a message asking patients to call back and providing an inbound call line number. An inbound call line will be maintained throughout the duration of outgoing calls and for 2 weeks after the final outgoing call is placed, and patients calling this number from the phone number of record will hear the IVR call script in its entirety, beginning with questions confirming the identity of the caller.

Data Upload Into Epic Electronic Health Record

Patient reports of prior immunization dates and location will be loaded through Epic's Inbound Immunization interface and will be incorporated into the patient's medical record. Data derived from portal questionnaires, including information on patient barriers, will be stored and available to the project team for analysis.

Patient-reported immunization type, mapped to "Codes for Vaccine Administered" (CVX code), date of vaccination, location of vaccination, and reasons for not being immunized will be sent to the study team by the company providing IVR calls. The patient's immunization history will be updated via Epic's Inbound Immunization interface, and transcriptions of all IVR responses will be stored for analysis by the project team.

Measures

We will draw on data from EHR records, brought into the EHR via several pathways. Information on influenza vaccines will be gathered by capturing data entered into the EHR via two routes: (1) direct documentation by RMG staff of influenza vaccines administered at RMG or reported in-person by the patient and entered manually into Epic EHR by staff or provider; (2) patient self-report of vaccines administered outside of RMG (self-report received via MyChart questionnaire or IVR).

Primary Outcome

Influenza Vaccine Outcomes

Our primary outcome will be percentage of eligible patients with influenza vaccines directly administered and documented in an RMG facility as of the end of the 2014-15 influenza season. Because the control groups will not be given the opportunity to self-report, immunizations captured solely through the MyChart questionnaire or the IVR will be excluded from the primary analysis. Our exclusion of self-reported vaccines from our outcome analysis avoids introducing bias through differential capture (intervention vs control) of self-reported outcomes.

Secondary Outcome

Influenza Vaccine Outcomes

We will perform a descriptive analysis, calculating the percentage of patients for whom self-report through our intervention was the sole method for documentation of influenza vaccination completion. We will assess this at the end of the 2014-15 influenza season. This analysis is intended to provide preliminary insights into the percentage of patients who are vaccinated outside of the RMG clinics and who choose to self-report these vaccines.

Process Measures

We will examine patients who receive portal messages and calculate (1) percentage of recipients who open messages and (2) percentage of recipients who complete questionnaires. We will examine patients who receive IVR calls and calculate (1) percentage of recipients who answer the call and (2) percentage of recipients who complete the calls by responding to questions.

Proposed Analyses

To determine the impact of our interventions on RMG vaccination rates for the 2014-15 influenza season, we will perform unadjusted and adjusted analyses of randomized patients (30,000 patients). Because of differential rates of vaccination at baseline between portal users and nonusers, analyses in these groups will be conducted separately. Intention-to-treat unadjusted chi-square analyses will include the analyses presented in Table 1.

We will examine the adequacy of randomization in the overall group and separately among e-portal users and non e-portal users by assessing whether there was differential representation in the intervention versus control groups by 5 patient characteristics readily available in the EHR. These will include (1) age group; (2) race/ethnicity; (3) sex; (4) influenza vaccination in previous year; and (5) completion of an office visit in the previous year; if differences are found we will carry out adjusted analyses using logistic regression to control for significant differences, modeling odds of receiving influenza vaccine.

Multivariate logistic regression analyses will also be performed. As in our unadjusted analyses, due to differential rates of vaccination at baseline between portal users and nonusers, adjusted analyses in these groups will be conducted separately. We will create dummy variables for assignment to the portal message arm (among portal users) and for assignment to the IVR call arm (among both portal users and, separately, among nonportal users). Including these dummy variables and adjusting for demographic and practice-level covariates, we will model odds of receiving an influenza vaccine in the 2014-15 influenza season. We will also examine the heterogeneity of treatment effects within each subgroup using logistic analysis.

Power and Sample Size

With our proposed sample size and using a factorial design, power calculations using baseline vaccination rate estimates indicated that 4286 participants per arm would give 80% power to detect a 3% improvement in influenza vaccination rates between groups (α=.05; 2-sided). Based on previous studies [29,30], we expect a 10-20% improvement in vaccination rates for either intervention compared with control.

Table 1. Analyses by arm.

Study question	Comparison
Among portal users, did portal message receipt alone increase the likelihood of influenza vaccine completion compared with control?	Compare percentage of vaccine completion among those randomized to receipt of portal messages versus those randomized to neither portal messages nor IVR calls (usual care). (Arm 2 vs 4)
Among portal users, did portal message receipt plus IVR call increase the likelihood of influenza vaccine completion compared with portal message alone?	Compare percentage of vaccine completion among those randomized to receipt of both portal messages and IVR calls versus those randomized to only portal messages. (Arm 1 vs 2)
Among portal users, did IVR call alone increase the likelihood of influenza vaccine completion compared with control?	Compare percentage of vaccine completion among those randomized to receipt of IVR calls versus those randomized to neither portal messages nor IVR calls (usual care). (Arm 3 vs 4)
Among those who do not use portals, did IVR call alone increase the likelihood of influenza vaccine completion compared with control?	Compare percentage of vaccine completion among those randomized to receipt of IVR calls versus those randomized to neither portal messages nor IVR calls (usual care). (Arm 5 vs 6)

Results

Intention-to-treat unadjusted chi-square analyses will be performed to assess the impact of portal messages, either alone or in combination with the IVR call, on influenza vaccination rates.

Discussion

This study will test the effectiveness of a patient-directed CDS intervention, aimed at improving rates of influenza vaccination within a primary care adult population. The approach described has important implications for future patient-directed CDS initiatives seeking to use tethered patient portals. As a low-cost and rapid means of communicating with patients who have activated their electronic accounts, patient portals are a promising channel through which CDS may be delivered. Targeting patients through portals aligns well with the "CDS Five Rights," which stipulate that effective CDS delivers the right information to the right people, via the right channels, in the right intervention formats and at the right points of workflow [31]. Our approach studies the possibility that the patient is the person best positioned to receive and act on information related to influenza vaccination.

Influenza vaccination has several characteristics that made it ideally suited for this study design. Influenza vaccinations are a single-dose annual vaccine, for which standing orders were already in place in our medical group. They are recommended almost universally across age groups, and therefore, we did not require that physicians review the list of patients to whom promotional messages were directed prior to sending, thereby reducing physician burden. There is widespread familiarity with influenza vaccination among the lay public, and numerous community sites and workplaces offer these vaccinations, thus

they are commonly administered outside of the medical group. Seeking to collect data on vaccinations given in the community was therefore a reasonable component of our outreach. This factor might be less appropriate for other preventive health behaviors. Guidelines calling for annual vaccination create a short recall period (2-3 months in our study design) for individuals reporting vaccination in a given season. The short recall period and widespread familiarity was our rationale for accepting patient self-report. With inputs from the physicians on our research team, we further reasoned that providers would be willing to update the EHR based on patient self-report of influenza completion during an in-person visit (without accompanying printed documentation) and that our collection of self-reported data via outreach was an acceptable alternative to in-person patient report. Our outreach may have the additional benefit of identifying patients with influenza vaccine allergy that has not previously been documented.

This protocol has some limitations. Although we collected self-report of influenza vaccinations completed in the community, our primary analysis focuses on RMG-documented vaccines, thus avoiding the bias that would be introduced through differential capture (intervention versus control) of self-reported data.

For our secondary outcome measurement, we will report percentage of patients self-reporting influenza vaccines completed in the community. Although self-report introduces the possibility for inaccuracies, self-reported vaccination status is a measure commonly used to assess vaccination status and is the standard used by the Behavioral Risk Surveillance System and the National Health Interview Survey [32-34]. Previous validation efforts for self-reported influenza vaccines documented high sensitivity (0.98 to 1.0) and moderate specificity (0.71-0.79) [32]. In addition to reviewing commonly accepted measures and published validation reports, we also considered the levels of ascertainment consistent with routine clinical care. Many clinicians accept a patient's verbal self-report of completed influenza vaccination and update the EHR accordingly (without requiring paper documentation). For all of these reasons, we chose to allow patient self-reported influenza vaccinations to be entered into the EHR.

An additional limitation of our study stems from the timing of outreach. After eligibility determination but prior to disseminating the outreach, we will have a 1-week gap built in for quality checks and data transfers to the company handling IVR calls. It is possible that during this 1-week gap, patients randomized to receipt of the intervention will obtain their influenza vaccines. Patients with vaccinations completed during this period should be evenly distributed across all arms, minimizing any associated bias. Once the intervention starts, IVR calls and patient portal messages will be disseminated in batches. While this is a standard protocol for delivering IVR appointment reminders and prevents outgoing portal messages from being labeled as spam by email servers, it also introduces the possibility that additional patients may get vaccinated prior to receiving the intervention. Again, patients vaccinated prior to receipt of messages should be evenly distributed across all arms.

While our single-site study is limited insofar as it cannot be considered representative on a national scale, a future study could address this by sampling from our population in proportion to national demographics. In addition, we have designed our intervention to be easily tested across diverse settings. This intervention will be implemented using Epic, one of the top EHR vendors in the country [35]. If successful, this study's intervention may be adapted by other large health care organizations using Epic and tested as a means of increasing vaccination rates among diverse populations.

Acknowledgments

This study was funded by Pfizer Independent Grants for Learning and Change.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Portal message example.

[PDF File (Adobe PDF File), 225KB - resprot_v5i2e56_app1.pdf]

References

1. Brenner SK, Kaushal R, Grinspan Z, Joyce C, Kim I, Allard RJ, et al. Effects of health information technology on patient outcomes: a systematic review. J Am Med Inform Assoc 2015 Nov 13. [doi: 10.1093/jamia/ocv138] [Medline: 26568607]
2. Clinical Decision Support: More Than Just 'Alerts' Tipsheet. URL: http://www.cms.gov/Regulations-and-Guidance/Legislation/EHRIncentivePrograms/Downloads/ClinicalDecisionSupport_Tipsheet-.pdf [accessed 2015-03-24] [WebCite Cache ID 6XGhTlwCC]
3. Cash JJ. Alert fatigue. Am J Health Syst Pharm 2009 Dec 1;66(23):2098-2101. [doi: 10.2146/ajhp090181] [Medline: 19923309]

4. van der Sijs Heleen, Aarts J, Vulto A, Berg M. Overriding of drug safety alerts in computerized physician order entry. J Am Med Inform Assoc 2006;13(2):138-147 [FREE Full text] [doi: 10.1197/jamia.M1809] [Medline: 16357358]
5. Ridgely M. and M. Greenberg. Too many alerts, too much liability: sorting through the malpractice implications of drug-drug interaction clinical decision support. J Health Law Policy 2012;5:257-296 [FREE Full text]
6. Kesselheim AS, Cresswell K, Phansalkar S, Bates DW, Sheikh A. Clinical decision support systems could be modified to reduce 'alert fatigue' while still minimizing the risk of litigation. Health Aff (Millwood) 2011 Dec;30(12):2310-2317 [FREE Full text] [doi: 10.1377/hlthaff.2010.1111] [Medline: 22147858]
7. Amante DJ, Hogan TP, Pagoto SL, English TM. A systematic review of electronic portal usage among patients with diabetes. Diabetes Technol Ther 2014 Nov;16(11):784-793. [doi: 10.1089/dia.2014.0078] [Medline: 24999599]
8. Tulu B, Trudel J, Strong DM, Johnson SA, Sundaresan D, Garber L. Patient Portals: An Underused Resource for Improving Patient Engagement. Chest 2016 Jan;149(1):272-277. [doi: 10.1378/chest.14-2559] [Medline: 26066707]
9. Hesse BW. Time to reboot: resetting health care to support tobacco dependency treatment services. Am J Prev Med 2010 Dec;39(6 Suppl 1):S85-S87 [FREE Full text] [doi: 10.1016/j.amepre.2010.08.017] [Medline: 21074683]
10. HealthIT.gov. What is a Patient Portal?. 2014. URL: http://www.healthit.gov/providers-professionals/faqs/what-patient-portal [accessed 2014-08-22] [WebCite Cache ID 6S1PTMAbZ]
11. Britto MT, Hesse EA, Kamdar OJ, Munafo JK. Parents' perceptions of a patient portal for managing their child's chronic illness. J Pediatr 2013 Jul;163(1):280-1.e1. [doi: 10.1016/j.jpeds.2013.02.041] [Medline: 23541773]
12. Kruse CS, Bolton K, Freriks G. The effect of patient portals on quality outcomes and its implications to meaningful use: a systematic review. J Med Internet Res 2015;17(2):e44 [FREE Full text] [doi: 10.2196/jmir.3171] [Medline: 25669240]
13. Kruse CS, Argueta DA, Lopez L, Nair A. Patient and provider attitudes toward the use of patient portals for the management of chronic disease: a systematic review. J Med Internet Res 2015;17(2):e40 [FREE Full text] [doi: 10.2196/jmir.3703] [Medline: 25707035]
14. Odone A, Ferrari A, Spagnoli F, Visciarelli S, Shefer A, Pasquarella C, et al. Effectiveness of interventions that apply new media to improve vaccine uptake and vaccine coverage. Hum Vaccin Immunother 2015;11(1):72-82 [FREE Full text] [doi: 10.4161/hv.34313] [Medline: 25483518]
15. Jacobson Vann Julie C, Szilagyi P. Patient reminder and patient recall systems to improve immunization rates. Cochrane Database Syst Rev 2005(3):CD003941. [doi: 10.1002/14651858.CD003941.pub2] [Medline: 16034918]
16. Lau Annie Y S, Sintchenko V, Crimmins J, Magrabi F, Gallego B, Coiera E. Impact of a web-based personally controlled health management system on influenza vaccination and health services utilization rates: a randomized controlled trial. J Am Med Inform Assoc 2012;19(5):719-727 [FREE Full text] [doi: 10.1136/amiajnl-2011-000433] [Medline: 22582203]
17. Staroselsky M, Volk LA, Tsurikova R, Pizziferri L, Lippincott M, Wald J, et al. Improving electronic health record (EHR) accuracy and increasing compliance with health maintenance clinical guidelines through patient access and input. Int J Med Inform 2006;75(10-11):693-700. [doi: 10.1016/j.ijmedinf.2005.10.004] [Medline: 16338169]
18. Centers for Diseases Control and Prevention (CDC). Influenza: Information for Specific Groups. Atlanta, GA: CDC; 2012. URL: http://www.cdc.gov/flu/groups.htm [accessed 2013-04-10] [WebCite Cache ID 6h2FiPRFk]
19. Molinari NAM, Ortega-Sanchez IR, Messonnier ML, Thompson WW, Wortley PM, Weintraub E, et al. The annual impact of seasonal influenza in the US: measuring disease burden and costs. Vaccine 2007 Jun 28;25(27):5086-5096. [doi: 10.1016/j.vaccine.2007.03.046] [Medline: 17544181]
20. Centers for Diseases Control and Prevention (CDC). Flu Seasons Are Unpredictable and Vary in Severity. Atlanta, GA: CDC URL: http://www.cdcfoundation.org/businesspulse/flu-prevention-infographic [accessed 2015-12-22] [WebCite Cache ID 6dyBWF4tt]
21. Centers for Diseases Control and Prevention (CDC). Estimated Influenza Illnesses and Hospitalizations Averted by Vaccination — United States, 2013-14 Influenza Season. Atlanta, GA: CDC; 2015. URL: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6349a2.htm [WebCite Cache ID 6dyB6u0yr]
22. Wogalter MS, DeJoy DM, Laughery KR. Warnings and Risk Communication. London, UK: Taylor & Francis; 1999.
23. Conzola VC, Wogalter MS. A communication–human information processing (C–HIP) approach to warning effectiveness in the workplace. J Risk Res 2001 Oct;4(4):309-322. [doi: 10.1080/13669870110062712]
24. Nagata JM, Hernández-Ramos I, Kurup AS, Albrecht D, Vivas-Torrealba C, Franco-Paredes C. Social determinants of health and seasonal influenza vaccination in adults ≥65 years: a systematic review of qualitative and quantitative data. BMC Public Health 2013;13:388 [FREE Full text] [doi: 10.1186/1471-2458-13-388] [Medline: 23617788]
25. Gerard MN, Trick WE, Das K, Charles-Damte M, Murphy GA, Benson IM. Use of clinical decision support to increase influenza vaccination: multi-year evolution of the system. J Am Med Inform Assoc 2008;15(6):776-779 [FREE Full text] [doi: 10.1197/jamia.M2698] [Medline: 18756001]
26. Gerard M, Das K, Trick WE, Charles-Damte M. Evolution of clinical decision support to increase influenza vaccination. AMIA Annu Symp Proc 2007:962. [Medline: 18694062]
27. Bates DW, Kuperman GJ, Wang S, Gandhi T, Kittler A, Volk L, et al. Ten commandments for effective clinical decision support: making the practice of evidence-based medicine a reality. J Am Med Inform Assoc 2003;10(6):523-530 [FREE Full text] [doi: 10.1197/jamia.M1370] [Medline: 12925543]

28. Minor DS, Eubanks JT, Butler KR, Wofford MR, Penman AD, Replogle WH. Improving influenza vaccination rates by targeting individuals not seeking early seasonal vaccination. Am J Med 2010 Nov;123(11):1031-1035. [doi: 10.1016/j.amjmed.2010.06.017] [Medline: 20843496]
29. McDowell I, Newell C, Rosser W. Comparison of three methods of recalling patients for influenza vaccination. CMAJ 1986 Nov 1;135(9):991-997 [FREE Full text] [Medline: 3093045]
30. Humair JP, Buchs CR, Stalder H. Promoting influenza vaccination of elderly patients in primary care. Fam Pract 2002 Aug;19(4):383-389 [FREE Full text] [Medline: 12110560]
31. Osheroff JA, Teich JA, Levick D. Improving Outcomes with Clinical Decision Support: An Implementer's Guide. Second edition. Chicago, IL: HIMSS; 2012.
32. Mac DR, Baken L, Nelson A, Nichol KL. Validation of self-report of influenza and pneumococcal vaccination status in elderly outpatients. Am J Prev Med 1999 Apr;16(3):173-177. [Medline: 10198654]
33. Centers for Disease ControlPrevention (CDC). Pneumococcal and influenza vaccination levels among adults aged > or = 65 years--United States, 1993. MMWR Morb Mortal Wkly Rep 1996 Oct 11;45(40):853-859 [FREE Full text] [Medline: 8927004]
34. Centers for Disease ControlPrevention (CDC). Influenza and pneumococcal vaccination coverage levels among persons aged > or = 65 years--United States, 1973-1993. MMWR Morb Mortal Wkly Rep 1995 Jul 14;44(27):506-7, 513 [FREE Full text] [Medline: 7596336]
35. HealthIT.gov. Health Care Professional EHR Vendors. 2015. URL: http://dashboard.healthit.gov/quickstats/pages/FIG-Vendors-of-EHRs-to-Participating-Professionals.php [accessed 2016-02-22] [WebCite Cache ID 6dyBeCNQ7]

Abbreviations

CDS: clinical decision support
EHR: electronic health record
IRB: Institutional Review Board
IVR: interactive voice recognition
RMG: Reliant Medical Group

Edited by G Eysenbach; submitted 23.12.15; peer-reviewed by C Kruse, T English; comments to author 13.01.16; accepted 22.01.16; published 06.05.16.

Please cite as:
Cutrona SL, Sreedhara M, Goff SL, Fisher LD, Preusse P, Jackson M, Sundaresan D, Garber LD, Mazor KM
Improving Rates of Influenza Vaccination Through Electronic Health Record Portal Messages, Interactive Voice Recognition Calls and Patient-Enabled Electronic Health Record Updates: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2016;5(2):e56
URL: http://www.researchprotocols.org/2016/2/e56/
doi:10.2196/resprot.5478
PMID:27153752

Protocol

Improving Vitamin D Status and Related Health in Young Women: The Safe-D study – Part B

Marjan Tabesh[1], MSc; Suzanne Marie Garland[2,3,4], MD; Alexandra Gorelik[1,5], MSc; Alison Nankervis[1,6], MD; Skye Maclean[1], MN(Prac); Emma Teresa Callegari[1], Biomed(Hons); Shanton Chang[7], PhD; Kayla Heffernan[7], MIS; John Dennis Wark[1,8], MD, PhD

[1]Department of Medicine, Royal Melbourne Hospital, University of Melbourne, VIC, Australia
[2]Murdoch Childrens Research Institute, Royal Children's Hospital, VIC, Australia
[3]Women's Centre for Infectious Diseases, Royal Women's Hospital, VIC, Australia
[4]Department of Obstetrics and Gynaecology, University of Melbourne, VIC, Australia
[5]Melbourne EpiCentre, Royal Melbourne Hospital, VIC, Australia
[6]Diabetes Service, Royal Women's Hospital, VIC, Australia
[7]Department of Computing and Information Systems, University of Melbourne, VIC, Australia
[8]Bone and Mineral Medicine, Royal Melbourne Hospital, VIC, Australia

Corresponding Author:
John Dennis Wark, MD, PhD
Department of Medicine
Royal Melbourne Hospital
University of Melbourne
Parkville
VIC, 3052
Australia
Phone: 61 8344 3258
Fax: 61 8344 3258
Email: jdwark@unimelb.edu.au

Abstract

Background: Vitamin D deficiency is highly prevalent and associated with increased risk of a number of chronic health conditions including cardiovascular disease, poor bone and muscle health, poor mental health, infection, and diabetes. Vitamin D deficiency affects millions of Australians, potentially causing considerable suffering, economic loss, and mortality.

Objective: To measure the effectiveness of a (1) mobile-based app (behavioral) and (2) pharmacological intervention to increase circulating 25-hydroxyvitamin D (serum 25 OHD) levels and health outcomes over 4 months of intervention compared with usual care in a cohort of young women with suboptimal serum 25 OHD levels (25-75 nmol/L).

Methods: Participants with 25 OHD levels 25 to 75 nmol/L are invited to participate in this study. Participants are randomized to one of three groups in 1:1:1 ratio: a mobile phone–based application, vitamin D supplementation (1000 IU/day), and a control group. Data collection points are at baseline, 4, and 12 months post baseline with the major endpoints being at 4 months. A wide-range of information is collected from participants throughout the course of this study. General health, behavioral and demographic information, medications, smoking, alcohol and other substance use, health risk factors, nutrition, eating patterns and disorders, and mental health data are sourced from self-administered, Web-based surveys. Clinical data include anthropometric measurements, a silicone skin cast of the hand, cutaneous melanin density, bone mineral density, and body composition scans obtained through site visits. Main analyses will be conducted in two ways on an intention-to-treat (ITT) basis using the last observation carried forward approach as an imputation for missing data, and on a per protocol basis to compare the intervention arms against the control group at 4 and 12 months.

Results: Publication of trial results is anticipated in 2017.

Conclusions: The study will allow assessment of the effects of a mobile-based app behavioral intervention and vitamin D supplementation on vitamin D status and will evaluate the effects of improving vitamin D levels on several health outcomes.

(JMIR Res Protoc 2016;5(2):e80) doi:10.2196/resprot.5465

KEYWORDS

vitamin D; young women; health outcomes; intervention; Safe-D study, behavioral intervention; app; vitamin D supplementation; eHealth

Introduction

Background

Low vitamin D status is an issue of concern in today's society and its prevalence has been reported to be high, with approximately 50% of the world population thought to be affected [1]. Low vitamin D levels have been shown to be associated with an increased risk of numerous chronic health conditions, including poor musculoskeletal health and cardiovascular disease [2]. Vitamin D deficiency also impacts on young women's ability to achieve optimal peak bone mass increasing the risks of osteoporosis and osteoporotic fractures, which are major public health problems in the aging population [3,4]. Twenty-seven percent of women across Australia achieve optimal vitamin D levels (defined as serum 25-hydroxyvitamin D (25 OHD) greater than 75 nmol/L) [5]. Individual factors such as habitual sun exposure and skin color are likely to play major roles in determining vitamin D status [5,6]. Vitamin D deficiency is an important health risk factor for young women, particularly during their childbearing years, when deficiency can harm both the mother and the unborn child [7]. Despite the potentially serious effects of vitamin D insufficiency (serum 25 OHD between 26 and 49 nmol/L) and deficiency (serum 25 OHD <25 nmol/L), very few vitamin D studies have focused on young women; the majority of studies in the literature have studied general population cohorts or have exclusively focussed on elderly participants [8]. This study is of particular importance as many risks factor for certain cancers, autoimmune diseases, infections, neurological diseases, diabetes, and poor mental health are established during youth [1]. Vitamin D status is one of the factors that may impact on these disease risks.

The Safe-D study aims to (1) examine the links between vitamin D and various health indicators in a young female cohort (part A) [9], and (2) evaluate the effectiveness of a smartphone app compared with vitamin D supplementation in improving both serum 25 OHD levels and several health measures that have been associated with vitamin D deficiency (part B). By focusing on a younger cohort and using a successful recruitment strategy via social media [10], the study aims to achieve a much larger sample size of this population than previous research [11,12]. In addition, the relationship between vitamin D status and health will be comprehensively studied using state-of-the-art information technology-based data collection methods that have not been used in any similar studies, which have based results largely on self-reported data [13].

While vitamin D deficiency is associated with many poor health outcomes, its potential impact on young Australian women's health has yet to be established. Moreover, there are evidence gaps about the safest and most effective interventions to improve vitamin D status. Of importance, much of the previous research has been limited by imprecise 25 OHD measurements [2].

Addressing factors that can lead to vitamin D deficiency earlier in life might be beneficial for long-term health, productivity, and quality-of-life of young women. Part A of the Safe-D study is described elsewhere [9]. Part B, a randomized controlled trial involving the use of a digital Web-based smartphone app, is described here.

Study Rationale

This study focuses on 16- to 25-year-old women, because of: (1) the high prevalence of vitamin D deficiency in young people [1,2,14,15], (2) the importance of this life stage, as individuals become more autonomous and independent, and individual environmental as well as behavioral factors play an increasing role in shaping health patterns that have long-term consequences [16], (3) the popularity in this demographic of communication using mobile and social media technologies with which we have previous experience, and harness in this study [10], (4) vitamin D deficiency impacting young women's bone mass increasing the risks of osteoporosis and osteoporotic fractures later in life [17], and (5) women's smaller skeletons make them more likely to develop osteoporosis due to biological sex differences in the skeleton with ageing [18].

While there have been many studies examining the associations between vitamin D and health, only small, restricted studies have been conducted with young women. Therefore, this study aims to ensure that comprehensive health data are collated for this population subgroup.

Methods

Study Design

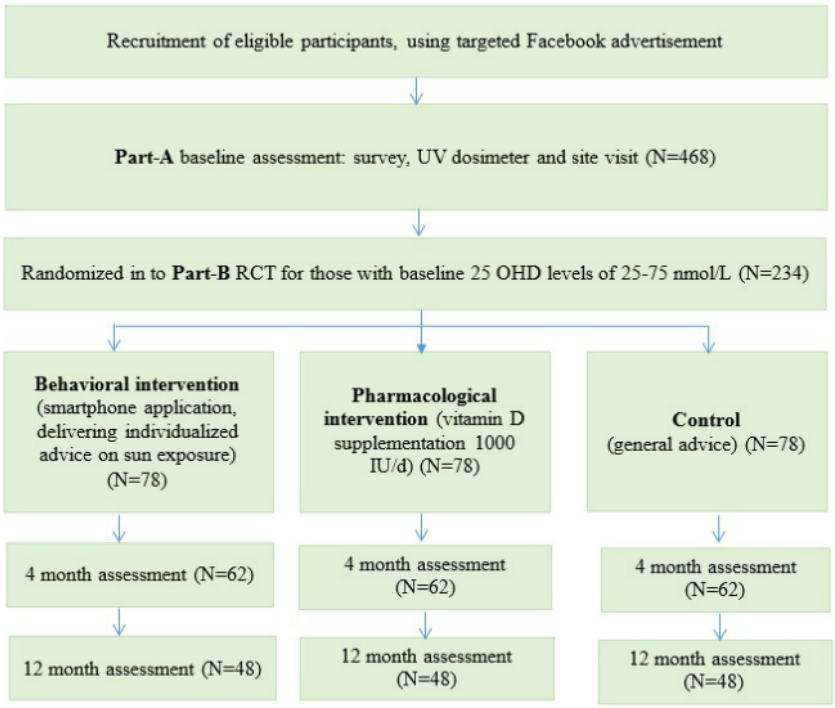
The Safe-D study comprises two distinct, but overlapping and interrelated components. Part A is a cross-sectional study of healthy women aged 16 to 25 years, aimed at investigating associations between 25 OHD levels and musculoskeletal health (bone density, bone turnover markers, muscle function), mood/mental health, body composition and weight, and atopic/allergic symptoms [9]. Part B is an open-label, blinded-endpoint, randomized controlled trial with three arms; a behavioral intervention, a pharmacological intervention, and control group [19,20]. Study participants are monitored for a period of 12 months. A comprehensive, Web-based questionnaire is completed by all participants at 0 and 12 months; an abbreviated version of this survey is completed at 4 months. The survey links are sent through Limesurvey (an open-source, password-protected, secure software survey tool) to each participants [21]. The questionnaires comprise five modules, which the participants are able to complete either altogether or on separate occasions over a 2-week period before their site visit. The modules cover health areas including demographics, medical history, use of health care professionals, use of medications and allergy data to establish current and/or past health conditions [14]. Nutrition, dietary behaviors, and weight management data are collected to identify change in body composition and weight and investigate the relationship between obesity and vitamin D. Body image, alcohol use,

tobacco use, and illicit drug use information is collected because it has been suggested that vitamin D has a neuroprotective effect on dopaminergic pathways in the adult brain and may have a role in the management of drug dependence, and also smoking and alcohol use can affect vitamin D status [22]. Diet, physical activity, pain and injuries, sun exposure, and mental health data are collected to assess dietary intake of vitamin D, to control for physical activity as a contributor to weight and to investigate a relationship between vitamin D and musculoskeletal health. Sun exposure is collected to investigate a relationship between change in vitamin D and ultraviolet (UV) exposure.

Dietary intake is a confounder for the relationship between vitamin D and obesity [23]. The Cancer Council Victoria Questionnaire (comprehensive dietary questionnaire) is used to evaluate the diet type and portion sizes [23].

In addition, site visits take place at our study center at each time point to collect a range of clinical health information, including blood tests, bone density (baseline and 12 months), and tests of muscle health (Figure 1).

Figure 1. Study flowchart of participants.



Subject Selection

Participants in this study are female, aged between 16 to 25 years upon inclusion in the study, and residing in Victoria, Australia, for the duration of the study. Inclusion criteria are completion of all components of part A of the Safe-D study, serum 25 OHD levels between 25 and 75 nmol/L, plus ownership and regular use of a smartphone with Apple or Android operating systems.

Exclusion criteria include a history of skin melanoma (or having a first-degree relative (parent or sibling) who has had a melanoma), current pregnancy, breastfeeding, an intention to conceive in the next 12 months, current supplementation with ≥800 IU vitamin D daily, an intention to move out of Australia during the course of the study, any chronic health condition or medication that may disturb vitamin D metabolism or action or cause safety concerns, any medical condition, or using any medication that increases sensitivity to sun light or UV radiation.

The inclusion and exclusion criteria were designed so that any harm to study participants is minimized as far as practically possible, while selecting as broad a sample as possible to maximize the generalizability of the findings. The exclusion and inclusion criteria also assist to reduce confounding of results. If participants meet any of the exclusion criteria, at any time in the study they are withdrawn from intervention as appropriate for good clinical care. Where possible, these participants complete all data collection including study visits for the purpose of an intention-to-treat (ITT) analysis.

Proposed Sample Size

A meta-analysis of 16 studies found an increased serum 25 OHD concentration of approximately 1 to 2 nmol/L for each 100 IU per day of supplemental vitamin D [24]. Assuming average supplementation of 1000 IU vitamin D/day, we expect changes in serum 25 OHD concentration of approximately 10 to 20 nmol/L in the pharmacological intervention group. By using ITT analysis, a sample size of 62 per arm at 4 months (corresponding to 78 per arm at baseline) will 85% power to detect a difference of 15 nmol/L in 25 OHD levels between groups (assuming a standard deviation of 25 nmol/L and total level of significance of 0.05). This gives an 80% power to detect

a 15 nmol/L difference in per protocol analysis, assuming 85% adherence to the protocol, and making the assumptions of at least 50% of participants fall in the range of 25 to 75 nmol/L at entry, 20% attrition at 4 months, and 30% total attrition at 12 months [25].

We expect to be able to include 48 participants per arm (n=56 for ITT analysis) in the 12-month per protocol analyses (accounting for attrition and noncompliance), giving us 80% power (85% in ITT) at a 5% significance level to detect a 9 to 10 nmol/L difference in change from baseline between the two intervention arms (assuming a lower standard deviation of 20 nmol/L due to seasonal matching).

Based of the above, the study team aim to recruit 468 young women into part A of the study, which should lead to approximately 234 participants in part B assuming at least 50% of participants fall in the serum 25 OHD range of 25 to 75 nmol/L, meet other eligibility criteria for part B and agree to participate.

Recruitment

Participants who complete part A of the Safe-D study (including completion of a comprehensive questionnaire, wearing of an UV dosimeter for a period of 14 consecutive days and participation in the study site visit) and meet the eligibility criteria for Part B are invited to participate in the study. Upon receipt of the serum 25 OHD and other pathology results from the laboratory, eligible participants are contacted by a member of the study team to inform them that they are eligible to participate. A verbal consent process takes place during the telephone call. Each volunteer is given sufficient time to review the detailed participant information and consent form (PICF), and is given the opportunity to ask questions about the study. Subjects are then asked to provide written informed consent in order to participate. All participants under 18 years are assessed as a mature minor and those deemed unable to provide informed consent require the consent of their parent or guardian to participate in the study [26].

All participants are offered compensation for their time in the form of an AU$30 gift voucher at each assessment. Participants identified as having high depressive and/or anxiety symptoms in study survey responses at any time point are sent information booklets (beyondblue booklet; “What works for anxiety disorders?” [27] and “What works for depression in young people”) [28]. Participants who answer positively to suicidal ideation are contacted by a study team member with Applied Suicide Intervention Skills Training, to ensure the participant’s safety and well-being [29].

Participants whose serum 25 OHD levels show moderate to severe deficiency (<25 nmol/L) are contacted by the study team and strongly advised to review the results with their primary care physician. This group is expected to be <8% of the target population and are not randomized into part B. Subjects whose levels drop below 25 nmol/L at 4 months are also immediately referred for appropriate treatment; however, they are encouraged to remain in the trial to reduce attrition.

Verbal, Written, and Electronic Consent

Verbal consent is obtained from all participants in this study by telephone communication. Participants then are sent email links, so that they can complete the Web-based surveys. Each of the surveys includes the PICF and this is being used as a means of obtaining electronic consent.

Prior to the site visit, all participants are sent a hard copy of the PICF with a welcome letter. The PICF is reviewed at the commencement of the study visit prior to the collection of any biological data.

An electronic consent (econsent) form is offered to participants, which is obtained through a secure link sent by the study team via LimeSurvey. Information contained in the PICF is displayed on screen and requires participants to click “I agree” to a statement that they have read and understood the information and freely agree to participate in the research project. Participants giving electronic consent are asked to provide written consent at the first subsequent opportunity to do so. The econsent form allows recruitment and allocates the participants to the intervention groups to allow for a more streamlined process. Eligible participants were randomized into one of three groups.

Trial Interventions

Behavioral Intervention Group

All participants randomized to the behavioral intervention group receive instructions on how to download the Safe-D study mobile-based app (Safe-D app) to use for 12 months following randomization [20]. The Safe-D app is designed for both Apple and Android operating systems.

The Safe-D app delivers advice about how to obtain safe and effective sun exposure daily, as per guidelines developed by the Safe-D team in conjunction with the SunSmart guidelines [20]. An algorithm was incorporated into the app to estimate the time required with direct exposure to sunlight to achieve adequate vitamin D levels [30]. The mechanics of algorithm are not apparent to users. It is the messages themselves that convey the complex information simply, and the use of game elements to further simplify understanding. In Safe-D app UV-exposure is shown as different shape of sunflower to users to convey message simply and effectively. Advice is tailored according to the individual’s characteristics and reported behaviors, including Fitzpatrick skin type [31], clothing, sunscreen use, and local UV forecast (location determined using the smartphone’s global positioning system or by manually entering location details) sourced from the Australia Bureau of Meteorology and the Australian Radiation Protection and Nuclear Safety Agency. As there is a need for improved education in the community about SunSmart behaviors and safe methods to achieve the best possible vitamin D production, general advice is also delivered.

The Safe-D app enables tracking of UV-exposure, records missed exposure, and monitors participant progress regarding time spent in the sun. Participants start the app timer when they are in direct sunlight and stop when they are no longer exposed. The app sends tailored messages to participants depending on

their sun exposure records. The messages are sent as push notification, rather than requiring participants to check the app daily [32-34]. Educational messages are also sent to maintain participant motivation and interest in the study. Messages encourage appropriate and safe levels of UV-exposure and explain the importance of vitamin D, especially in women, health consequences of vitamin D deficiency, and tips to improve vitamin D status. Three types of messages are sent to participants through the app: automatic push notifications, automatic in-app messages, and tailored and personalized mail messages [35]. Participants are able to turn off the automatic push notification, though they are encouraged by the study team during their randomization call not to do so. Safety is monitored within the app and any participant who exceeds the recommended time in the sun receives an autogenerated safety warning and the application reports any consequences of overexposure to study staff. Use of the application is also measured by the number of times participants open it [20].

Pharmacological Intervention Group

All participants in this group receive a 1-year supply of 1000 IU vitamin D supplements. Participants are informed of the prescribed dose and route of administration of the supplements (oral), and the recommended storage conditions. Participants are sent weekly regular SMS text messaging with (short message service, SMS) reminders to take the equivalent dose of 1 capsule per day, and reminded that if they miss any doses throughout the week, that they may take the missed tablets all at once that day, without any risk of toxicity. Messages are sent weekly for the first month of participation, taper to fortnight, then monthly. Standard protocols for the receipt, dispensing, return, and disposal of these supplements have been developed with the assistance of a research pharmacist.

Control group

All participants in this group receive general advice in the form of the “How much sun is enough?” pamphlet produced by Cancer Council Victoria [36]. This pamphlet is sent to participants via email. It provides information about achieving adequate vitamin D status using safe levels of UV exposure and diet, and a contact number to obtain further advice, with links to SunSmart Victoria’s Web-based vitamin D resources.

Randomization

Participants are randomized into one of the three intervention groups using stratified block randomization with computer-generated varying block sizes (3, 6, and 9), based on baseline serum 25 OHD levels 25 to 49 nmol/L and 50 to 74 nmol/L. The study statistician (AG) is responsible for the generation of the randomization schedule and preparing the codes. An electronic process is used to generate the codes. As each eligible participant is identified from part A of the Safe-D study and consented, the statistician is emailed by an unblinded researcher, and a randomly generated allocation group is assigned, details of which are kept in the participant’s notes and entered into the unblinded database. All other study team members who collect outcome data are blinded to intervention group allocation.

Blinding

As far as practically possible, procedures are in place to maintain blinding of team members who collect outcome data. They are blinded to the participant’s treatment allocated Two databases are used to avoid inadvertent unblinding, one for blinded members and one for unblinded members. Participants are blinded to their vitamin D stratification, and only receive the details of their vitamin D results during the trial if clinically necessary. All vitamin D results will be provided to participants upon conclusion of the study.

Data Collection

A wide-range of information is collected from participants throughout the course of this study [9]. These data are sourced from self-administered Web-based surveys and clinical data are obtained through site visits. Data are collected from all participants at baseline (0 month) and at the end of the study (after 12 months of study participation). All data except the bone density scans are collected at 4 months, which is the approximate duration predicted for vitamin D levels to reach a steady state with intervention [37]. A modified version of the questionnaires is used at 4 months. Bone density testing is not performed at 4 months because significant changes are unlikely to be detected at that time-point.

Questionnaires Content

The Cancer Council Victoria Questionnaire was comprised of dietary intake and portion sizes data. The other questionnaires comprise four modules, which the participants are able to complete either altogether or on separate occasions over a 2-week period before the site visit. The modules cover groups of health areas as described as follows:

1. Module A: demography, medical history, use of health care professionals, use of medications and allergy data.
2. Module B: nutrition, dietary behaviors, and weight management data.
3. Module C: body image, alcohol use, tobacco use, and illicit drug use information.
4. Module D: diet, physical activity, pain and injuries, sun exposure, and mental health data.

Site Visit Assessment and Rationale

Participants are asked to attend Royal Melbourne Hospital for a 2-hour study site visit baseline and 12 months for a health check including a physical examination, blood collection, silicone skin cast of the hand, skin reflectance, bone density and body composition scans, and Leonardo mechanography testing [38]. They are also asked to attend for a 1-hour visit at the 4-month follow-up for the above tests except that bone density tests are not performed at this time point.

Physical Examination

Blood pressure, resting heart rate, waist circumference, hip circumference, height, and weight are measured for general health assessment. Blood pressure is measured twice with two different machines and recorded as systolic and diastolic blood pressure. Height is measured to the closest of 0.1 cm by using a wall-mounted stadiometer. Weight is measured to the closest of 0.01 kg.

Blood Collection

A fasting, morning blood sample is collected to test for analytes by standard methods including 25 OHD, thyroid stimulating hormone, prolactin, insulin, HbA1c, glucose, lipids (total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglyceride), calcium, parathyroid hormone, albumin, creatinine and C-reactive protein [9]. VivoPharm Laboratories employ a highly-sensitive, accurate, and precise liquid chromatography-tandem mass spectrometry (LC-MS/MS) method using Applied Biosystems 4000 Q Trap and Agilent LC-MS/MS instruments, which is used to measure serum 25 OHD3 and serum 25 OHD2 concentrations for this study. Serum 25 OHD concentration is the best indicator of vitamin D status. Ligand-binding assays are the standard method for measuring serum 25 OHD but have some limitations including poor agreement between assays and laboratories [39], inability to distinguish between serum 25 OHD2 and 25 OHD3, and systematic under- or overestimation of 25 OHD levels [40]. The current "gold standard" method for determining vitamin D levels is LC-MS/MS, which is more accurate and precise, uses standards of defined concentrations, needs smaller sample volume and shorter turnaround time than alternative methods, and distinguishes between D2 and D3 metabolites. For these reasons, we chose the LC-MS/MS method to measure vitamin D levels.

Skin Cast of Hand

Actinic skin damage is measured at baseline, after 4 and 12 months of intervention by taking a silicone rubber cast of the dorsum of the hand to assess skin damage [41]. The Beagley and Gibson grading system is used to score the skin casts [42]. This visual system of grading is not time-consuming and it is well suited for use in studies with large sample size. Skin casts are graded on a scale of 1 to 6, with 1 indicating undamaged skin that is evenly spaced with fine lines of equal depth. Grade 6 is indicative of maximum photo-damage, specifically with a more flattened appearance to the skin surface [43].

Skin Reflectance

Cutaneous melanin density is measured at each visit using a spectrophotometer as skin color is a covariate to be controlled for in assessing vitamin D response. Melanin density is measured at both a UV-unexposed region (inner side of upper arm) and exposed regions (back of hand and facial cheek).

Bone Density and Body Composition Scans

Participants attend the Bone Densitometry Unit at the Royal Melbourne Hospital for dual energy x-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT) scanning. DXA is used to measure areal bone mineral density and bone mineral content as well as soft tissue composition. The parts of the body to be scanned are lumbar spine, total hip, femoral neck, and total body [44]. Peripheral QCT of the tibia is used to assess volumetric bone density, bone geometry, and muscle cross-sectional area to investigate the relationship between 25 OHD and these measures [45].

Leonardo Mechanography

Muscle measurements are taken using a Leonardo jumping mechanography ground reaction force platform for muscle strength and muscle performance, to examine the relationship between these measurements and 25 OHD [38]. Single two leg jump, multiple one leg hop, and balance testing are performed to estimate muscle strength, efficiency of movement, maximum voluntary force, maximum acceleration, stiffness, energy storage capacity, and Esslinger Fitness Index.

Sun Exposure/SunSmart Behavior

Real-time UVB exposure is measured objectively in all participants at baseline, at 4 and after 12 months of intervention using a small, discreet, wearable UV dosimeter, with a sampling interval of 30 seconds to provide real-time profiles of UV-exposure during 14 consecutive days before the visit. The dosimeter is worn on the wrist like a watch. Participants also complete a log and standard questionnaire about sunlight exposure and SunSmart behavior [46], for comparison with the objective data. Logs are to report clothing worn, sunscreen use, sunburn, and when they took the watch off/put on.

Statistical Analysis

The primary outcome in this study is the change in serum 25 OHD concentration at 4 months. Secondary outcomes include: objectively measured sunlight exposure, SunSmart behavior, compliance rates for the two interventions, and musculoskeletal health measures at 12 months. Exploratory outcomes include metabolic profiles, body composition and weight, atopic/allergic symptoms, mood and mental health, knowledge about sun-safe behavior, as well as defining the determinants of vitamin D status in young women using baseline data and investigating the effects of vitamin D improvement on metabolic profiles, body composition and weight, atopic/allergic symptoms, mood, and mental health after 4 months. Main analyses will be conducted on an ITT basis to compare the intervention arms against the control group at 4 months, using various imputation strategies to account for missing data arising from sample attrition.

Due to possible protocol violations (eg, noncompliance with the prescribed treatment and unblinding occurrences), a secondary per protocol analysis designed to adjust for noncompliance will be undertaken at 4 and 12 months and results compared with the ITT analysis. Subjects in the control and behavioral intervention arms who start taking vitamin D supplements during the trial and noncompliers with the interventions will be excluded from the per protocol analysis.

Kolmogrov-Smirnov test and histogram chart will be used to assess the normality of continuous variables. Baseline general characteristics will be examined using one-way analysis of variance (ANOVA) for continuous variables and chi-square for categorical variables. Two-way ANOVA will be used to determine the effects of supplementation and behavioral intervention. Tukey's post-hoc comparisons will be used to identify pair wise differences when we reach a significant finding in multivariate regression. P values <0.05 will be considered as significant. All statistical analyses will be

performed using the Statistical Package for Social Science version 22.

Compliance and Withdrawal

The measurement of study compliance may vary between the three groups. The app contains built-in timers and data that allow the study team to determine how often the participants in the behavioral intervention group access the app.

Unblinded study staff undertake a manual count of the supplements at the 4 and 12 months visits, on return of the container of supplements. These data are recorded and a compliance percentage is determined. Unblinded study staff call participants in the control group to ask if they have read and understood the information brochure 2 weeks after randomization and then each month.

Any participants who have commenced vitamin D supplementation throughout the course of the study, and are not in the pharmacological intervention arm, remain in the study, and their data are analysed using the ITT analysis. Subsequently, per protocol analyses are performed, excluding the results of these participants.

Any participant who fails to meet the eligibility criteria for the duration of the study is invited to complete their remaining study visits for ITT analyses. In addition, any participant who commences participation in the study but, at any stage of the study, withdraws their consent, is withdrawn from the study. Any data that they have contributed to the study continues to be used, unless the participant states specifically that they would like their data to be deleted. This process is formally stated to the participant before they commence the study.

The study team make reasonable attempts to contact a participant before withdrawing them from the study. This includes sending emails, text messages, making telephone calls, and sending written letters to the participant's home address. If no contact can be made with the participant using all mentioned methods three times, the participant is withdrawn from the study and a letter is sent to them to explain this decision.

Ethical and Legal Considerations

This study has received approval from the Melbourne Health Human Research and Ethics Committee (HREC) and is conducted according to the principles and rules laid down in the Declaration of Helsinki and its subsequent amendments. It is carried out according to the revised National Statement on Ethical Conduct in Research Involving Humans (2007) produced by the National Health and Medical Research Council of Australia [38]. This national statement was developed to protect the interests of people who participate in research studies.

Mandatory reporting requirements pertaining to physical or sexual abuse of minors are adhered to by the study team and incorporated into the PICF so that participants are aware of the obligations of the study team. Data are kept confidential except if required by law. Information regarding illegal drug use may be disclosed to relevant authorities if required by law.

Clinically-Significant Results

All participants who have an abnormal pathology result, which is considered to be clinically significant after review by the principal investigator are contacted and/or receive the results by mail or telephone, depending on the urgency of the matter. Specifically, any participant who records a serum 25 OHD result lower than 25 nmol/L is withdrawn and is referred to their treating general practitioner (GP) for advice and follow-up.

Adverse Events

An adverse event is defined as any occurrence that has unfavorable and/or unintended effects on research subjects, regardless of severity or study-relatedness. Adverse events may manifest as new findings (signs, symptoms, diagnoses, laboratory results) or alterations in pre-existing conditions. All adverse events occurring during the study are recorded whether or not they are considered to be serious and/or related to the study. Any major adverse events are reported in writing to the Melbourne Heath HREC. Based on the self-reported and UV dosimeter data, any subjects receiving UV-B exposure at levels deemed to place them at risk are advised that they are at high risk and provided with further information about SunSmart behaviour and safe sun exposure.

Results

Recruitment is currently underway. Publication of trial results is anticipated in 2017.

Discussion

Trial Implications

Causes of vitamin D deficiency include decreased sun exposure, use of UV-B blocking sunscreens, low dietary intake of vitamin D, obesity, and possibly smoking. Sunlight exposure is the major source of vitamin D (through the internal synthesis of vitamin D3), accounting for 80% to 90% of circulating vitamin D metabolites, few foods other than fatty fish contain vitamin D [47].

To the investigators' knowledge, this study is the first randomized trial to assess the effectiveness of an eHealth lifestyle intervention to safely improve vitamin D status in young women, and addresses the limitations of previous studies that have been small, limited by the imprecision of traditional assays for measuring 25 OHD levels, and/or lacking data on adolescents and younger women. In addition, recruitment via Facebook and subsequent enrolment into an intervention trial is novel in this study. Recruitment via Facebook can be effective at reaching a large number of potential participants, as well as improving affiliated costs. Also it is affordable and reach a wide diverse population, thus increasing generalizability [48]. If successful, the smartphone eHealth intervention developed for this study would be readily deployable throughout Australia and internationally, translatable to different demographics, and has the potential to be incorporated into health promotion initiatives and clinical care. The extensive data collection being undertaken by this study allows for the identification of possible relationships between vitamin D status and a range of other

health conditions. As there are seasonal differences in 25 OHD levels, all measurements are repeated after 1 year of intervention.

Limitations

This study has a number of limitations. First, blinding is a difficult issue to address. As far as practically possible, study staff are blinded to the group to which participants are allocated throughout the study. However, we are not able to blind participants to their intervention group allocation. Another limitation of our study is using Facebook advertising for recruitment, which can cause selection bias. However, in the pilot study on feasibility for the same age group reasonable representativeness with the general population was achieved apart from selecting those with a higher level of education [10]. This is common to most methods used for recruitment of subjects from general populations.

Acknowledgments

Authors would like to thank the Boosted Human members for developing the Safe-D application, Amanda Hawker, Anna-Louise Ponsonby and Robyn Lucas, Ashwin Swaminathan, Rachel Slatyer, Jessica Cargill for skin casting and photographing, Cancer Council Victoria, Melbourne Health Pathology Service and Stefanie Hartley, Adele Rivers, Anna Leigh Scobie, Jemma Christie, Ashwini Kale, Asvini Subasinghe, Yasmin Jayasinghe, Kerryn King, Catherine Segan, Adrian Bickerstaffe, Elisa Young, Jen Makin, Alison Brodie, Johannes Willnecker, Maria Bisignano, George Varigos, Kim Bennell, Nicola Reavley, Marie Pirotta, Steve Howard (dec.), Tony Jorm Peter Gies and all other members of the Safe-D study and YFHI study. Authors also would like to thank all participants for their time and effort. The Safe-D study has received in-kind support from Swisse Wellness to provide the supplements. This project is funded by a NHMRC project grant, APP1049065.

References

1. Holick M, Chen T. Vitamin D deficiency: a worldwide problem with health consequences. Am J Clin Nutr 2008;87:1080S-1086S [FREE Full text] [Medline: 18400738]
2. Theodoratou E, Tzoulaki I, Zgaga L, Ioannidis JPA. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. BMJ 2014;348:g2035 [FREE Full text] [Medline: 24690624]
3. Colón-Emeric C, Saag K. Osteoporotic fractures in older adults. Best Pract Res Clin Rheumatol 2006;20:695-706.
4. Marjo KL, Timo TM, Ilpo ON, Kerttu MI, Aila EL, Jorma SV. Vitamin D and attainment of peak bone mass among peripubertal Finnish girls: a 3-y prospective study1-3. Am J Clin Nutr 2002;76:1446-1453.
5. Faden VB, Day NL, Windle M, Windle R, Grube JW, Molina BSG, et al. Collecting longitudinal data through childhood, adolescence, and young adulthood: methodological challenges. Alcohol Clin Exp Res 2004;28:330-340 [FREE Full text] [Medline: 15112941]
6. Australian Bureau of Statistics (ABS). National Health Survey. Canberra (ACT): Catalogue 21 2001;4364.
7. World Health Organisation (WHO). Women and Health: Today's Evidence Tomorrow's Agenda, November. 2009. URL: http://www.refworld.org/docid/4af82d3d2.html [accessed 2016-04-07] [WebCite Cache ID 6gbRhm6Et]
8. Bruyère O, Cavalier E, Souberbielle J, Bischoff-Ferrari H, Beaudart C, Buckinx F, et al. Effects of vitamin D in the elderly population: current status and perspectives. Arch Public Health 2014;72:32.
9. Callegari ET, Reavley N, Garland SM, Gorelik A, Wark JD. Vitamin D status, bone mineral density and mental health in young Australian women: the Safe-D Study. J Public Health Res 2015;4:594 [FREE Full text] [doi: 10.4081/jphr.2015.594] [Medline: 26753163]
10. Fenner Y, Garland S, Moore E, Jayasinghe Y, Fletcher A, Tabrizi S, et al. Web-based recruiting for health research using a social networking site: an exploratory study. J Med Internet Res 2012;14:e20 [FREE Full text] [doi: 10.2196/jmir.1978] [Medline: 22297093]
11. Institute of Medicine. Dietary Reference Intakes for Calcium and vitamin D. Washington, DC: The National Academies Press; 2011.
12. Putman MS, Pitts SAB, Milliren CE, Feldman HA, Reinold K, Gordon CM. A randomized clinical trial of vitamin D supplementation in healthy adolescents. J Adolesc Health 2013;52:592-598 [FREE Full text] [doi: 10.1016/j.jadohealth.2012.10.270] [Medline: 23608721]
13. Suliivan SS, Cobb JL, Rosen CJ, Holick MF, Chen TC, Kimlin M, et al. Assessment of sun exposure in adolescent girls using activity diaries. Nutr Res 2003;23:631-644.
14. Daly RM, Gagnon C, Lu ZX, Magliano DJ, Dunstan DW, Sikaris KA, et al. Prevalence of vitamin D deficiency and its determinants in Australian adults aged 25 years and older: a national, population-based study. Clin Endocrinol (Oxf) 2012;77(1):26-35. [doi: 10.1111/j.1365-2265.2011.04320.x] [Medline: 22168576]
15. Gordon CM, DePeter KC, Feldman HA, Grace E, Emans SJ. Prevalence of vitamin D deficiency among healthy adolescents. Arch Pediatr Adolesc Med 2004;158:531-537. [doi: 10.1001/archpedi.158.6.531] [Medline: 15184215]
16. WHO. Diet, nutrition, the prevention of chronic diseases. Report of a WHO Study Group 1990:6-13.

17. Barnes M, Robson P, Bonham M, Strain J, Wallace JMW. Effect of vitamin D supplementation on vitamin D status and bone turnover markers in young adults. Eur J Clin Nutr 2006;60:727-733. [doi: 10.1038/sj.ejcn.1602374] [Medline: 16391584]
18. Orwoll E, Bliziotes M. Heterogeneity in osteoporosis. Men versus women. Rheumatic diseases clinics of North America 1994;20.
19. Cancer Council Victoria, Be SunSmart. 2015. URL: http://www.cancervic.org.au/preventing-cancer/be-sunsmart [accessed 2016-04-07] [WebCite Cache ID 6gbS4xuGi]
20. Heffernan K, Chang S, Maclean S, Callegari E, Garland S, Reavley N, et al. The potential of eHealth apps to support targeted complex health messages. J Gen Practice 2014:182.
21. LimeSurvey project team. LimeSurvey: An open Source Survey Tool URL: https://www.limesurvey.org/ [accessed 2016-04-07] [WebCite Cache ID 6gbS8mJdb]
22. Eserian J. Vitamin D as an effective treatment approach for drug abuse and addiction. Journal of Medical Hypotheses and Ideas 2013;7(2):35-39.
23. Ireland P, Jolley D, Giles G, O'Dea K, Powles J, Rutishauser I, et al. Development of the Melbourne FFQ: a food frequency questionnaire for use in an Australian prospective study involving an ethnically diverse cohort. Asia Pac J Clin Nutr 1994;3:19-31 [FREE Full text] [Medline: 24351203]
24. Cranney A, Horsley T, O'Donnell S, Weiler H, Puil L, Ooi D, et al. Effectiveness and safety of vitamin D in relation to bone health. Evid Rep Technol Assess 2007:231-235.
25. Leonard A, Hutchesson M, Patterson A, Chalmers K, Collins C. Trials. Recruitment and retention of young women into nutrition research studies: practical considerations 2014;16:15-23.
26. Sanci LA, Sawyer SM, Weller PJ, Bond LM, Patton GC. Youth health research ethics: time for a mature-minor clause? Med J Aust 2004;180:336-338. [Medline: 15059054]
27. Reavley N, Allen N, Jorm A, Morgan A, Purcell R. beyondblue: Melbourne. 2010. A Guide to What Works for Anxiety Disorders URL: https://www.beyondblue.org.au/docs/default-source/resources/bl-0762-guide-to-what-works-for-anxiety-02-14.pdf?sfvrsn=2 [accessed 2016-04-07] [WebCite Cache ID 6gbSDJ8Wg]
28. Jorm AF, Allen N, Morgan A, Purcell R. beyondblue: Melbourne, August. 2009. A Guide to What Works for Depression URL: https://www.beyondblue.org.au/docs/default-source/resources/bl-0556-guide-to-what-works-for-depression-12-14.pdf?sfvrsn=2 [accessed 2016-04-07] [WebCite Cache ID 6gbSECSEw]
29. LivingWorks Australia. http://www.livingworks.com.au/. Australia: Living works,; 2015. ASIST URL: http://www.livingworks.com.au/programs/asist/ [accessed 2016-04-04] [WebCite Cache ID 6gbShiwVi]
30. McKenzie R, Liley J, Björn L. UV radiation: balancing risks and benefits. Photochem Photobiol 2009:88-98.
31. Sachdeva S. Fitzpatrick skin typing: applications in dermatology. Indian J Dermatol Venereol Leprol 2009;75:93-96 [FREE Full text] [Medline: 19172048]
32. Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. Arch Dermatol 1988;124:869-871. [Medline: 3377516]
33. Fogg B. A Behavior Model for Persuasive Design. 2009 Presented at: ACM Proceedings of the 4th International Conference on Persuasive Technology ; 40; 2009; Claremont, CA.
34. Fine MR. Beta Testing for Better Software. New York: John Wiley & Sons; 2002.
35. Dolan R, Matthews J. Maximizing the utility of customer product testing: beta test design and management. Journal of Product Innovation Management 1993;10:318-330.
36. How much sun is enough?. URL: http://www.sunsmart.com.au/downloads/vitamin-d/how-much-sun-is-enough-vitamin-d.pdf [accessed 2016-04-07] [WebCite Cache ID 6gbT6mlBk]
37. Wootton AM. Improving the measurement of 25-hydroxyvitamin D. Clin Biochem Rev 2005;26:33-36 [FREE Full text] [Medline: 16278775]
38. Matheson L, Duffy S, Maroof A, Gibbons R, Duffy C, Roth J. Intra- and inter-rater reliability of jumping mechanography muscle function assessments. J Musculoskelet Neuronal Interact 2013;13:480-486.
39. Singh RJ. Are clinical laboratories prepared for accurate testing of 25-hydroxy vitamin D? Clin Chem 2008;54:221-223 [FREE Full text] [doi: 10.1373/clinchem.2007.096156] [Medline: 18160734]
40. Carter GD, Carter R, Jones J, Berry J. How accurate are assays for 25-hydroxyvitamin D? Data from the international vitamin D external quality assessment scheme. Clin Chem 2004;50:2195-2197 [FREE Full text] [doi: 10.1373/clinchem.2004.040683] [Medline: 15375018]
41. Lucas RM, Ponsonby A, Dear K, Taylor BV, Dwyer T, McMichael AJ, et al. Associations between silicone skin cast score, cumulative sun exposure, and other factors in the ausimmune study: a multicenter Australian study. Cancer Epidemiol Biomarkers Prev 2009;18:2887-2894 [FREE Full text] [doi: 10.1158/1055-9965.EPI-09-0191] [Medline: 19843682]
42. Battistutta D, Pandeya N, Strutton GM, Fourtanier A, Tison S, Green AC. Skin surface topography grading is a valid measure of skin photoaging. Photodermatol Photoimmunol Photomed 2006;22:39-45. [doi: 10.1111/j.1600-0781.2006.00194.x] [Medline: 16436180]
43. Holman CD, Armstrong BK, Evans PR, Lumsden GJ, Dallimore KJ, Meehan CJ, et al. Relationship of solar keratosis and history of skin cancer to objective measures of actinic skin damage. Br J Dermatol 1984;110:129-138. [Medline: 6696833]

44. Crabtree NJ, Arabi A, Bachrach LK, Fewtrell M, El-Hajj FG, Kecskemethy HH, International Society for Clinical Densitometry. Dual-energy X-ray absorptiometry interpretation and reporting in children and adolescents: the revised 2013 ISCD Pediatric Official Positions. J Clin Densitom 2014;17:225-242. [doi: 10.1016/j.jocd.2014.01.003] [Medline: 24690232]
45. Neu CM, Manz F, Rauch F, Merkel A, Schoenau E. Bone densities and bone size at the distal radius in healthy children and adolescents: a study using peripheral quantitative computed tomography. Bone 2001;28:227-232. [Medline: 11182383]
46. Glanz K, Yaroch A, Dancel M, Saraiya M, Crane L, Buller D, et al. Measures of sun exposure and sun protection practices for behavioral and epidemiologic research. Archives of dermatology 2008;144:217.
47. National HealthMedical Research Council (NHMRC). National Statement on Ethical Conduct in Research Involving Humans. 2007. URL: http://www.nhmrc.gov.au/book/national-statement-ethical-conduct-human-research [accessed 2016-04-07] [WebCite Cache ID 6gbTFDE2p]
48. Lane TS, Armin J, Gordon JS. Online Recruitment Methods for Web-Based and Mobile Health Studies: A Review of the Literature. J Med Internet Res 2015;17:e183 [FREE Full text] [doi: 10.2196/jmir.4359] [Medline: 26202991]

Abbreviations

25 OHD: 25-hydroxyvitamin D
ANOVA: analysis of variance
ANZCTR: Australian New Zealand Clinical Trials Registry
DXA: dual energy x-ray absorptiometry
HREC: Human Research and Ethics Committee
ITT: intention to treat
LC-MS/MS: liquid chromatography-tandem mass spectrometry
NHMRC: National Health and Medical Research Council
PQCT: peripheral quantitative computed tomography
PICF: participant information and consent form
SMS: short message service
UV: ultraviolet

Edited by G Eysenbach; submitted 21.12.15; peer-reviewed by S Alley, E Nelson; comments to author 30.01.16; revised version received 09.03.16; accepted 18.03.16; published 10.05.16.

Please cite as:
Tabesh M, Garland SM, Gorelik A, Nankervis A, Maclean S, Callegari ET, Chang S, Heffernan K, Wark JD
Improving Vitamin D Status and Related Health in Young Women: The Safe-D study – Part B
JMIR Res Protoc 2016;5(2):e80
URL: http://www.researchprotocols.org/2016/2/e80/
doi:10.2196/resprot.5465
PMID:27166214

Protocol

A Multimodal mHealth Intervention (FeatForward) to Improve Physical Activity Behavior in Patients with High Cardiometabolic Risk Factors: Rationale and Protocol for a Randomized Controlled Trial

Stephen Agboola[1,2,3], MD MPH; Ramya Sita Palacholla[1,2,3], MD MPH; Amanda Centi[1], PhD; Joseph Kvedar[1,2,3], MD; Kamal Jethwani[1,2,3], MD MPH

[1]Center for Connected Health, Boston, MA, United States
[2]Massachusetts General Hospital, Boston, MA, United States
[3]Harvard Medical School, Boston, MA, United States

Corresponding Author:
Stephen Agboola, MD MPH
Center for Connected Health
25 New Chardon St
Boston, MA,
United States
Phone: 1 617 643 0291
Fax: 1 617 643 0291
Email: sagboola@partners.org

Abstract

Background: Physical inactivity is one of the leading risk factors contributing to the rising rates of chronic diseases and has been associated with deleterious health outcomes in patients with chronic disease conditions. We developed a mobile phone app, FeatForward, to increase the level of physical activity in patients with cardiometabolic risk (CMR) factors. This intervention is expected to result in an overall improvement in patient health outcomes.

Objective: The objective of this study is to evaluate the effect of a mobile phone–based app, FeatForward, on physical activity levels and other CMR factors in patients with chronic conditions.

Methods: The study will be implemented as a 2-arm randomized controlled trial with 300 adult patients with chronic conditions over a 6-month follow-up period. Participants will be assigned to either the intervention group receiving the FeatForward app and standard care versus a control group who will receive only usual care. The difference in physical activity levels between the control group and intervention group will be measured as the primary outcome. We will also evaluate the effect of this intervention on secondary measures including clinical outcome changes in global CMR factors (glycated hemoglobin, fasting blood glucose, blood pressure, waist circumference, Serum lipids, C-reactive protein), health-related quality of life, health care usage, including attendance of scheduled clinic visits and hospitalizations, usability, and satisfaction, participant engagement with the FeatForward app, physician engagement with physician portal, and willingness to engage in physical activity. Instruments that will be used in evaluating secondary outcomes include the Short-Form (SF)-12, app usability and satisfaction questionnaires, physician satisfaction questionnaire. The intention-to-treat approach will be used to evaluate outcomes. All outcomes will be measured longitudinally at baseline, midpoint (3 months), and 6 months. Our primary outcome, physical activity, will be assessed by mixed-model analysis of variance with intervention assignment as between-group factor and time as within-subject factor. A similar approach will be used to analyze continuous secondary outcomes while categorical outcomes will be analyzed by chi-square test.

Results: The study is still in progress and we hope to have the results by the end of 2016.

Conclusions: The mobile phone–based app, FeatForward, could lead to significant improvements in physical activity and other CMR factors in patients.

(JMIR Res Protoc 2016;5(2):e84) doi:10.2196/resprot.5489

KEYWORDS

mobile app; physical activity; randomized clinical trial; type 2 diabetes mellitus; exercise; cardiometabolic risk factors

Introduction

Background and Significance

Physical inactivity has been identified as one of the leading risk factors contributing to the rising rates of chronic diseases [1]. Current estimates suggest that over half (52%) of adults in the United States do not meet the recommended physical activity levels [2]. Physical inactivity is an important and well-established cardiometabolic risk (CMR) factor and it has been reported that individuals with chronic diseases such as diabetes are less likely to meet current physical activity guidelines compared with the general population [3]. A number of studies to date have also confirmed the dose-response protective effect of increasing physical activity on the development of diabetes and cardiovascular disease [4,5].

The majority of the worldwide population fails to reach the recommended ≥150 minutes per week of moderate intensity exercise with "lack of time" being the most highly cited barrier to participation in sufficient physical activity in addition to a lack of motivation [5]. There is evidence that encouraging people with recently diagnosed chronic diseases such as diabetes to increase their physical activity and decrease their sedentary time may have beneficial effects on several CMR factors [6]. Therefore, it would be beneficial to develop strategies that maximize exercise adaptation, support patient goals, and offer education on health benefits of regular exercise to such patient populations.

In 2013, a dynamic text messaging intervention, TextToMove (TTM), was designed with the goals of increasing physical activity in patients with type 2 diabetes mellitus (T2DM), improving self-management of the disease, and lowering glycated hemoglobin (HbA1c) concentrations [7]. The text message (short message service, SMS) intervention program comprised of three content categories: education, feedback, and motivation. As a text messaging program, TTM was successful. However, keeping in mind, the increasing adoption of smartphones and the capability for enhanced function, we developed a more dynamic and robust mobile app, FeatForward. Additionally, there is increasing evidence that the smartphone phenomenon is reducing, as opposed to exacerbating, disparities and that smartphones are helping to bridge the digital divide among socioeconomic groups [8,9]. Therefore, FeatForward affords us the opportunity to enhance the function of the previous intervention and also extend the reach to a wider pool of patients

Our primary goal is to help users increase their level of physical activity and improve their overall health outcomes. Therefore, we hypothesize those participants using FeatForward will be more physically active and will achieve greater improvements in their CMR factors than a usual care control group that will not use the app.

Specific Aims

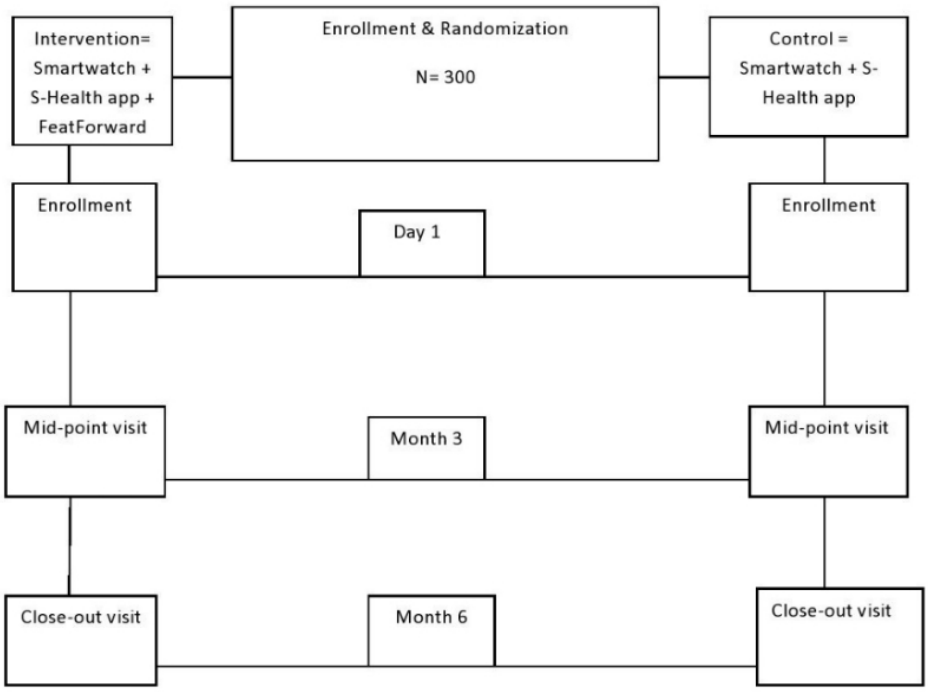
Our primary aim is to evaluate the effect of FeatForward on physical activity levels. Secondary outcomes to be assessed include evaluating the effects of FeatForward on: (1) clinical outcomes by measuring changes in global CMR factors (HbA1c, fasting blood glucose, blood pressure (BP), waist circumference (WC), serum lipids, C-reactive protein (CRP)), (2) health-related quality of life, (3) health care usage, including attendance of scheduled clinic visits and hospitalizations, (4) usability and satisfaction with FeatForward, (5) participant engagement with FeatForward, and (6) physician engagement with the FeatForward physician portal, (7) continuum of behavioral regulation in exercise.

Methods

Trial Design

The study will be implemented as a 2-arm randomized controlled trial (RCT) with repeated assessments at baseline, midpoint (3 months), and at the end of study (6 months). Figure 1 shows the research design.

Figure 1. Schematic summary of the trial design.



Participant Inclusion/ Exclusion Criteria

Patients must meet all eligibility requirements to be enrolled into the study. Eligible patients are aged 18 years or older with diagnosis of any of the following: prediabetes (HbA1c > 5.7% and body mass index (BMI) ≥ 25 kg/m^2), T2DM (HbA1c >7.0%), prehypertension (BP of 130/90 mm Hg and family history of high BP), hypertension (BP > 140/90), and/or obesity (BMI ≥ 30 kg/m^2). They must also be willing to attend all three study visits, able to read and speak fluent English, physically independent (ie, ability to walk without assistance), able to consent for oneself, willing to switch to a provided study smartphone and appropriate phone plan to use as their primary phone for the 6-month study duration, and willing to wear a study smartwatch during all hours excluding sleep for the duration of the study.

Ineligible patients will be defined as those who (1) have severe depression assessed by scoring ≥20 on the patient health questionnaire 8 (PHQ-8) screening questionnaire for depression, (2) have a self-reported eating disorder and/or other psychiatric disorders, (3) are currently or previously (within 3 months of enrollment) in a weight loss program, (4) had a prior or planned bariatric surgery procedure, (5) medications known to cause significant (≥5%) long-term changes in body weight or BP, (6) are pregnant or planning to get pregnant within 6 months of enrollment, (7) have a disability, dementia, or neurological deficits, and other medical or surgical conditions preventing them from engaging in self-care, (8) have serious comorbid conditions (eg, terminal cancers, end-stage renal disease) that preclude safe participation in moderate levels of physical activity, under discretion of the participants' primary care provider.

Recruitment Procedure

All male and female outpatients meeting the inclusion criteria will be recruited from a network of 20 primary care practices and community health centers associated with a large academic medical center in the greater Boston area. Study investigators will solicit the participation of primary care providers at these clinics and ask them to refer potentially eligible patients for the study. Potential participants undergo telephone prescreening by the study staff to ensure eligibility. This is done before any study procedure is conducted. The participants are enrolled formally only after signing the informed consent form at the enrollment visit. The participants are then asked to complete all enrollment surveys and undergo randomization procedures. All participants are typically advised to continue receiving routine medical care from physicians. Subjects in the intervention group will receive a smartphone with the FeatForward app to track physical activity and other biometric parameters, and a smartwatch. Participants in the control group will also receive a Smartphone with the sHealth app to track physical activity, and a smartwatch. All the subjects randomized to the intervention arm are taught how to use the functions of the application.

Intervention

In collaboration with industry partner (Samsung), Partners Connected Health Innovation designed a smartphone app, FeatForward, with input from clinicians, researchers, and dieticians to help users increase their physical activity levels and lead to improvements in CMR factors. The FeatForward intervention is designed to be hyperpersonalized to respond specifically to individual users' behavior patterns so that the app simulates an intelligent health coach partnering with users to achieve better health outcomes. The intervention also includes machine learning components for the messaging algorithm, tailoring of message frequency based on users' activity levels,

integrating patient data into the electronic medical record (EMR) through the remote monitoring data repository (our data storage infrastructure), inputs to improve the generalizability of feedback regarding health metrics (eg, weight, blood glucose), as well as a community feature to enable interactions with other similar participants and a comprehensive educational library.

Messaging

This features stage-specific messaging tailored to meet participants where they are in terms of their motivation level (as assessed by stage of change). While the content of the messages is tailored to a user's stage of change, the messaging frequency and timing is uniform; all users receive two messages per day and can customize timing of these messages. There are two types of messages: motivational messages encourage physical activity, and educational messages offering information about the users' specific medical conditions. A machine-learning algorithm will be used to select the best-fit message from a bank of messages stored in our database instead of sending random text messages that may or may not impact the participant's behavior. These messages were developed by a team of psychologists, clinicians, and behavioral therapists. The algorithm will use the baseline data collected from participants' at enrollment, phone usage information, and data input into app to deliver messages that are relevant to each participant. For example, if a user is meeting his/her goals on a daily basis, the program first encourages the user to set a more challenging goal. If the user then goes on to meet these new activity goals on a consistent basis, messaging responds by tailoring the content. In addition, the app algorithm is also designed to provide feedback that reflects the perceived barriers that are experienced by the user. In this way, the app mimics the role of an engaged health coach by actively monitoring and responding to the users' progress. For example, a motivational message sent to our participants could be "A journey of a thousand miles begins with a single step. All you need to do is take that first step."

Motivational messages are tailored to users based on their readiness to commit to behavior change. At registration, users complete a questionnaire based off of the Prochaska's (Transtheoretical) Stage of Change theory. Users are categorized into one of the five stages of change: precontemplation, contemplation, preparation, action, or maintenance depending on their response to this questionnaire. Users then only receive motivational messages corresponding to their specific stage of change. This helps to "meet users where they are" and maximize engagement. Every 2 weeks the app's algorithm reassesses the user's stage of change, based off of their weekly step totals. As users move throughout the stages (both forward and backward), their messages adapt appropriately. Motivational messages also feature questions and answers to maximize engagement.

Coaching

The types of messages received are also tailored to the user. Educational messages only cover the medical conditions the user reports at registration (including diabetes, prediabetes, hypertension, prehypertension, and obesity). Messages are divided into modules. For example, the diabetes-related message bank includes modules on the glycemic index, blood glucose, how exercise affects blood glucose levels, diabetes-related complications, and so on. Modules include 'quiz' messages where users are asked to answer questions on the information they've received. These quiz messages help to keep the user engaged.

Tracking

Users are able to track their physical activity levels. They can also monitor body weight, BP, blood glucose, and heart rate using a smartwatch.

Community

The Community feature was designed with the aim of further educating and motivating users. Through groups, users can encourage one another and share strategies and tips that will activate or motivate health behavior change. Additionally, users in the later stages of change (preparation, action, and maintenance) can view their progress compared with users like them (based off of age, gender, etc.). This friendly competition is designed to help encourage users.

Educational Library

All the participants need to have easy access to accurate disease-specific information to enable them to effectively self-manage their condition. Moreover, newly diagnosed patients can feel very emotional and overwhelmed as a result of being inundated with information regarding their new health condition. Many patients simply can't process or digest new information given their emotional state, and they often don't have the chance to review important information regarding their diagnosis with their physicians. Through the FeatForward app, users have unrestricted access to a comprehensive library with information regarding a wide array of topics that are relevant to their health condition.

Provider Engagement

The app syncs with a physician-facing portal that is accessible through the EMRs and includes the following additional functionalities: (1) physician access to details regarding patient activity levels and trends with optional activity reports (see Appendix 1), (2) physician ability to send self-created messages to patients through the provider portal, and (3) physician access to patient responses to messages. Not only can physicians be view patient step counts, they can also be able to send messages to individuals if they choose to do so. We believe that engaging physicians in FeatForward will also effectively engage participants and lead to improve health outcomes.

Depression Assessments

Because depression can impede behavior change, the app prompts users to complete the PHQ-8 on a monthly basis. Completing this survey is voluntary. If a participant chooses to complete the survey, the score will be updated in the EMR for their physician to review.

Screenshots of the FeatForward mobile intervention are shown in Figures 2 and 3. Figure 2 shows the homepage of the app and a sample of the educational messages. In Figure 3 , the additional features of the intervention are shown. These include push notifications, physical activity, and blood glucose tracking.

Figure 2. Overview of FeatForward homepage and sample message based on activity trends.

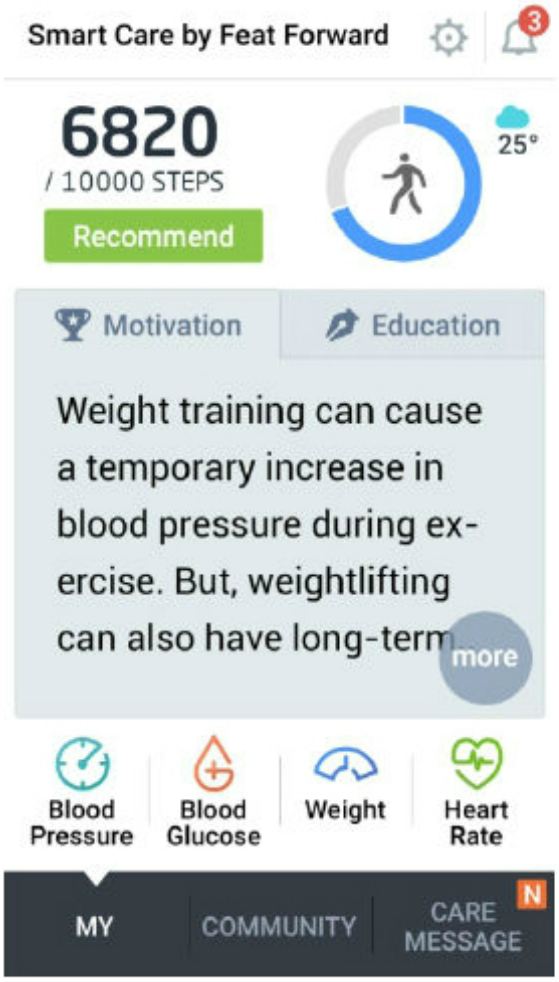
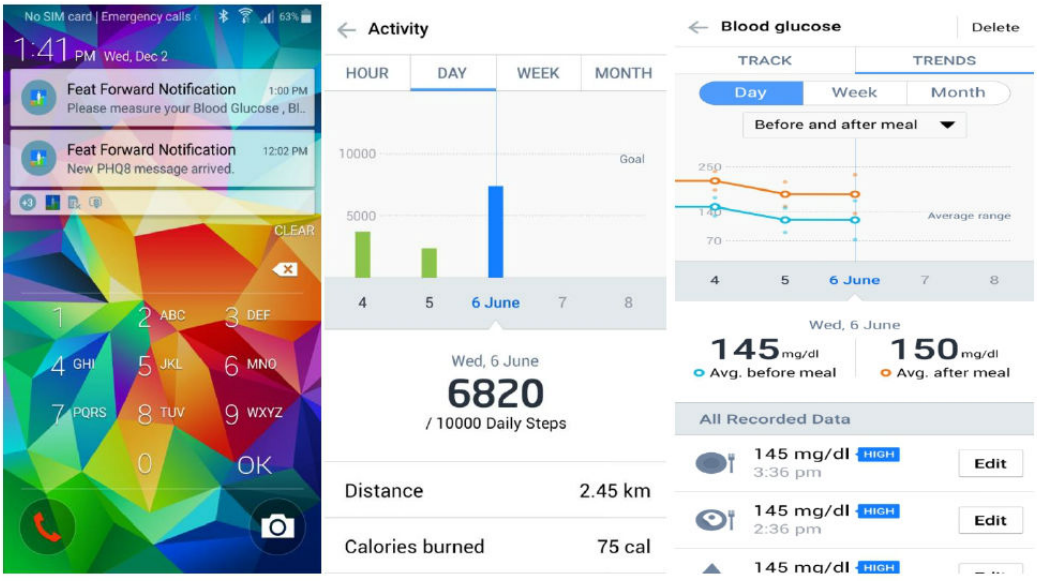


Figure 3. Intervention features (left to right): push notifications (reminders), physical activity tracking, and blood glucose tracking.



Outcomes Measurement

The difference in physical activity levels between the control group (smartphone with sHealth app, smartwatch, and routine medical care) and intervention group (smartphone with FeatForward app, smartwatch, routine medical care) will be measured as the primary outcome of interest for this study. The participants will track physical activity using the activity trackers provided.

All secondary outcomes will be assessed at enrollment, midpoint, and at the end of the study. Body weight is measured with participants dressed in light clothing and without shoes to the nearest 0.1 kg with a validated digital scale. Changes in global CMR factors are assessed in the following ways: measurement of fasting glucose level, HbA1c, and serum lipids will occur in a standard laboratory by fasting venous blood samples collected by at baseline, the midstudy visit, and at the final study visit. Phlebotomy is performed by research nurses who will adhere to standard institutional guidelines. Additionally, high sensitivity CRP is measured at the initial visit and final study visit. BP is measured by validated automated digital BP monitors and is performed by nurses who will adhere to standard BP measurement guidelines based on American Heart Association guidelines. At each visit, the participant's BP will be established by a minimum of two BP measurements taken at least 5 minutes apart, and the average of these readings will represent the participant's BP. If there is greater than 5 mm Hg difference between the first and second readings, an additional reading will be obtained, and then the average of these three readings will be used to represent the participant's BP. WC is measured at the midpoint between the iliac crest and the lowest rib. Two measurements are taken following expiration and the average of these readings will represent the participant's WC. If there is greater than 1-cm difference between the first and second measurements, an additional measurement will be obtained, and then the average of these three measurements is used to represent the participant's WC.

A clustered cardiometabolic risk (CCMR) score will be constructed by summing *z* scores (units of standard deviation (SD) from the population mean) of baseline values for WC, systolic blood pressure (SBP), fasting blood glucose, serum lipids, weight, HbA_{1c}, using sex-specific baseline means and SDs (CCMR = (value − mean)/SD), from which *z* scores of the follow-up variables will be computed. We will divide both the mean and SD by 6, separately, to account for the number of variables included. Change in the CCMR will be calculated by subtracting the follow-up CCMR from the baseline CCMR [10]. In addition, all the CMR factors will be evaluated individually to assess the effect of the app on each of the risk factors.

The health-related quality of life will be assessed using a validated questionnaire (short form (SF)-12). Health care usage will be assessed by emergency department visits, attendance of scheduled visits and inpatient hospitalizations. These usage data will be collected from the Partners Healthcare's Research Patient Data Registry (RPDR) at the end of the study. The RPDR is the centralized clinical data warehouse that operates under Partners Research Information Services. It securely stores all data from across Partners hospital systems in one place, and ensures security and confidentiality of patient information [11].

Usability and satisfaction will be assessed at close-out via questionnaires specifically designed for this project. Participant engagement will be measured via app usage data including overall frequency of use, frequently visited pages, time spent on these pages, responses to messages and user entries (weight, BP, glucose, heart rate). Lastly, physician engagement will be measured via time logged in the physician portal and questionnaire designed to measure portal satisfaction .

Data Collection

Users can able to track their physical activity levels, body weight, BP, blood glucose, and heart rate every day. In addition, data will be collected at various time-points (baseline, months 3 and 6) as described in Table 1. All anthropometric measurements, venous blood samples, and survey data are obtained in a standardized fashion by nurses/trained research assistants. This study uses several validated and study-specific instruments for data collection in person at enrollment, midpoint (month 3) and close-out (month 6): (1) the SF-12 instrument assesses the health-related quality of life [12], (2) the usability and satisfaction questionnaires designed specifically for this study (see Appendix 2) assess usability and satisfaction, (3) the PHQ 8 screens for depression that may impede behavioral change, (4) the app usage data will be used to measure participant engagement, (5) physician portal and questionnaire designed to measure portal satisfaction will be used to measure physician engagement with FeatForward: this via time logged in the questionnaire (Appendix 3), and (6) the Behavioral Regulation in Exercise Questionnaire to measure the continuum of behavioral regulation in exercise among users [13] . The PHQ-8 is administered via the FeatForward app on a monthly basis and all other questionnaires along with PHQ-8 will be administered at the three study visits (see Table 1). All data collected is stored in a secure electronic database (REDCap). REDCap is secure Web application for building and managing Web-based surveys and databases. While REDCap is specifically geared to support data capture for participant enrollment and study progress it can be used to collect other types of data during the course of this study. All paper documentation including the signed consent forms will be stored in a secure cabinet, and access will be available only to institutional review board (IRB) approved study staff.

Table 1. Data collection schedule: the table depicts the schedule for data collection.

Intervention/control group data collection	At entry	Monthly	3 months	6 months (close-out)	Every day
Physical activity					X
HbA1c	X		X	X	
Serum lipids	X		X	X	
Waist circumference	X		X	X	
Blood pressure	X		X	X	
C-reactive protein	X		X	X	
Patient health questionnaire 8	X	X	X	X	
Short form-12	X		X	X	
Usability and satisfaction questionnaire			X	X	
Physician engagement questionnaire			X	X	
Behavioral regulation in exercise questionnaire	X		X	X	

Statistical Analysis Plan

Sample Size Estimation

A total of 300 patients (150 participants per group) will be recruited for this study. There is an 80% probability that the study will detect a treatment difference at a two-sided 0.05 significance level, if the true difference in mean step counts between the control arm and the intervention arms is 1000 steps/day. This is based on the assumption that the SD of the response variable is 2750 and accounting for an attrition rate of 20%. Participants will be followed up for a total of 6 months.

Randomization

Following enrollment, participants will be randomized (via a computer program) to one of two groups (intervention or control) in a ratio of 1:1 (150 participants per group), using random permutated blocks to optimize balance in each treatment group at any given point in time during the study. Treatment assignment is concealed in sealed envelopes prepared by third party staff not directly involved in the study. Due to the nature of the intervention, it would be challenging to blind subjects as well as research assistants to treatment assignment but we will ensure that the data analyst(s) and study investigators will be blinded until the conclusion of the study by de-identifying all the participant data.

Analysis

Analysis will be done using the Data Analysis and Statistical Software: STATA, version 14 with an alpha of 0.05 set a priori. We will summarize the baseline data by group assignment using descriptive statistics: means and SD will be used for continuous data with normal distribution, medians, and interquartile range for skewed data, and percentages for categorical data. Our primary outcome, physical activity, measured longitudinally over 6 months, will be assessed by mixed-model analysis of variance with intervention assignment as between-group factor and time as within-subject factor. Continuous data will be compared between control and intervention groups using the *t* -test or the Wilcoxon Mann-Whitney test and the categorical variables will be compared using the chi-square test. All analyses will be based on intention-to-treat in all randomized patients.

Ethics and Informed Consent

Procedures of our methods have been reviewed and approved by the IRB and the study is registered at clinicaltrials.gov [NCT02551640]. The app is secure and complies with all Health Insurance Portability and Accountability Act Regulations requirements. Subjects will require a secure pass code to be able to access the app. However, if any data breach or adverse event occurs, the investigator will ensure that they are well-documented and reported according to the IRB's requirements, regardless of causality.

For those who attend the enrollment visit, a member of the research staff will review the informed consent form with them. Details of the study, including the purpose, procedures, and expected duration will be explained to the candidate participant. Study staff will clearly communicate that the participant's participation or nonparticipation will not affect their medical care, and that they have the right to withdraw from the study at any time. Candidate participants will be given an opportunity to ask questions about the study, and they will be informed of their right to withdraw from the study at any time. The candidate participant may then voluntarily sign and date the informed consent form, thereby providing study staff permission to enroll them in the study if they meet all inclusion criteria. If for any reason the candidate participant desires more time to consider the decision, they will be provided a copy of the unsigned consent form for reference and instructed to call the study phone number if they decide to participate in the study. All participants who sign the consent form and are screened will be documented on a screening log. All enrolled participants will be assigned a unique study identification number, and a note will be made in the source documentation verifying that the participant has willingly signed the consent form prior to participation in any study procedures in the enrollment log.

Results

The study is still in progress and we hope to have the results by the end of 2016.

Discussion

Trial Implications

The study examines how to creatively apply a mHealth technology to increase and maintain physical activity in patients with chronic diseases. Our expectation is that engaging patients to take charge of their health and empowering them with essential information will lead to improved health outcomes and quality of life. The FeatForward mobile app mimics a health coach to help engage users and increase their physical activity through education, tracking, feedback, and social network. The mobile app also features a physician-facing portal, which will serve as a channel of communication between the physicians and patients to improve the overall health outcomes.

Sedentary behavior and physical inactivity have been associated with increased risk for chronic diseases [1]. In addition to being the most common CMR, physical inactivity also happens to be the easiest to target [1]. A study by Lamb and colleagues [3] found that increasing the amount of time spent being physically active and decreasing the time spent sedentary may be an important strategy for self-management of chronic diseases such as diabetes early in the course of the disease. In recent times, several patient-centered interventions have been used to engage users and help them increase their level of physical activity, thereby improving the health outcomes over time. Such interventions use mobile apps and employ a range of features including providing feedback based on physical activity tracking, providing motivational messages, demonstrating the right way to exercise, setting and monitoring personalized goals, incorporating social media, and helping users schedule their exercise regimes [7].

A trial evaluating a mobile phone app, MyBehavior, designed to track physical activity and eating behavior data with personalized feedback demonstrated that the app was associated with increased physical activity [10]. Furthermore, a recent study by Block [14] used a fully automated, algorithm-driven behavioral intervention, Alive-PD, delivered via the Web, mobile phone, and automated phone calls for diabetes prevention. The intervention was associated with improved glycemic control, and decreased body weight, BMI, WC, triglycerides/high-density lippoproteins ratio, and diabetes risk [14].

While data demonstrating the positive impact of mobile health on clinical outcomes is growing, there is however mixed evidence of the impact of digital health technologies on health care costs. Results from a recent study by Bloss et al [15] concluded that there are no differences in health care costs or usage outcomes in patients using mHealth technologies for management of chronic diseases compared with a control group that received a standard disease management program [15]. Another study, a systematic literature review *of the cost-utility and cost-effectiveness of telemedicine and mHealth systems*, reported mixed effect that s *ome studies demonstrated that telemedicine can reduce the costs while some others showed no impact on the health care cost reduction [16]*. On the other hand, a meta-analysis of 11 randomized controlled trials including 5702 patients with heart failure showed that remote monitoring facilitated by electronic devices was associated with significant decreases in health care usage and costs [17]. With capabilities such as real-time remote monitoring of patients and data sharing with care providers, digital health technologies allow early intervention for high-risk patients in need of attention and thereby prevent unforeseen health care expenses [17]. Literature on cost effectivess of mHealth technologies is sparse and further research is warranted to demonstrate the impact of mHealth applications on cost and usage outcomes in the management ofchronic diseases.

The FeatForward app features a care provider portal integrated with the EMRs that allows physicians to monitor the patients' progress and intervene when appropriate. We believe that early intervention by care providers will lead to a decrease in the number of emergency department and unscheduled clinic visits, thereby decreasing health care costs in the long run. Furthermore, mHealth technologies foster patient engagement for self-care and enhance their knowledge about their conditions to help them make informed health care decisions. Thus, these informed patients have better outcomes than uninformed patients [16,18]. The FeatForward app provides participants with an unrestricted access to a comprehensive library with information regarding a wide range of topics that are relevant to their health. We believe that increasing participants' awareness of their conditions will help them better manage their illnesses and lead to improved outcomes.

Limitations

An important limitation is that the FeatForward app is designed to support only android devices for this trial. This is important because a sizeable proportion of the US population own Apple operating system (iOS) devices and this can potentially affect the study's accrual rates. While there is no robust data about the differences in demographics or the dynamics of user preferences of iOS versus Android users, early reports suggest that loyalty rates are usually high among users of either platform. Therefore, we speculate that some eligible iOS users may be reluctant to switch to Android for the duration of the study. Additionally, the impact of this limitation on the study's generalizability is yet to be determined but we do not envisage any significant differences in the demographics of people using either of the platforms. Despite these limitations, this study demonstrates the potential of using personalized messages and activity tracking to deliver a theory-driven intervention to users. As we move into a time where increasingly more people are employing technology to monitor their health, we believe that FeatForward holds great promise in increasing disease knowledge and improving health outcomes.

Conclusions

Given the high prevalence of physical inactivity and chronic diseases in today's society, findings from this study, may potentially help participants engage in healthier lifestyles and lead to decreased health care costs and improved patient health outcomes. Additionally, we hope that the research from our trial will generate data for large, multicenter trials on similar evidence-based approaches.

Acknowledgments

This trial is funded by Samsung Electronics, Co. Ltd.

Conflicts of Interest

The authors of this article designed FeatForward but are not responsible for the day-to-day running of the trial.

Multimedia Appendix 1

Physican Portal Sample Views.

[PDF File (Adobe PDF File), 126KB - resprot_v5i2e84_app1.pdf]

Multimedia Appendix 2

Usability Questionnaire.

[PDF File (Adobe PDF File), 30KB - resprot_v5i2e84_app2.pdf]

Multimedia Appendix 3

Physician Engagement Questionnaire.

[PDF File (Adobe PDF File), 30KB - resprot_v5i2e84_app3.pdf]

References

1. Centers for Disease ControlPrevention. Chronic Diseases and Health Promotion. 2015. URL: http://www.cdc.gov/chronicdisease/overview/index.htm [accessed 2015-12-30] [WebCite Cache ID 6eAUrdshv]
2. Centers for Disease ControlPrevention. Facts about Physical Activity. 2015. URL: http://www.cdc.gov/physicalactivity/data/facts.html [accessed 2015-12-30] [WebCite Cache ID 6eAVKROgY]
3. Lamb MJE, Westgate K, Brage S, Ekelund U, Long GH, Griffin SJ, et al. Prospective associations between sedentary time, physical activity, fitness and cardiometabolic risk factors in people with type 2 diabetes. Diabetologia 2016;59:110-120 [FREE Full text] [doi: 10.1007/s00125-015-3756-8] [Medline: 26518682]
4. Kelley D, Goodpaster BH. Effects of exercise on glucose homeostasis in Type 2 diabetes mellitus. Med Sci Sports Exerc 2001;33(6 Suppl):S495-S501; discussion S528. [Medline: 11427776]
5. Kohl HW. Physical activity and cardiovascular disease: evidence for a dose response. Med Sci Sports Exerc 2001;33(6 Suppl):S472-S483; discussion S493. [Medline: 11427773]
6. Shepherd SO, Wilson OJ, Taylor AS, Thøgersen-Ntoumani C, Adlan AM, Wagenmakers AJM, et al. Low-volume high-intensity interval training in a gym setting improves cardio-metabolic and psychological health. PLoS One 2015;10:e0139056. [doi: 10.1371/journal.pone.0139056]
7. Agboola S, Lopez L, O'Keefe S, Kvedar J, Jethwani K. TEXT TO MOVE – randomized controlled trial of personalized text messaging to improve physical activity in a diverse patient population with type 2 diabetes mellitus. J Mob Tech ed 2013;2:8. [doi: 10.7309/jmtm.2.4S.6]
8. Zonderman AB, Ejiogu N, Norbeck J, Evans MK. The influence of health disparities on targeting cancer prevention efforts. Am J Prev Med 2014;46(3 Suppl 1):S87-S97 [FREE Full text] [doi: 10.1016/j.amepre.2013.10.026] [Medline: 24512936]
9. Bert F, Giacometti M, Gualano MR, Siliquini R. Smartphones and health promotion: a review of the evidence. J Med Syst 2014;38:9995. [doi: 10.1007/s10916-013-9995-7] [Medline: 24346929]
10. Bailey DP, Boddy LM, Savory LA, Denton SJ, Kerr CJ. Associations between cardiorespiratory fitness, physical activity and clustered cardiometabolic risk in children and adolescents: the HAPPY study. Eur J Pediatr 2012;171:1317-1323. [doi: 10.1007/s00431-012-1719-3]
11. Nalichowski R, Keogh D, Chueh HC, Murphy SN. Calculating the Benefits of a Research Patient Data Repository. 2006 Presented at: AMIA Annu Symp Proc; 2006; Washington D.C p. 1044.
12. Ware JE, Kosinski M, Turner-Bowker DM, Gandek B. How to score version 2 of the SF-12 health survey (with a supplement documenting version 1). QualityMetric Incorporated 2002.
13. Gunnell KE. Validity theory and validity evidence for scores derived from the behavioural regulation in exercise questionnaire. In: Wilson PM, Zumbo BD, Crocker PR, MaCK DE, Schellenberg BJ, editors. Validity and Validation in Social, Behavioral, and Health SciencesSpringer International Publishing. Switzerland: Springer International Publishing; 2014:175-191.
14. Block G, Azar KM, Romanelli RJ, Block TJ, Hopkins D, Carpenter HA, et al. Diabetes Prevention and Weight Loss with a Fully Automated Behavioral Intervention by Email, Web, and Mobile Phone: A Randomized Controlled Trial Among Persons with Prediabetes. J Med Internet Res 2015;17:e240 [FREE Full text] [doi: 10.2196/jmir.4897] [Medline: 26499966]

15. Bloss CS, Wineinger NE, Peters M, Boeldt DL, Ariniello L, Kim JY, et al. A prospective randomized trial examining health care utilization in individuals using multiple smartphone-enabled biosensors. URL: https://peerj.com/articles/1554/ [accessed 2016-04-19] [WebCite Cache ID 6gtEQiQJc]
16. de la Torre-Díez I, López-Coronado M, Vaca C, Aguado JS, de Castro V. Cost-utility and cost-effectiveness studies of telemedicine, electronic, and mobile health systems in the literature: a systematic review. Telemed J E Health 2015;21:81-85 [FREE Full text] [doi: 10.1089/tmj.2014.0053] [Medline: 25474190]
17. Popescu GH. The economic implications of ehealth and mhealth technologies. Am J Med Research Oct 2014;1:31.
18. Steinhubl SR, Muse ED, Topol EJ. Can mobile health technologies transform health care? JAMA 2013;310:2395-2396. [doi: 10.1001/jama.2013.281078] [Medline: 24158428]

Abbreviations

BMI: body mass index
BP: blood pressure
CCMR: clustered cardiometabolic risk score
CMR: cardiometabolic risk factor
CRP: C-reactive protein
EMR: electronic medical record
HbA1c: glycated hemoglobin
iOS: Apple operating system
IRB: institutional review board
RCT: randomized controlled trial
RPDR: research patient data registry
LMR: longitudinal medical record
PHQ-8: patient health questionnaire 8
SBP: systolic blood pressure
SD: standard deviation
SF-12: short form 12
SMS: short message service
T2DM: type 2 diabetes mellitus
TTM: TextToMove
WC: waist circumference

Edited by G Eysenbach; submitted 04.01.16; peer-reviewed by J Long; comments to author 30.01.16; revised version received 19.02.16; accepted 20.02.16; published 12.05.16.

Please cite as:
Agboola S, Palacholla RS, Centi A, Kvedar J, Jethwani K
A Multimodal mHealth Intervention (FeatForward) to Improve Physical Activity Behavior in Patients with High Cardiometabolic Risk Factors: Rationale and Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2016;5(2):e84
URL: http://www.researchprotocols.org/2016/2/e84/
doi:10.2196/resprot.5489
PMID:27174783

Original Paper

Organizational-Level Strategies With or Without an Activity Tracker to Reduce Office Workers' Sitting Time: Rationale and Study Design of a Pilot Cluster-Randomized Trial

Charlotte L Brakenridge[1], BPsySc (hons); Brianna S Fjeldsoe[1], PhD; Duncan C Young[2], BBuild; Elisabeth A H Winkler[1], PhD; David W Dunstan[1,3,4,5,6,7,8], PhD; Leon M Straker[9], PhD; Christian J Brakenridge[1], BClinExPhys (hons); Genevieve N Healy[1,3,9], PhD

[1]The University of Queensland, School of Public Health, Brisbane, Australia

[2]Lendlease, Sydney, Australia

[3]Baker IDI Heart and Diabetes Institute, Melbourne, Australia

[4]School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia

[5]School of Exercise and Nutrition Sciences, Deakin University, Melbourne, Australia

[6]Department of Medicine, Monash University, Melbourne, Australia

[7]School of Sport Science, Exercise and Health, The University of Western Australia, Perth, Australia

[8]Mary MacKillop Institute for Health Research, Australian Catholic University, Melbourne, Australia

[9]School of Physiotherapy and Exercise Science, Curtin University, Perth, Australia

Corresponding Author:
Charlotte L Brakenridge, BPsySc (hons)
The University of Queensland
School of Public Health
Level 4, Public Health Building, Herston Rd
Brisbane, 4006
Australia
Phone: 61 0733655163
Fax: 61 0733655540
Email: c.brakenridge@uq.edu.au

Abstract

Background: The office workplace is a key setting in which to address excessive sitting time and inadequate physical activity. One major influence on workplace sitting is the organizational environment. However, the impact of organizational-level strategies on individual level activity change is unknown. Further, the emergence of sophisticated, consumer-targeted wearable activity trackers that facilitate real-time self-monitoring of activity, may be a useful adjunct to support organizational-level strategies, but to date have received little evaluation in this workplace setting.

Objective: The aim of this study is to evaluate the feasibility, acceptability, and effectiveness of organizational-level strategies with or without an activity tracker on sitting, standing, and stepping in office workers in the short (3 months, primary aim) and long-term (12 months, secondary aim).

Methods: This study is a pilot, cluster-randomized trial (with work teams as the unit of clustering) of two interventions in office workers: organizational-level support strategies (eg, visible management support, emails) or organizational-level strategies plus the use of a waist-worn activity tracker (the LUMOback) that enables self-monitoring of sitting, standing, and stepping time and enables users to set sitting and posture alerts. The key intervention message is to 'Stand Up, Sit Less, and Move More.' Intervention elements will be implemented from within the organization by the Head of Workplace Wellbeing. Participants will be recruited via email and enrolled face-to-face. Assessments will occur at baseline, 3, and 12 months. Time spent sitting, sitting in prolonged (≥30 minute) bouts, standing, and stepping during work hours and across the day will be measured with activPAL3 activity monitors (7 days, 24 hours/day protocol), with total sitting time and sitting time during work hours the primary outcomes. Web-based questionnaires, LUMOback recorded data, telephone interviews, and focus groups will measure the feasibility and acceptability of both interventions and potential predictors of behavior change.

Results: Baseline and follow-up data collection has finished. Results are expected in 2016.

Conclusions: This pilot, cluster-randomized trial will evaluate the feasibility, acceptability, and effectiveness of two interventions targeting reductions in sitting and increases in standing and stepping in office workers. Few studies have evaluated these intervention strategies and this study has the potential to contribute both short and long-term findings.

(JMIR Res Protoc 2016;5(2):e73) doi:10.2196/resprot.5438

KEYWORDS

wearable device; self-monitoring; sedentary lifestyle; office workers; light intensity activity; ecological model; workplace; trial; objective; activity monitor

Introduction

Background

The workplace is a key health promotion setting [1,2], with now extensive evidence demonstrating the effectiveness of interventions targeting physical activity in this environment [3]. Generally, physical activity programs in workplaces have had a beneficial impact on health risk biomarkers, work attendance, and job stress [3]. However, a common criticism has been that workplace physical activity interventions typically only reach those who are already fit and motivated to be active [4], and have had negligible impact on reductions in sitting [5,6]. These two issues may be addressed through a shift in focus to organization-wide interventions that have the potential to reach a greater proportion of employees than conventional individually centered approaches, and to interventions that target change across the activity spectrum including: sedentary time (sitting or lying with low energy expenditure, ≤1.5 metabolic equivalents (METS) [7]); light intensity activities (such as standing or incidental movement, >1.5 to <3 METS [8]); as well as moderate- and vigorous-intensity physical activities (MVPA, ≥3 to <9 METS [8]).

Sedentary and light intensity behaviors occupy much of the waking day [8], more than 95% on average in adults. The distribution of time spent between these two behaviors is increasingly being recognized as having potentially important implications for health and well-being [9,10]. Higher levels of light intensity activity are associated with improved blood glucose levels [11], physical health and well-being [12], and decreased depression [13]. Although several behaviors fall within the light intensity spectrum, there is preliminary evidence to suggest that even just postural shifts to standing could have some metabolic benefit [14,15]. In contrast, high levels of daily sitting time have been detrimentally associated with outcomes such as all-cause mortality, cardiovascular disease incidence and mortality, type 2 diabetes incidence [16,17], and cancer incidence and mortality [17], as well as risk indicators for these [18]. In addition, there is growing evidence suggesting that the manner in which sitting is accumulated may be important, with more breaks (or interruptions: either with activity or standing) in sedentary time showing beneficial associations with cardiometabolic indicators including waist circumference [15,19,20], blood glucose [15,19-22], insulin [21,22], and triglycerides [15,18-20].

Sitting in the Workplace

For office workers, workplace sedentary time is a large contributor to overall sedentary time [23,24], with studies showing that office workers spend, on average, three-quarters of their work hours sitting [23-27]. Given this pervasive nature of sitting in the office, and that office workers are the largest individual occupational sector [28], the office workplace has been identified as a key setting to target reductions in sitting time [29].

Office workers generally have the advantage of being colocated, which means a wide range of influences can be targeted within intervention approaches. Based on workplace health promotion frameworks [1,30] and behavioral models for understanding sitting and activity [31,32], common influences are organizational, environmental, and individual factors, with the notion that individual-level strategies alone are unlikely to be sufficient for sustained behavior change [32]. Organizational-level strategies are seen as particularly important for program implementation [33], to change the culture of an organization [30,34], and for programs to be institutionalized into the organization and sustained [30]. Key organizational-level strategies include having management support for programs [33,34] and implementing the program from within the organization via dedicated onsite staff or workplace ‘champions’ [35].

Despite these frameworks, workplace interventions targeting MVPA have typically targeted the individual and not the organizational- or environmental-level influences [36,37]. Similarly, there have been very few studies that have implemented organizational-level strategies in workplace sitting interventions. The studies that have addressed the organizational level have done so in combination with individual-level strategies (eg, health coaching) and/or physical environment (eg, sit-stand workstation) strategies [27,38-41]. Findings from these multicomponent interventions have shown significant and large reductions in sitting both at the workplace (eg, −125 minutes/8-hour workday [38], −89 minutes/8-hour workday [39]) and across the whole day (eg, −66 minutes/day [40]). While organizational elements were reported as important in these studies [38,39], and a lack of management support reported as a key issue for those studies that have reported less success [27,41], no study to date has identified how much change results from the organizational-level component alone. If found to be effective, an added benefit of this organizational-level approach is that the intervention elements are minimal both in terms of cost and employee burden, which may be beneficial for organizations that have limited employee time or funds.

Activity Trackers as Intervention Tools

While organizational-level strategies may be sufficient on their own, it is also important to consider individualized elements to

possibly enhance the success of the intervention. Evidence suggests that individual, self-monitoring devices such as pedometers are a common element of successful workplace physical activity interventions [36,42] that can increase activity [43-48] and decrease sedentary time [43,44]. Recent advances in technology have seen the emergence of more sophisticated wearable activity trackers that go beyond just simple step counting to incorporate many of the strategies known to support behavior change [49]. Such strategies, including the provision of detailed, real-time feedback, long-term tracking, prompts, and goal setting, as well as the measurement of multiple behaviors, give activity trackers the potential to be effective behavior intervention tools [49,50]. Indeed, their potential as low-cost behavior change support tools has been recognized by several workplace wellness programs in the United States, where activity trackers are distributed to encourage employees to get healthy and reduce their insurance premiums [51,52].

There has been minimal research on the feasibility, acceptability, and effectiveness of activity trackers as intervention tools. A recent review highlighted the large heterogeneity in the small field of research studies and the mixed quality of the research [53]. However, there was some indication that activity trackers may lead to pre-post physical activity increases and are feasible to wear [53]. There was, however, very limited evidence for long-term physical activity increases [53]. In fact, only four studies out of the 11 in the review evaluated long-term outcomes (≥6 months), with only one study resulting in a significant change in physical activity [53]. There is even less evidence supporting the use of activity trackers to target sitting and standing: the activities that are most common in the office workplace setting [38,39]. As recently highlighted in a review [6], interventions that focus on increasing only physical activity do not necessarily result in changes in sitting; likewise, activity trackers that focus on steps and activity may not necessarily elicit changes in sitting time.

As such, the current study will pilot a waist-worn activity tracker (the LUMOback) that measures and notifies wearers of their sitting time, and also measures activities across the spectrum including number of steps and time spent standing, walking, and running [54]. Given the importance of organizational-level strategies [1,30], and the evidence suggesting self-monitoring tools are effective with additional strategies [42,53,55], the activity tracker will be implemented in conjunction with organizational-level support strategies. To evaluate whether the intervention strategies can also be sustained long-term, assessments will occur in the short (3 months) and long-term (12 months).

Aims

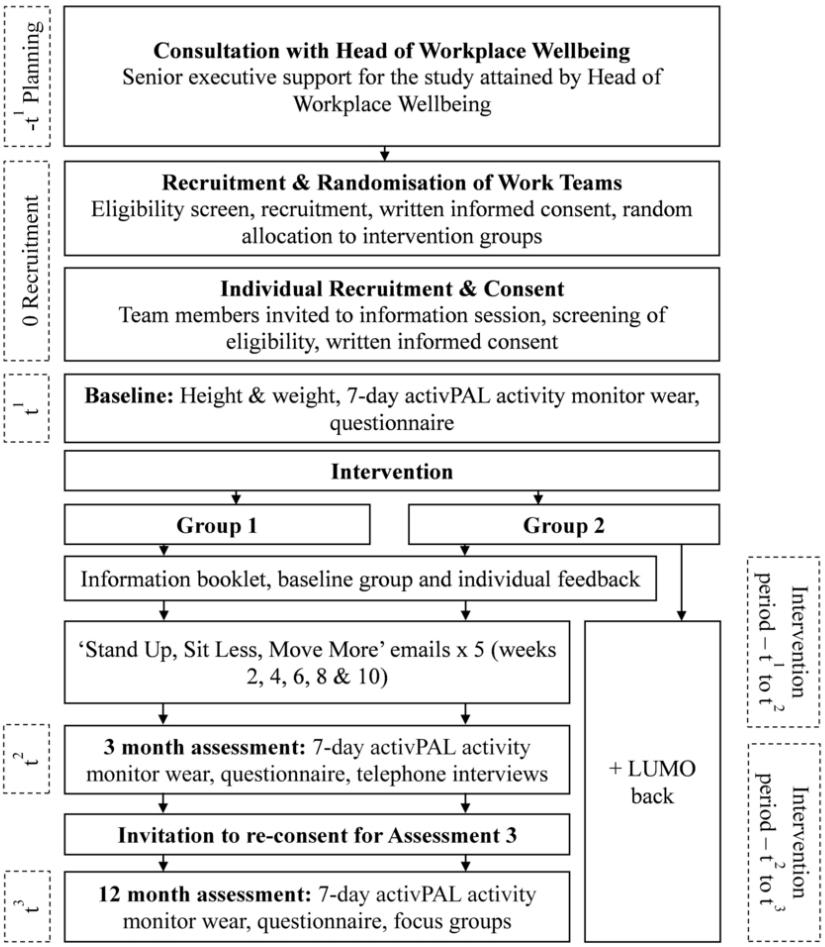
The primary aims of this pilot study are to assess two interventions (organizational-level strategies only; organizational-level strategies plus an activity tracker) in office workers regarding their feasibility, acceptability, and short-term (3 month) effectiveness for sitting reduction. The primary effectiveness outcomes are sitting time at work and overall. Secondary aims are to examine the short-term effectiveness of the interventions for other activities, and health- and work-related outcomes; the relative effectiveness of the two interventions for changes in sitting time and other activities; predictors of changes in sitting and activity; and the long-term (12 month) feasibility, acceptability, and effectiveness of the interventions.

Methods

Design

A cluster-randomized design will be used, with data collection occurring at baseline, 3, and 12 months (see Figure 1). The cluster-randomized design (with work teams as the unit of clustering) was chosen to minimize contamination among participants from the two intervention groups. The trial has been approved by the University of Queensland Behavioural and Social Sciences Ethical Review Committee (approval number: 2014000089) and is prospectively registered with the Australian New Zealand Clinical Trials Registry [registration number: ACTRN12614000252617].

Figure 1. Overview of study design, consent processes, intervention, and assessment elements.



Participants

Participants will be office workers, recruited from work teams from two Australian capital cities (~1000-km apart) within the one organization, Lendlease, an international property and infrastructure group. Inclusion criteria are office-based workers, working at least 0.6 full-time equivalent (ie, at least 60% of full-time work hours) and ambulatory (able to walk at least 10 meters). Exclusion criteria are pregnancy at baseline, allergies to adhesive tape (Opsite and Hypafix required for assessments), and a planned absence from work for longer than 2 weeks during the first 3-month study period. Employees who have their own activity-permissive workstation at the baseline assessment will also be ineligible.

Recruitment

Recruitment of Organization

The study liaison and workplace champion for the trial will be the Lendlease Head of Workplace Wellbeing (DCY). The workplace champion, located in Sydney (site A), will work in partnership with the research team to tailor the intervention to Lendlease and to create strong buy-in from senior management. Project staff will be based in Brisbane (site B).

Recruitment of Managers and Teams

Workplace teams (typically with 10-15 individuals in each team) will be selected from site A and site B by the workplace champion. Teams will be defined as having a line manager, being physically colocated, and having regular group meetings. Eligible teams will need to be desk-based and have a sufficient number of team members with access to a Bluetooth-enabled mobile phone required for the activity tracker to function. Team managers will be approached by the workplace champion for their consent.

Recruitment of Participants

Once the team manager has consented, the workplace champion will email individual team members the information sheet detailing the study and the required level of commitment, along with the consent form. Teams randomized to receive the activity tracker will receive additional details regarding the LUMOback. Interested team members will be invited to attend a face-to-face information session where they will have their eligibility assessed by project staff, and then be invited to sign the consent

form and proceed to the baseline assessment. Initial consent will only be for baseline and 3-month assessments; participants will be invited to reconsent for the 12-month assessment (see Figure 1).

Randomization

Following manager consent, and prior to the information session, each team will be numbered randomly, using a random number generator, and then listed in numeric order. Teams will then be randomized to either Group 1 (organizational-level strategies only) or Group 2 (organizational-level strategies plus activity tracker), across location strata (site A and B) and team size strata within site A (small/large) using a randomization website [56]. The randomization schedule will be created by a university staff member not involved in the study. A project staff member will then apply the randomization schedule to the list of teams. Neither project staff nor participants will be blinded to participants' randomization condition.

Organizational-Level Intervention

All participants will receive the organizational-support intervention elements, which are based on the *Stand Up Australia* intervention [57]. The key intervention message is 'Stand Up, Sit Less, Move More' [57], which encourages staff to interrupt sitting at least every 30 minutes with a change in posture; replace sitting with standing or moving (working toward having equal amounts of sitting and upright activities in the day); increase physical activity of any intensity level; and to make these changes across the whole day, both during and outside of work hours.

Information Booklet and Participant Feedback

All participants will receive a booklet from the workplace champion, developed by the research team and customized to Lendlease's branding and corporate style requirements. The booklet will cover the study rationale (ie, evidence on prolonged sitting and detrimental health outcomes) and purpose; general guidelines on optimal workplace activity; behavior change strategies related to the key intervention messages; and general information about the study procedure and timeline. All participants will also receive a summary email from the workplace champion of the aggregate results from the baseline assessment regarding sitting, standing and stepping, as well as individual feedback on sitting, standing and stepping time after each of the assessment points (to be emailed individually by project staff; adapted from a previous study [39]).

Stand Up, Sit Less, Move More Emails

The workplace champion will create five emails in consultation with project staff (adapted from a previous study [58]). One email will be sent every 2 weeks during the initial 3-month intervention period. The emails will consist of a 'tip of the week,' a study update from the workplace champion, a quote from a participant and/or manager, and an infographic or a picture of Lendlease staff engaging in the 'Stand Up, Sit Less, Move More' message. Project staff will be included on the emails to enable tracking of email content for process evaluation. While the emails will cease after week 10, it is expected that team managers will continue to implement the strategies promoted in the emails with their team throughout the rest of the 12-month intervention period.

Executive Management Support

In addition to the staff, managers and senior managers participating in the trial, senior global executives (eg, Chief Executive Officer) will also take part in the baseline assessment and will receive the information booklet and 'Stand Up, Sit Less, Move More' emails. The participation of the global executives, which demonstrates visible support for the intervention, will be communicated to staff by the workplace champion.

Activity Tracker

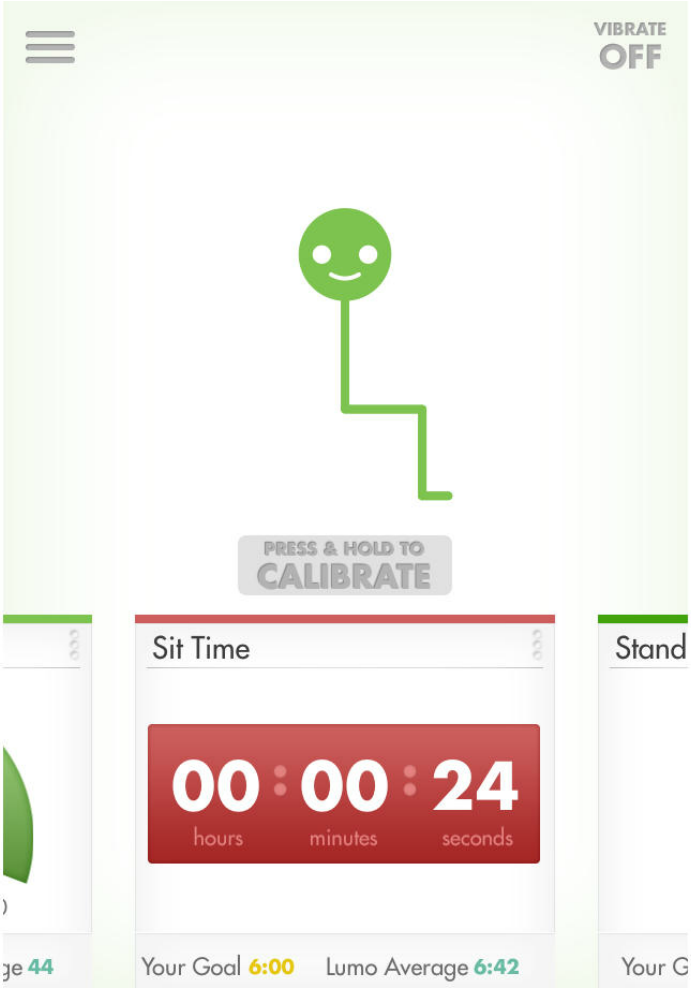
Participants in Group 2 will be given the LUMOback activity tracker in addition to the organizational-level strategies. The LUMOback is worn around the waist as a belt, collecting information, and providing real-time feedback on sitting, standing, stepping, breaks from sitting, posture, and sleep. The LUMOback assesses activity by inertial sensors, which collect data at a constant 25 Hz [59], and is controlled through a mobile app via a Bluetooth connection that can be used by both iPhone operating system and Android platforms. Up to 3 weeks of data can be collected by the LUMOback before it must be synced with the app, with data transferred between the LUMOback and the app at 600 bytes/second. In the app, participants can view graphs, averages, and goals related to their sitting, standing, stepping, sitting breaks, posture (represented by an avatar, see Figure 2), and sleep. The device can monitor behavior, track attainment of the wearer's goals, and provide real-time feedback. Participants can use the app to select the LUMOback to vibrate when they are sitting or standing in a 'poor' lumbar posture as identified by pelvic tilt angle [59], and to send a push notification to their mobile phone when they have been sitting too long. Vibrations can be chosen to be more or less intense, more or less exact about posture, or turned off; sitting notifications can be selected to range in time between 15 minutes and 2 hours of sitting, or turned off. The app also contains many learning videos about maintaining a good posture.

The LUMOback shows strong correlations and good agreement, in free-living conditions, with measures from the activPAL activity monitor in total time spent sitting (R^2=0.89 [60]; mean absolute percent error (MAPE)=9.5% [61]), standing (R^2=0.86 [60]), and number of steps (MAPE=0.4%, intraclass correlation coefficient (ICC)=0.99 [62]). In laboratory conditions, the LUMOback shows excellent agreement in step counts when tested against the Optogait treadmill test (MAPE=0.2%, ICC=0.99 [62]).

A LUMOback and a four-page instruction booklet that covers an introduction to the device, set-up instructions, and frequently asked questions will be distributed to Group 2 participants by the workplace champion following baseline assessments. On receipt of the device, participants will be asked to download the free app and sync the LUMOback with their phone. Participants will be asked to use their work email to set up their device as this will later be used to request the data from the company LUMO Bodytech. Participants can wear the device as much or as little as they like and their self-directed usage

will be tracked. However, participants will be instructed by project staff to wear their LUMOback during the 3-month assessment period both to gather validity data and to estimate the intervention effectiveness while wearing the LUMOback. Participants will be allowed to keep the LUMOback.

Figure 2. Representation of the LUMOback avatar while seated in a good posture.



Data Collection

Data collection will occur at baseline, 3, and 12 months, and has been approved by the organization to occur during work hours. At each assessment, participants will be asked to wear an activPAL3 activity monitor continuously (24 hours/day) for 7 days, and to complete a concurrent electronic work and sleep diary. They will also be emailed a link to a Web-based questionnaire, using LimeService [63] covering demographic information (baseline assessment only), health- and work-related information (all assessments), and feasibility and acceptability (3- and 12-month assessments). Height and weight will be measured by a trained Lendlease staff member (site A) or project staff member (site B) during a face-to-face baseline assessment session that is expected to take approximately 15 minutes.

Individual qualitative interviews on the feasibility and acceptability of both of the interventions will occur following the 3-month assessment via telephone. Focus groups covering the long-term feasibility and acceptability of the interventions will be conducted as part of the 12-month assessment. Project staff will request LUMOback usage data from Lumo Bodytech every 2 weeks during the initial 3-month intervention period and then periodically throughout the rest of the study.

Measures

An overview of the study feasibility, acceptability, and effectiveness outcome measures is provided in Table 1. In addition, a range of measures covering demographics, job, and health characteristics, psychosocial variables and technology confidence will also be collected.

Feasibility

Feasibility information will be examined in terms of participation, retention rates, and intervention delivery indicators, including the number of emails received (for the organizational intervention) and the degree of usage of the LUMOback activity tracker and app (assessed from the device and self-report). Ease of LUMOback data download and amount of lost or missing LUMOback data will also be evaluated. Table 1 displays an overview of the feasibility indicators and Multimedia Appendix 1 contains the questionnaire items created for the study.

The LUMOback data will be used to determine number of days, hours, and peak levels of usage. The data is expressed as a percentage of a 5-minute window spent in each activity type (sitting and standing in a good or bad posture, lying, sitting in

a car, walking, and running), and step counts, calorie counts, and not worn/charging. No data is recorded over periods the device self-registers as off.

Telephone interviews and focus groups will be used to further evaluate both organizational support and LUMOback intervention strategies. Telephone interviews will identify: strategies implemented by the managers and organization; key facilitators and barriers of the intervention (including those specific to the LUMOback); and, any organizational culture changes that occurred (see Multimedia Appendix 2 for questions). Focus groups will discuss the impact of the interventions on the workplace culture and environment, long-term barriers and facilitators of the intervention strategies, and will identify any other key themes (see Multimedia Appendix 3).

Acceptability

Participants will be asked via questionnaire to rate how useful the emails and tips were, their satisfaction with the emails and information, and if they had experienced any discomfort or injury as a result of their study participation. Participants who indicate they have used a LUMOback device will also be asked to rate their comfort, ease of use, and perceived usefulness of the LUMOback (see Multimedia Appendix 1 for full list of questionnaire items). Participants who indicate they were given a LUMOback (whether they wore it or not) will also be asked would they recommend the LUMOback to a friend, how likely they were to use the LUMOback in the next 6 months, did they have any adverse experiences from using the LUMOback, and if they had any comments about the LUMOback or app. A shorter questionnaire at 12-month follow-up (to reduce participant burden and maintain compliance) will collect information relating to long-term LUMOback usage, adverse experiences, and comments. Telephone interviews and focus groups will also assess the acceptability of both interventions over the short and long-term (see Multimedia Appendices 2 and for questions).

Effectiveness

Activity Outcomes

The activPAL3 activity monitor will be used to measure the primary and secondary activity outcomes. The activPAL is a small device worn on the thigh (53×35×7 mm; 15 g). It has excellent interdevice reliability (ICC=0.79-0.99 [64]). It shows excellent validity relative to direct observation in measuring sitting/lying, hereafter termed 'sitting,' standing, and stepping, and for alterations between sitting and upright posture [64-66]. The activPAL has also shown responsiveness to change in sitting [66]. Correlations with direct observation of total time spent sitting, standing, and stepping, and total number of postural transitions are close to 1, mean differences reported are small and nonsignificant (eg, sitting and breaks measures all <2% bias) [65]. The agreement with direct observation of activity classification (sitting, standing, or stepping) moment by moment is also excellent (eg, 98.5% correct in a controlled setting, 93.6% correct during activities of daily living) [64]. Also, participants cannot extract activity data (real-time or otherwise) from the activPAL3, limiting reactivity.

The primary activity outcomes are time spent sitting at work and time spent sitting overall (ie, across all waking hours on work and nonwork days). The other activity outcomes relating to the 'Stand Up, Sit Less, Move More' message are listed in Table 1. In line with the exploratory nature of the pilot study, a range of other sedentary and physical activity measures (eg, usual sitting bout duration, number of steps) will be assessed and reported in addition to the study outcomes.

Health Outcomes

Physical and mental health-related quality of life [67] will be measured by the Short Form (SF)-12 version 1 at each assessment. The SF-12 correlates highly with the SF-36 (r=0.95 and 0.97) and has good test-retest scores (r=0.89 and 0.76) for the physical and mental components respectively [67]. Overall stress will be measured at each assessment by one item from the Health and Work Questionnaire [68].

Work Outcomes

Work-related outcomes will be measured via questionnaire at all assessments. These are work performance [69] and two measures from the Health and Work Questionnaire [68]: work satisfaction (four items, with α for internal consistency=0.84), and job control (one item).

Table 1. Overview of study outcomes.

Measurement tools	Outcomes
Feasibility	
Organizational support questionnaire items	Number of emails received
	What participants did with email (eg, read then delete)
	Perceived level of support to 'Stand Up, Sit Less and Move More' from (1) organization, (2) main manager, and (3) colleagues
LUMOback questionnaire items	Ever used (eg, yes, given but never used, no)
	Date of first use
	Setting of use (eg, workplace)
	Frequency of recalibration, app checking, goal checking, vibration and sitting alerts
LUMOback data	Days of usage
	Hours of usage/day
	Peak levels of usage
	Ease of data download
	Amount of missing data
Telephone interviews	Strategies implemented by manager and organization, organizational culture change, key elements of intervention, barriers of wearing the LUMOback at work and at home
Focus groups	Long term sustainability of changes, barriers and facilitators, key themes
Acceptability	
Organizational support questionnaire items	Usefulness of emails and tips
	Satisfaction with emails and information received
	Adverse experiences from program in general
LUMOback questionnaire items	Comfort of LUMOback
	Ease of set up of LUMOback and app, navigating app, calibrating LUMOback
	Usefulness of LUMOback and app
	Likelihood of using LUMOback in next 6 months, adverse experiences from LUMOback, comments about the LUMOback
Telephone interviews	Acceptability of program, acceptability of the LUMOback
Focus groups	Acceptability of program, acceptability of long-term LUMOback wear
Effectiveness	
Activity	
activPAL	Stand up: standing time at work and overall
	Sit less: sitting time at work and overall (primary effectiveness outcomes); prolonged (>=30 mins) sitting time at work and overall
	Move more: stepping time at work and overall
Health	
SF-12 v1	Physical and Mental health-related quality of life
Health and Work Questionnaire	Overall stress
Work	
Work performance rating scale	Work performance
Health and Work Questionnaire	Work satisfaction, job control

Demographics and Job Characteristics

Height and weight will be measured with shoes removed using a stadiometer (to the nearest 0.1 cm) and calibrated electronic scales (to the nearest 0.1 kg) at baseline only. Similarly, participants will be asked at baseline only their age, gender, Aboriginal or Torres Strait Islander status, highest level of education completed, and length of time at the workplace. Pregnancy status will be measured at 3- and 12-month follow-ups only, while current smoking status and smoking while at work will be measured at each assessment.

Full-time equivalence, job category, and percent of work time spent at desk, away from desk, and outside the workplace [58] will be measured at all assessments. Frequency and duration of working with colleagues [58] will be assessed at baseline and 3-month follow-up only. At 3- and 12-month follow-ups, workplace location will be assessed to account for any office relocations. Data on team location and team size will be collected by project staff at baseline.

Other Measures

Several additional individual, work, health, and intervention factors will be assessed to explore whether they predict changes in sitting and activity, and for consideration as potential confounders for relative effectiveness. The additional individual factors to be assessed include: confidence with technology and use of any other apps or wearable devices to help increase activity (see Multimedia Appendix 1), as well as psychosocial measures such as preference for sitting and standing at work, and knowledge of the health impacts of sitting [58]. These psychosocial variables have been derived from previous *Stand Up Australia* research [58], have moderate to good test-retest reliability (Spearman's ρ=0.67-0.78) [38,58], and will be assessed at baseline and 3-month follow-up only. The additional health-related factors include perceived stress and musculoskeletal health. Specifically, at baseline and 3-month assessments only, perceived stress will be measured using the 4-item version of the Perceived Stress Scale [70]. The 4-item Perceived Stress Scale has good internal consistency (α=0.82) and correlates moderately with the Impact of Event Scale (r=0.58), 12-item Posttraumatic Stress-Arousal Scale (r=0.70), and the mental health component of the Medical outcomes Scale-SF 36 (r=0.70) [71]. Musculoskeletal health will be measured at each assessment using a modified 36-item version of the Nordic Musculoskeletal Questionnaire [72]. Modifications are that items will refer to the last 1 month (instead of 12 months) [73] and items will be added to assess how intense the pain was in the body part in the last 1 month (on a 0-9 scale, where 0 means no complaints and 9 means pain as bad as it can be) for those who indicated that they experienced a problem [74] (questions can be found in Multimedia Appendix 1). Work factors such as perception of supervisor relations (two items from the Health and Work Questionnaire [68], with α for internal consistency=0.85) will be measured at each assessment. Use of workplace strategies to sit less and move more (adapted from *Stand Up Australia* [58], full list of questions Multimedia Appendix 1) will be measured at all three assessments. Self-report activity will also be collected via the Occupational Sitting and Physical Activity Questionnaire (OSPAQ) [75]. Assessment of sitting using the OSPAQ correlates moderately with accelerometer (Actigraph GT1M) measured sedentary time (Spearman ρ=0.65) [75].

Assessment Procedures

activPAL Procedure

At baseline, the activPAL monitors and required adhesive materials (several Hypafix patches and alcohol swabs) will be provided to participants during a face-to-face assessment session. An in-person demonstration will be given at this session on how to wear the device (ie, on the dominant thigh on the midline, approximately one-third of the way down between the hip and the knee, attached using hypoallergenic adhesive material (Hypafix)). Participants will be asked to wear the monitor for seven consecutive days, 24 hours per day, removing only in circumstances during which the monitor is likely to be lost or damaged, but not for routine showering/bathing or swimming, as monitors will be waterproofed (with latex finger cots and hypoallergenic Opsite). Instructions will also be sent by email. Participants not able to attend the face-to-face baseline assessment session will receive an activPAL from the workplace champion after the session. At follow-up assessments, the activPALs will be distributed to participants by the workplace champion (site A) and either the workplace champion or by project staff to participants at site B. Site A participants will be instructed to return their monitor in sealed packs to the workplace champion, who will post these packs to project staff for download and processing. Site B assessment packs will be collected in person by project staff.

Concurrent diaries, covering waking hours, periods wearing/removing the activPAL, work days and times that are similar to previous paper-based versions [39,58] will be piloted in electronic forms (via LimeService and via a macroenabled excel-based file), with paper versions provided as an alternative option for those experiencing any difficulties with the electronic versions. The diary for Group 2 participants at 3-month follow-up will also cover LUMOback wear/removals, frequency of checking the LUMOback app, usage, and setting type of the vibrations and sitting time alerts, and usage of goal setting over the 7-day assessment period. Participants who do not complete all aspects of their diary will be recontacted to provide further details.

activPAL Data Processing

The measures for activity overall and activity during work hours will be extracted from the events-based activPAL data using procedures similar to a previous study [58] via a customized SAS program (version ≥9.3). Activity recorded by the activPAL during relevant periods (eg, working, awake, and wearing the monitor) will be ascertained from a combination of the diary information and the participant's movement as recorded by the activPAL. When wear/waking hours are not reported, these will be inferred from the movement data. Bouts of activity will be assigned the classification (eg, awake/not, working/not) that applies to most (≥50%) of the bout. Sleeping periods will be adjusted to exclude any short bouts (<20 minutes duration) at the beginning or end of the sleeping period. Studies use a variety of definitions for 'valid' days of activPAL data [76]. Days will

be considered valid for activity at work if the activPAL was worn for ≥80% of the time at work; entire waking days will be considered valid for activity if the activPAL is worn for ≥80% of waking hours and for ≥10 hours if waking hours are inferred from the activPAL rather than reported by the participant. Time spent in each activity will be calculated for each day then averaged over the valid days. Information about duration of bouts of activity (eg, usual sitting bout duration) will be calculated across all of the relevant time periods on valid days.

Quality control checks will be performed both prior to processing for the diary (missing information, nonconsecutive dates, activities finishing prior to starting, short waking days <10 hours), and postprocessing. The processed data will be checked visually (heatmaps) to verify the activity patterns were consistent with the classifications of the data as included (waking wear on valid days) or excluded (removal, sleep, or invalid days) and data will be reprocessed when errors are identified.

Questionnaire Procedure

At baseline, 3-, and 12-month assessments participants will be emailed a link to a Web-based questionnaire (LimeService) by project staff after they have finished wearing the activPAL. At baseline, questionnaires are to be completed before the intervention begins. At all stages, participants will be provided with the opportunity to opt out of the questionnaire.

Qualitative Interview and Focus Group Procedures

Semistructured telephone interviews will be conducted at the 3-month assessment. Attempts will be made to contact all participants in Group 2, with a similar number of participants recruited from Group 1, sampling purposively for diversity, starting with the two most disparate team members per team on age, gender, job category, and sitting time change. All team managers will also be approached for a telephone interview. All interviews will include questions to evaluate the organizational support intervention; Group 2 interviews will also assess the LUMOback. Interviews will be recorded using Audacity (version 2.0.6) and transcribed verbatim with idiosyncratic elements of speech removed. All participants who remain in the study at 12-month follow-up will be invited to take part in focus group interviews, which will be capped at 10 participants each. Participants will be offered a chance to win an activity tracker (single prize; randomized prize draw; value ~AU$500) for participating in the focus groups. Focus group interviews will be audio-recorded and transcribed.

Sample Size

For this pilot study, the sample size was selected based on what the workplace deemed feasible (18 teams). With a usual team size of 10 to 15, and two-thirds expected to be eligible and participate (just over eight per team), we anticipate approximately 150 participants in total, with 75 randomized to each group. This sample size will provide adequate power (≥80% power) with 5% two-tailed significance, to detect short term (3 month) changes within groups (primary effectiveness aim) of our minimum difference of interest (MDI) in our primary outcomes of work and overall sitting time (see Table 2). All calculations are based on no multiple comparison adjustment to significance (in line with the exploratory nature of the study), an anticipated 30% attrition, and strong clustering (ICC=0.1) [58] with an anticipated design effect of 1.48 (ie, 1+0.1×4.83, with an average 5.83 participants per team). Under these same assumptions, power to detect changes equal to the MDIs for the secondary activity outcomes with 5% two-tailed significance are presented in Table 2 , along with the minimum detectable differences (MDDs) between groups for relative effectiveness (secondary aim). This pilot did not power a priori on other research questions, such as health outcomes and long-term changes (12 months). The MDIs and MDDs all reflected modest effects for activity. The assumptions regarding standard deviations (SD), pre-post correlations and clustering were informed by published and unpublished data from previous workplace interventions [38,58] and Australian population data from the AusDiab study.

Table 2. Power to detect changes within groups (effectiveness) and minimum detectable differences between groups (relative effectiveness) with 5% significance, two-tailed.

Outcome	MDI[a]	Assumed values		Effectiveness	Relative effectiveness
		SD[b,c]	Pre-post r[c]	Power	MDD[d]
Primary outcomes					
Work sitting time	45 minutes	90	0.6	90%	50 minutes
Overall sitting time	45 minutes	90	0.6	90%	50 minutes
Secondary outcomes					
Work prolonged sitting time	45 minutes	120	0.6	67%	65 minutes
Overall prolonged sitting time	45 minutes	120	0.6	67%	65 minutes
Work standing time	30 minutes	70	0.6	79%	35 minutes
Overall standing time	30 minutes	70	0.6	79%	35 minutes
Work stepping time	15 minutes	20	0.7	>99%	10 minutes
Overall stepping time	15 minutes	30	0.7	96%	15 minutes

[a]minimum difference of interest.

[b]standard deviation.

[c]assumed values based on unpublished data from the *Stand Up Victoria* trial

[d]minimum detectable difference with 80% power

Statistical Analyses

Statistical analyses will be conducted in SPSS Statistics version ≥22 and Stata version ≥13 with statistical significance set at P <.05, two-tailed. Within-group changes in activity, work and health outcomes (continuous) will be assessed, using linear mixed-models that account for repeated measures and clustering, to determine the effectiveness of each intervention for these outcomes in the short- and long-term. To compare the relative effectiveness of the combined organizational-level and activity tracker intervention to organizational support alone, mixed-models will be used, adjusting for baseline values and potential confounders; these address both repeated measures and clustering. Confounders will initially be chosen a priori from the literature and retained in models if they are associated with the outcome at P <.2. Models will be checked for linearity, normality, and heteroscedasticity. Analyses will follow intention-to-treat principles. Per-protocol analyses will also be conducted to evaluate what the efficacy of the intervention is specifically for those who use the activity tracker, because activity tracker usage is self-directed. Assumptions regarding missing data will be checked and sensitivity analyses will be conducted to evaluate the impact of missing data on findings. Predictors of changes in activity will be evaluated by linear regression, adjusting for baseline values, and correcting for clustering. Predictors will be considered separately and also mutually adjusted. Characteristics of individuals will be considered as potential predictors including demographics (eg, age), psychosocial (eg, preference for sitting at work), health (eg, musculoskeletal problems) and work-related characteristics (eg, perception of relationship with supervisor), and engagement with the intervention (eg, LUMOback usage).

Feasibility and Acceptability

Feasibility and acceptability data acquired by questionnaire, LUMOback data, and participation and retention rates will be reported using descriptive statistics. Content analyses in NVivo (version 10) will be conducted with the telephone interviews to derive reception toward both interventions, barriers and facilitators, and any other themes. Data from the focus groups will be thematically analyzed by two independent authors and discussed with a third author. Any discrepancies in themes will be discussed until consensus is reached.

Results

Baseline and follow up data collection has finished. Results are expected in 2016.

Discussion

This paper describes the background, design, and methods of a pilot, cluster-randomized trial that will compare two interventions, one that targets organizational-level strategies and another that targets organizational-level strategies plus the use of a wearable activity tracker, the LUMOback, in office workers. The study will determine if either intervention can produce changes in sitting (during all waking hours and work hours), as well as prolonged sitting, standing, and stepping in the short (3 month) and long-term (12 month), as well as the feasibility and acceptability of each intervention. The impact of each intervention on health- and work-related outcomes, and the predictors of sitting and activity change will also be examined. In addition, the study will provide preliminary evidence regarding the additional impact of the LUMOback on sitting and activity compared with organizational-level strategies alone.

The interventions in this study are designed to be easily disseminated on a large scale. Specifically, the intervention elements will come from the Head of Workplace Wellbeing, making the implementation of the intervention similar to that which may realistically occur in office workplaces. The intervention messages are delivered via a low cost, feasible mechanism (emails), with the LUMOback device also being relatively low cost, and comparable in price with other popular fitness trackers on the market (~US$150). Another strength of the intervention is that support and participation will come from multiple levels of the organization (ie, general staff, managers, senior global executives). In addition, sitting, standing and stepping will be measured at and away from the workplace, with a validated and objective measure. Many workplace studies have only measured workplace activity, and have often not used objective, posture-based measures.

Methodological Considerations

Because we will work in partnership with the organization, it will not be possible to recruit a control group who will not receive the organizational intervention. As such, the effectiveness of each intervention can only be evaluated as per a single-group pre–post design. Accordingly, effectiveness findings will be considered in light of the usual findings within other studies' control groups. For example, in prior *Stand Up Australia* research [38,39], there were no significant changes in sitting, standing, and stepping within control groups. Another consideration is contamination. Despite randomization occurring at the team level to reduce contamination, we will not know in advance the degree of interaction between the teams, and therefore the extent to which the participants randomized to Group 1 may receive visual cues to stand up by witnessing LUMOback wearers (Group 2) arise in response to device prompting. Focus groups will attempt to evaluate if any potential contamination occurred. In addition, another consideration is that the Head of Workplace Wellbeing will select the teams for participation. While this is not inconsistent with what might realistically occur in office wellness programs, it may introduce some selection bias, which may limit the generalizability of the results.

Conclusions

The interventions evaluated in this study have the potential to decrease sitting and increase standing and stepping in the office workplace. There has been minimal evaluation of organizational-level strategies alone, and whether these strategies can impact on sitting and activity behaviors when delivered as part of a worksite driven, 'real-world' intervention. Furthermore, there is minimal evidence on the feasibility, acceptability, and effectiveness of activity trackers for use in office workers and their effectiveness for reducing sitting and increasing standing and stepping. Despite the detrimental effects of sitting, very few activity trackers measure or target this behavior. If effective, the findings from this research may prompt developers to include sitting measures and prompts in their activity trackers. While only a pilot, this study aims to address these gaps and will provide information to guide future physical activity and sedentary behavior interventions and workplace health promotion programs.

Acknowledgments

This work is supported by a Vanguard Grant (Award ID: 100216) from the National Heart Foundation of Australia. The authors would also like to acknowledge Lendlease for providing additional support for this work and for the Office Ergonomics Research Committee (OERC) for providing funding to conduct the 12-month follow-up. The National Health and Medical Research Council (NHMRC) of Australia through a Centre of Research Excellence Grant (#1057608) to GNH and DWD, provides salary support to EAHW, and a top up scholarship to CLB. CLB is also supported by an Australian Postgraduate Award. DWD is supported by an NHMRC Senior Research Fellowship (#1078360). LMS is supported by an NHMRC Australia Senior Research Fellowship (#1019980). GNH is supported by a Heart Foundation Postdoctoral Fellowship (#PH 12B 7054) and NHMRC Career Development Fellowship (#108029).

Authors' Contributions

CLB participated in the design and lead the coordination of the study, and drafted the manuscript. BSF, EAHW, DWD, and LMS participated in the design of the study and helped draft the manuscript. DCY and CJB participated in the design and coordination of the study. GNH conceived the study, participated in the design and helped draft the manuscript. All authors contributed to, read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Questionnaire items created or modified for study.

[PDF File (Adobe PDF File), 71KB - resprot_v5i2e73_app1.pdf]

Multimedia Appendix 2

Telephone interview questions.

[PDF File (Adobe PDF File), 50KB - resprot_v5i2e73_app2.pdf]

Multimedia Appendix 3

Focus group questions.

[PDF File (Adobe PDF File), 42KB - resprot_v5i2e73_app3.pdf]

References

1. Burton J. World Health Organization. 2010. WHO Healthy Workplace Framework and Model: Background and Supporting Literature and Practices URL: http://www.who.int/occupational_health/healthy_workplace_framework.pdf [accessed 2015-04-01] [WebCite Cache ID 6dl9FXWNM]
2. Goetzel RZ, Ozminkowski RJ. The health and cost benefits of work site health-promotion programs. Annu Rev Public Health 2008;29:303-323. [doi: 10.1146/annurev.publhealth.29.020907.090930] [Medline: 18173386]
3. Conn VS, Hafdahl AR, Cooper PS, Brown LM, Lusk SL. Meta-analysis of workplace physical activity interventions. Am J Prev Med 2009;37:330-339 [FREE Full text] [doi: 10.1016/j.amepre.2009.06.008] [Medline: 19765506]
4. Marshall AL. Challenges and opportunities for promoting physical activity in the workplace. J Sci Med Sport 2004;7(1 Suppl):60-66. [Medline: 15214603]
5. Chau JY, van der Ploeg HP, van Uffelen JGZ, Wong J, Riphagen I, Healy GN, et al. Are workplace interventions to reduce sitting effective? A systematic review. Prev Med 2010;51:352-356. [doi: 10.1016/j.ypmed.2010.08.012] [Medline: 20801153]
6. Martin A, Fitzsimons C, Jepson R, Saunders DH, van der Ploeg HP, Teixeira PJ, EuroFIT consortium. Interventions with potential to reduce sedentary time in adults: systematic review and meta-analysis. Br J Sports Med 2015;49:1056-1063. [doi: 10.1136/bjsports-2014-094524] [Medline: 25907181]
7. Sedentary Behaviour Research Network. Letter to the editor: standardized use of the terms "sedentary" and "sedentary behaviours". Appl Physiol Nutr Metab 2012;37:540-542. [doi: 10.1139/h2012-024] [Medline: 22540258]
8. Norton K, Norton L, Sadgrove D. Position statement on physical activity and exercise intensity terminology. J Sci Med Sport 2010;13:496-502. [doi: 10.1016/j.jsams.2009.09.008] [Medline: 20005170]
9. Hamilton MT, Healy GN, Dunstan DW, Zderic TW, Owen N. Too little exercise and too much sitting: inactivity physiology and the need for new recommendations on sedentary behavior. Curr Cardiovasc Risk Rep 2008;2:292-298 [FREE Full text] [doi: 10.1007/s12170-008-0054-8] [Medline: 22905272]
10. Straker L, Healy GN, Atherton R, Dunstan DW. Excessive occupational sitting is not a "safe system of work": time for doctors to get chatting with patients. Med J Aust 2014;201:138-140. [Medline: 25128944]
11. Healy GN, Dunstan DW, Salmon J, Cerin E, Shaw JE, Zimmet PZ, et al. Objectively measured light-intensity physical activity is independently associated with 2-h plasma glucose. Diabetes Care 2007;30:1384-1389. [doi: 10.2337/dc07-0114] [Medline: 17473059]
12. Buman MP, Hekler EB, Haskell WL, Pruitt L, Conway TL, Cain KL, et al. Objective light-intensity physical activity associations with rated health in older adults. Am J Epidemiol 2010;172:1155-1165 [FREE Full text] [doi: 10.1093/aje/kwq249] [Medline: 20843864]
13. Loprinzi PD. Objectively measured light and moderate-to-vigorous physical activity is associated with lower depression levels among older US adults. Aging Ment Health 2013;17:801-805. [doi: 10.1080/13607863.2013.801066] [Medline: 23731057]
14. Thorp AA, Kingwell BA, English C, Hammond L, Sethi P, Owen N, et al. Alternating sitting and standing increases the workplace energy expenditure of overweight adults. J Phys Act Health 2016;13:24-29. [doi: 10.1123/jpah.2014-0420] [Medline: 25872228]
15. Healy GN, Winkler EAH, Owen N, Anuradha S, Dunstan DW. Replacing sitting time with standing or stepping: associations with cardio-metabolic risk biomarkers. Eur Heart J 2015;36:2643-2649. [doi: 10.1093/eurheartj/ehv308] [Medline: 26228867]
16. Wilmot EG, Edwardson CL, Achana FA, Davies MJ, Gorely T, Gray LJ, et al. Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis. Diabetologia 2012;55:2895-2905. [doi: 10.1007/s00125-012-2677-z] [Medline: 22890825]
17. Biswas A, Oh PI, Faulkner GE, Bajaj RR, Silver MA, Mitchell MS, et al. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. Ann Intern Med 2015;162:123-132. [doi: 10.7326/M14-1651] [Medline: 25599350]
18. Brocklebank LA, Falconer CL, Page AS, Perry R, Cooper AR. Accelerometer-measured sedentary time and cardiometabolic biomarkers: A systematic review. Prev Med 2015;76:92-102 [FREE Full text] [doi: 10.1016/j.ypmed.2015.04.013] [Medline: 25913420]
19. Healy GN, Dunstan DW, Salmon J, Cerin E, Shaw JE, Zimmet PZ, et al. Breaks in sedentary time: beneficial associations with metabolic risk. Diabetes Care 2008;31:661-666. [doi: 10.2337/dc07-2046] [Medline: 18252901]

20. Healy GN, Matthews CE, Dunstan DW, Winkler EAH, Owen N. Sedentary time and cardio-metabolic biomarkers in US adults: NHANES 2003-06. Eur Heart J 2011;32:590-597 [FREE Full text] [doi: 10.1093/eurheartj/ehq451] [Medline: 21224291]
21. Dunstan DW, Kingwell BA, Larsen R, Healy GN, Cerin E, Hamilton MT, et al. Breaking up prolonged sitting reduces postprandial glucose and insulin responses. Diabetes Care 2012;35:976-983 [FREE Full text] [doi: 10.2337/dc11-1931] [Medline: 22374636]
22. Peddie MC, Bone JL, Rehrer NJ, Skeaff CM, Gray AR, Perry TL. Breaking prolonged sitting reduces postprandial glycemia in healthy, normal-weight adults: a randomized crossover trial. Am J Clin Nutr 2013;98:358-366 [FREE Full text] [doi: 10.3945/ajcn.112.051763] [Medline: 23803893]
23. Parry S, Straker L. The contribution of office work to sedentary behaviour associated risk. BMC Public Health 2013;13:296 [FREE Full text] [doi: 10.1186/1471-2458-13-296] [Medline: 23557495]
24. Clemes SA, O'Connell SE, Edwardson CL. Office workers' objectively measured sedentary behavior and physical activity during and outside working hours. J Occup Environ Med 2014;56:298-303. [doi: 10.1097/JOM.0000000000000101] [Medline: 24603203]
25. Thorp AA, Healy GN, Winkler E, Clark BK, Gardiner PA, Owen N, et al. Prolonged sedentary time and physical activity in workplace and non-work contexts: a cross-sectional study of office, customer service and call centre employees. Int J Behav Nutr Phys Act 2012;9:128 [FREE Full text] [doi: 10.1186/1479-5868-9-128] [Medline: 23101767]
26. Ryan CG, Dall PM, Granat MH, Grant PM. Sitting patterns at work: objective measurement of adherence to current recommendations. Ergonomics 2011;54:531-538. [doi: 10.1080/00140139.2011.570458]
27. Parry S, Straker L, Gilson ND, Smith AJ. Participatory workplace interventions can reduce sedentary time for office workers--a randomised controlled trial. PLoS One 2013;8:e78957 [FREE Full text] [doi: 10.1371/journal.pone.0078957] [Medline: 24265734]
28. U.S. Bureau of Labor Statistics. 2015. Occupational Employment and Wages — May 2014 URL: http://www.bls.gov/news.release/pdf/ocwage.pdf [accessed 2015-06-30] [WebCite Cache ID 6dl2aEYXS]
29. Healy G, Lawler S, Thorp A, Neuhaus M, Robson E, Owen N, et al. VicHealth. 2012. Reducing Prolonged Sitting in the Workplace URL: https://www.vichealth.vic.gov.au/media-and-resources/publications/creating_healthy_workplaces [accessed 2015-01-13] [WebCite Cache ID 6dl3KZZDS]
30. McLeroy KR, Bibeau D, Steckler A, Glanz K. An ecological perspective on health promotion programs. Health Educ Q 1988;15:351-377. [Medline: 3068205]
31. Owen N, Sugiyama T, Eakin EE, Gardiner PA, Tremblay MS, Sallis JF. Adults' sedentary behavior determinants and interventions. Am J Prev Med 2011;41:189-196. [doi: 10.1016/j.amepre.2011.05.013] [Medline: 21767727]
32. Sallis JF, Cervero RB, Ascher W, Henderson KA, Kraft MK, Kerr J. An ecological approach to creating active living communities. Annu Rev Public Health 2006;27:297-322. [doi: 10.1146/annurev.publhealth.27.021405.102100] [Medline: 16533119]
33. Wierenga D, Engbers LH, Van EP, Duijts S, Hildebrandt VH, Van MW. What is actually measured in process evaluations for worksite health promotion programs: a systematic review. BMC Public Health 2013;13:1190 [FREE Full text] [doi: 10.1186/1471-2458-13-1190] [Medline: 24341605]
34. Aldana SG, Anderson DR, Adams TB, Whitmer RW, Merrill RM, George V, et al. A review of the knowledge base on healthy worksite culture. J Occup Environ Med 2012;54:414-419. [doi: 10.1097/JOM.0b013e31824be25f] [Medline: 22446571]
35. Pronk N. Best practice design principles of worksite health and wellness programs. ACSM's Health & Fitness Journal 2014;18:42-46.
36. To QG, Chen TTL, Magnussen CG, To KG. Workplace physical activity interventions: a systematic review. Am J Health Promot 2013;27:e113-e123. [doi: 10.4278/ajhp.120425-LIT-222] [Medline: 23631453]
37. Harden A, Peersman G, Oliver S, Mauthner M, Oakley A. A systematic review of the effectiveness of health promotion interventions in the workplace. Occup Med (Lond) 1999;49:540-548 [FREE Full text] [Medline: 10658308]
38. Healy GN, Eakin EG, Lamontagne AD, Owen N, Winkler EAH, Wiesner G, et al. Reducing sitting time in office workers: short-term efficacy of a multicomponent intervention. Prev Med 2013;57:43-48. [doi: 10.1016/j.ypmed.2013.04.004] [Medline: 23597658]
39. Neuhaus M, Healy GN, Dunstan DW, Owen N, Eakin EG. Workplace sitting and height-adjustable workstations: a randomized controlled trial. Am J Prev Med 2014;46:30-40. [doi: 10.1016/j.amepre.2013.09.009] [Medline: 24355669]
40. Pronk NP, Katz AS, Lowry M, Payfer JR. Reducing occupational sitting time and improving worker health: the Take-a-Stand Project, 2011. Prev Chronic Dis 2012;9:E154 [FREE Full text] [doi: 10.5888/pcd9110323] [Medline: 23057991]
41. Verweij LM, Proper KI, Leffelaar ER, Weel ANH, Nauta AP, Hulshof CTJ, et al. Barriers and facilitators to implementation of an occupational health guideline aimed at preventing weight gain among employees in the Netherlands. J Occup Environ Med 2012;54:954-960. [doi: 10.1097/JOM.0b013e3182511c9f] [Medline: 22850353]
42. Dugdill L, Brettle A, Hulme C, McCluskey S, Long A. Workplace physical activity interventions: a systematic review. Intl J of Workplace Health Mgt 2008;1:20-40. [doi: 10.1108/17538350810865578]

43. Macniven R, Engelen L, Kacen MJ, Bauman A. Does a corporate worksite physical activity program reach those who are inactive? Findings from an evaluation of the Global Corporate Challenge. Health Promot J Austr 2015;26:142-145. [doi: 10.1071/HE14033] [Medline: 25917174]
44. Freak-Poli R, Wolfe R, Backholer K, de Courten M, Peeters A. Impact of a pedometer-based workplace health program on cardiovascular and diabetes risk profile. Prev Med 2011;53:162-171. [doi: 10.1016/j.ypmed.2011.06.005] [Medline: 21762721]
45. Ribeiro MA, Martins MA, Carvalho CR. Interventions to increase physical activity in middle-age women at the workplace: a randomized controlled trial. Med Sci Sports Exerc 2014;46:1008-1015. [doi: 10.1249/MSS.0000000000000190] [Medline: 24126967]
46. Gilson ND, Faulkner G, Murphy MH, Meyer MR, Washington T, Ryde GC, et al. Walk@Work: an automated intervention to increase walking in university employees not achieving 10,000 daily steps. Prev Med 2013;56:283-287. [doi: 10.1016/j.ypmed.2013.01.022] [Medline: 23415624]
47. Borg J, Merom D, Rissel C. Staff walking program: a quasi-experimental trial of maintenance newsletters to maintain walking following a pedometer program. Health Promot J Austr 2010;21:26-32. [Medline: 20406149]
48. Faghri PD, Omokaro C, Parker C, Nichols E, Gustavesen S, Blozie E. E-technology and pedometer walking program to increase physical activity at work. J Prim Prev 2008;29:73-91. [doi: 10.1007/s10935-007-0121-9] [Medline: 18213518]
49. Lyons EJ, Lewis ZH, Mayrsohn BG, Rowland JL. Behavior change techniques implemented in electronic lifestyle activity monitors: a systematic content analysis. J Med Internet Res 2014;16:e192 [FREE Full text] [doi: 10.2196/jmir.3469] [Medline: 25131661]
50. Fogg B. Persuasive Technology: Using Computers to Change What We Think and Do. San Francisco: Morgan Kaufmann; 2002.
51. Zielinski D. Wearable Wellness. HRMagazine 2014;59:58-61.
52. Nield D. Fortune. 2014. In corporate wellness programs, wearables take a step forward URL: http://fortune.com/2014/04/15/in-corporate-wellness-programs-wearables-take-a-step-forward/ [accessed 2015-04-21] [WebCite Cache ID 6dl3eOJwn]
53. Lewis ZH, Lyons EJ, Jarvis JM, Baillargeon J. Using an electronic activity monitor system as an intervention modality: A systematic review. BMC Public Health 2015;15:585 [FREE Full text] [doi: 10.1186/s12889-015-1947-3] [Medline: 26104189]
54. Lumo Bodytech. Lumo Back URL: http://www.lumobodytech.com/lumo-back/ [accessed 2015-06-01] [WebCite Cache ID 6dl3loc5j]
55. Evans L. Entrepreneur. 2014. Using Wearable Devices to Help Promote Employee Wellness URL: http://www.entrepreneur.com/article/236370 [accessed 2015-04-21] [WebCite Cache ID 6dl4LyVRj]
56. Randomization.com. 2013. URL: http://www.randomization.com/ [accessed 2014-03-12] [WebCite Cache ID 6g5jeGZI5]
57. Neuhaus M, Healy GN, Fjeldsoe BS, Lawler S, Owen N, Dunstan DW, et al. Iterative development of Stand Up Australia: a multi-component intervention to reduce workplace sitting. Int J Behav Nutr Phys Act 2014:21 [FREE Full text] [doi: 10.1186/1479-5868-11-21] [Medline: 24559162]
58. Dunstan DW, Wiesner G, Eakin EG, Neuhaus M, Owen N, LaMontagne AD, et al. Reducing office workers' sitting time: rationale and study design for the Stand Up Victoria cluster randomized trial. BMC Public Health 2013;13:1057 [FREE Full text] [doi: 10.1186/1471-2458-13-1057] [Medline: 24209423]
59. Perkash R. Lumo Bodytech. 2013. The Science of Lumo Back URL: http://www.lumobodytech.com/the-science-of-lumo-back/ [accessed 2015-08-07] [WebCite Cache ID 6dl4YclWL]
60. Rosenberger M, Haskell W, Buman M, LaStofka B, Carstensen L. Abstract P128: a new device for objective measurement of sedentary behavior. Circulation 2014;129(Suppl 1):AP128.
61. Rosenberger ME, Buman MP, Haskell WL, McConnell MV, Carstensen LL. 24 hours of sleep, sedentary behavior, and physical activity with nine wearable devices. Med Sci Sports Exerc 2016;48:457-465. [doi: 10.1249/MSS.0000000000000778] [Medline: 26484953]
62. Kooiman TJM, Dontje ML, Sprenger SR, Krijnen WP, van der Schans CP, de Groot M. Reliability and validity of ten consumer activity trackers. BMC Sports Sci Med Rehabil 2015;7:24 [FREE Full text] [doi: 10.1186/s13102-015-0018-5] [Medline: 26464801]
63. LimeService. URL: https://www.limeservice.com/en/ [accessed 2016-03-18] [WebCite Cache ID 6g5hRqsXr]
64. Grant PM, Ryan CG, Tigbe WW, Granat MH. The validation of a novel activity monitor in the measurement of posture and motion during everyday activities. Br J Sports Med 2006;40:992-997 [FREE Full text] [doi: 10.1136/bjsm.2006.030262] [Medline: 16980531]
65. Lyden K, Kozey Keadle SL, Staudenmayer JW, Freedson PS. Validity of two wearable monitors to estimate breaks from sedentary time. Med Sci Sports Exerc 2012;44:2243-2252 [FREE Full text] [doi: 10.1249/MSS.0b013e318260c477] [Medline: 22648343]
66. Kozey-Keadle S, Libertine A, Lyden K, Staudenmayer J, Freedson PS. Validation of wearable monitors for assessing sedentary behavior. Med Sci Sports Exerc 2011;43:1561-1567. [doi: 10.1249/MSS.0b013e31820ce174] [Medline: 21233777]
67. Ware J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996;34:220-233. [Medline: 8628042]

68. Shikiar R, Halpern MT, Rentz AM, Khan ZM. Development of the Health and Work Questionnaire (HWQ): an instrument for assessing workplace productivity in relation to worker health. Work 2004;22:219-229. [Medline: 15156087]
69. Sundstrom E, Town JP, Rice RW, Osborn DP, Brill M. Office noise, satisfaction, and performance. Environ Behav 1994;26:195-222. [doi: 10.1177/0013916594026002004]
70. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983;24:385-396. [Medline: 6668417]
71. Mitchell AM, Crane PA, Kim Y. Perceived stress in survivors of suicide: psychometric properties of the Perceived Stress Scale. Res Nurs Health 2008;31:576-585. [doi: 10.1002/nur.20284] [Medline: 18449942]
72. Kuorinka I, Jonsson B, Kilbom A, Vinterberg H, Biering-Sørensen F, Andersson G, et al. Standardised Nordic questionnaires for the analysis of musculoskeletal symptoms. Appl Ergon 1987;18:233-237. [Medline: 15676628]
73. Kjaer P, Wedderkopp N, Korsholm L, Leboeuf-Yde C. Prevalence and tracking of back pain from childhood to adolescence. BMC Musculoskelet Disord 2011:98 [FREE Full text] [doi: 10.1186/1471-2474-12-98] [Medline: 21575251]
74. Andersen LL, Clausen T, Burr H, Holtermann A. Threshold of musculoskeletal pain intensity for increased risk of long-term sickness absence among female healthcare workers in eldercare. PLoS One 2012;7:e41287 [FREE Full text] [doi: 10.1371/journal.pone.0041287] [Medline: 22911772]
75. Chau JY, Van Der Ploeg HP, Dunn S, Kurko J, Bauman AE. Validity of the occupational sitting and physical activity questionnaire. Med Sci Sports Exerc 2012;44:118-125. [doi: 10.1249/MSS.0b013e3182251060] [Medline: 21659903]
76. Edwardson CL, Winkler EAH, Bodicoat DH, Yates T, Davies MJ, Dunstan DW, et al. Considerations when using the activPAL monitor in field based research with adult populations. J Sport Health Sci 2016 (forthcoming). [doi: 10.1016/j.jshs.2016.02.002]

Abbreviations

ICC: intraclass correlation coefficient
MAPE: mean absolute percent error
MDD: minimum detectable difference
MDI: minimum difference of interest
METS: metabolic equivalents
MVPA: moderate- and vigorous-intensity physical activities
OSPAQ: Occupational Sitting and Physical Activity Questionnaire
SD: standard deviation
SF: short form

Edited by G Eysenbach; submitted 16.12.15; peer-reviewed by A Müller, Z Lewis; comments to author 05.01.16; revised version received 18.01.16; accepted 19.01.16; published 25.05.16.

Please cite as:
Brakenridge CL, Fjeldsoe BS, Young DC, Winkler EAH, Dunstan DW, Straker LM, Brakenridge CJ, Healy GN
Organizational-Level Strategies With or Without an Activity Tracker to Reduce Office Workers' Sitting Time: Rationale and Study Design of a Pilot Cluster-Randomized Trial
JMIR Res Protoc 2016;5(2):e73
URL: http://www.researchprotocols.org/2016/2/e73/
doi:10.2196/resprot.5438
PMID:27226457

Protocol

Graded Exercise Therapy Guided Self-Help Trial for Patients with Chronic Fatigue Syndrome (GETSET): Protocol for a Randomized Controlled Trial and Interview Study

Lucy V Clark[1], PhD; Paul McCrone[2], PhD; Damien Ridge[3], PhD; Anna Cheshire[3], PhD; Mario Vergara-Williamson[4], ClinPsyD; Francesca Pesola[5], PhD; Peter D White[1], MD

[1]Centre for Psychiatry, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, United Kingdom

[2]King's Health Economics, Health Service and Population Research Department, King's College London, London, United Kingdom

[3]Faculty of Science and Technology, University of Westminster, London, United Kingdom

[4]Kent & Medway NHS and Social Care Partnership Trust, Kent and Medway CFS/ME Service, Maidstone, United Kingdom

[5]Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, United Kingdom

Corresponding Author:
Lucy V Clark, PhD
Centre for Psychiatry
Wolfson Institute of Preventive Medicine
Queen Mary University of London
Robin Brook Centre
St Bartholomew's Hospital
London, EC1A 7BE
United Kingdom
Email: l.clark@qmul.ac.uk

Abstract

Background: Chronic fatigue syndrome, also known as myalgic encephalomyelitis (CFS/ME), is characterized by chronic disabling fatigue and other symptoms, which are not explained by an alternative diagnosis. Previous trials have suggested that graded exercise therapy (GET) is an effective and safe treatment. GET itself is therapist-intensive with limited availability.

Objective: While guided self-help based on cognitive behavior therapy appears helpful to patients, Guided graded Exercise Self-help (GES) is yet to be tested.

Methods: This pragmatic randomized controlled trial is set within 2 specialist CFS/ME services in the South of England. Adults attending secondary care clinics with National Institute for Health and Clinical Excellence (NICE)-defined CFS/ME (N=218) will be randomly allocated to specialist medical care (SMC) or SMC plus GES while on a waiting list for therapist-delivered rehabilitation. GES will consist of a structured booklet describing a 6-step graded exercise program, supported by up to 4 face-to-face/telephone/Skype™ consultations with a GES-trained physiotherapist (no more than 90 minutes in total) over 8 weeks. The primary outcomes at 12-weeks after randomization will be physical function (SF-36 physical functioning subscale) and fatigue (Chalder Fatigue Questionnaire). Secondary outcomes will include healthcare costs, adverse outcomes, and self-rated global impression change scores. We will follow up all participants until 1 year after randomization. We will also undertake qualitative interviews of a sample of participants who received GES, looking at perceptions and experiences of those who improved and worsened.

Results: The project was funded in 2011 and enrolment was completed in December 2014, with follow-up completed in March 2016. Data analysis is currently underway and the first results are expected to be submitted soon.

Conclusions: This study will indicate whether adding GES to SMC will benefit patients who often spend many months waiting for rehabilitative therapy with little or no improvement being made during that time. The study will indicate whether this type of guided self-management is cost-effective and safe. If this trial shows GES to be acceptable, safe, and comparatively effective, the GES booklet could be made available on the Internet as a practitioner and therapist resource for clinics to recommend, with the caveat that patients also be supported with guidance from a trained physiotherapist. The pragmatic approach in this trial means that GES findings will be generalizable to usual National Health Service (NHS) practice.

Trial Registration: International Standard Randomized Controlled Trial Number (ISRTCTN): 22975026; http://www.isrctn.com/ISRCTN22975026 (Archived by WebCite at http://www.webcitation.org/6gBK00CUX)

(JMIR Res Protoc 2016;5(2):e70) doi:10.2196/resprot.5395

KEYWORDS

Fatigue; Chronic Fatigue Syndrome; Myalgic Encephalomyelitis; Secondary Care; Graded Exercise Therapy; Self-Help; Guidance

Introduction

Background

Chronic fatigue syndrome, also known as myalgic encephalomyelitis (CFS/ME), is a condition characterized by chronic disabling fatigue, which is not better explained by an alternative diagnosis [1-3]. The prevalence of CFS/ME in the population is between 0.4 and 2.5% [3-5]. A working group, reporting to the Chief Medical Officer for England, concluded the following: "CFS/ME is a relatively common clinical condition, which can cause profound, often prolonged, illness and disability, and can have a substantial impact on the individual and the family" [4]. The prognosis is poor with a median of 7% recovering without treatment [6].

The National Institute for Health and Clinical Excellence (NICE) guidelines recommend that patients with CFS/ME are offered GET (or cognitive behavior therapy [CBT]) [7]. In support of this guidance, two systematic reviews showed no harm to patients from GET [8,9]; however, it was concluded that larger trials should be completed to confirm the recommendations. The PACE trial (pacing, graded activity, and cognitive behavior therapy: a randomized evaluation) is the largest ever trial testing GET and CBT for CFS with 641 secondary care patients recruited [10]. Specialist medical care (SMC) alone was compared with SMC plus one of three therapies (adaptive pacing therapy, CBT, or GET). GET was found to be an effective and safe treatment, with 82% being satisfied with GET [11]. In contrast to this research, surveys of ME charity members have suggested that GET is perceived as a harmful and unacceptable treatment. In a recent survey, 56% of those who had received GET reported feeling “worse” afterwards, with 53% reporting GET to be unacceptable [12]. Specialist therapist-delivered GET is also intensive and expensive, with up to 15 sessions required over a 3 to 6-month period [9,11], and United Kingdom (UK) National Health Service (NHS) access is often poor and with long waiting lists [13]. An effective and safe guided self-help GET approach would be helpful to all involved.

Self-help approaches can benefit patients with chronic fatigue in the community [14]. In one study, fatigued patients attending their GP were given an educational CBT self-help booklet [15], complemented by 15 minutes of advice from a research nurse. After 3 months, patients who received the booklet were significantly less fatigued than the usual care group. This booklet has since been used in another primary care trial in which fatigued patients were offered 6 sessions of therapy with a trained GET or CBT therapist at their GP surgery or given the booklet without guidance as an alternative to usual care [16]. A third of patients receiving the booklet significantly improved compared to half receiving the face-to-face therapies. However, these two studies recruited patients from primary care, and thus included those with less disabling fatigue than that found in secondary care patients. In another study, a guided CBT self-help treatment was tested in secondary care patients with CFS/ME [17]. In this trial, significant decreases in both fatigue and disability were observed in the guided self-help group compared to the waiting list control. A clinically significant improvement in fatigue (27% versus 7% of waiting list patients) and 6-point difference in mean SF-36 physical functioning subscale scores between groups at follow-up resulted. However, problems with respect to engagement and acceptability of psychotherapeutic approaches such as CBT for patients with CFS/ME have been reported [4].

Self-management techniques have consistently been shown to result in substantial improvements in patients with a range of mental illnesses [18-21] and physical illnesses [22,23]. A US study showed that patients with CFS/ME seemed to prefer self-management approaches, particularly social support services [24]. However, no study has investigated guided GET self-help for CFS/ME. In the UK, patients report difficulties accessing specialist services either because there is no local service, because of long waits for referral and/or subsequent treatment, or because they are too ill to travel to the clinic [25]. Approximately 40% reported waiting 6 months to see a specialist. Thus, effective guided self-help could open up a more accessible treatment option for many CFS patients and might make face-to-face therapy either unnecessary, or reduce the need for a full course of therapy.

Rationale and Piloting

Physiotherapists trained to deliver GET within the PACE trial developed and tested the GES guide. It was developed so that diagnosed patients attending clinics could help themselves using such an approach with advice from their specialist clinician and therapist. The booklet was extensively piloted by secondary care CFS/ME patients and reviewed by several specialists in CFS/ME and a professor of physiotherapy. This led to significant revisions, and review, before “translation” of the guide into lay language by a professional editor.

Hypotheses

First, we will test the null hypothesis that GES plus specialist medical care (SMC) will be no more effective at improving either physical disability or fatigue than usual SMC alone, as shown by no statistically significant difference between the two arms of the trial 12 weeks after randomization. Second, we will test the hypothesis that GES will be acceptable to patients diagnosed as having CFS/ME in specialist secondary care clinics, as demonstrated by less than 25% of eligible patients declining participation in the trial, and more than 75% of those participating being satisfied with the approach. Third, we will

assess the difference in the number of participants suffering serious adverse effects, serious adverse reactions, or a serious deterioration across the study arms.

We will also assess whether there is a statistically significant difference in cost-effectiveness between the two interventions, although this is not a hypothesis.

Methods

Study Design

This is a pragmatic [26] randomized controlled trial of outpatients attending two specialist CFS/ME secondary clinics who have been diagnosed by a specialist doctor as having CFS/ME and referred for practitioner-delivered therapy. All participants will be on a waiting list for therapist-delivered treatment. Standard medical care (SMC) will be compared with SMC plus GES.

Participants

Adults aged 18 and over will be recruited after assessment at two CFS/ME specialist clinics in the United Kingdom (UK): one at St Bartholomew's Hospital (East London Foundation NHS Trust) and the other in Kent (Kent and Medway NHS and Social Care Partnership Trust). These services each provide assessment and/or treatment for approximately 125 new adults each year, referred mainly from general practitioners. Adults are given a diagnosis after a clinical assessment, with a physical and mental state examination, and screening blood tests according to the guidelines produced by the National Institute for Health and Care Excellence [7]. Approximately 57% of adults referred to specialist CFS services have CFS/ME [27] based on one of three possible criteria [1,2,7]; however, they must meet NICE criteria to be entered into this trial. We chose the NICE criteria to maximize generalizability of the trial to a more representative sample of UK secondary care attendees, as they are more inclusive (requiring a shorter duration and fewer symptoms).

Inclusion/Exclusion Criteria

Patients will be included if they meet NICE criteria for CFS/ME [7]. To meet these criteria, patients must have clinically evaluated, unexplained, persistent or relapsing chronic fatigue of more than 4 months with a definite onset. Their fatigue needs to have resulted in a substantial reduction in activity, be characterized by postexertional fatigue or malaise and be accompanied by at least 1 of 10 possible symptoms (eg, headaches, muscle and/or joint pain, difficulty sleeping, and concentration problems). Patients meeting these criteria will be referred for treatment in the service as usual and will be asked if they would be willing to be contacted about possible participation in the trial. Patients will not be offered trial participation if they do not speak and read English adequately, have current suicidal thoughts or comorbid psychiatric conditions requiring exclusion, have read the GES guide previously, have had previous GET therapy at one of the trial clinics, or have physical contraindications to exercise.

Recruitment

Potentially eligible patients identified by the clinician in the initial assessment will be informed about the study and given an information sheet. The clinician will obtain consent from the patient to be contacted by a researcher. If the patient is willing, the researcher will contact the patient and arrange to meet at the clinic or via a Skype™ telephone appointment to provide and discuss further information about the study.

The recruiting researcher will explain the rationale for the study and its design, uncertainties about the effectiveness of the intervention, options available outside of the trial, and the right not to take part in the study or to withdraw at any time up to the analysis. Those willing to take part in the study will be asked to consent to randomization and sign the consent form. If informed consent is subsequently provided, the patient will partake in an assessment. Consent to have guidance sessions recorded will not be required to be included in the trial.

Randomization

The recruiting researcher will log in to the Web-based automated randomization service/system operated by the UK Clinical Research Collaboration (UKCRC) registered King's Clinical Trials Unit at the Institute of Psychiatry, King's College London for the intervention allocation, which will be conveyed to the participant by the recruiting researcher. Allocation will be at the level of the individual, using block randomization with randomly varying block sizes, to preserve allocation concealment. Randomization will be stratified by (1) depression (Hospital Anxiety and Depression Scale; cut-off = 11); (2) severity of disability (SF-36 physical functioning subscale ≤40 and ≥45, which was close to the mean score from all participants in the PACE trial [11]; and (3) by center. This will help to ensure equal proportions of depressed and more severely disabled participants in each treatment arm. Automatic emails will confirm the intervention allocation. If for any reason the randomization service is unobtainable, randomization will be completed during the next working day and the participant will be told of the result by telephone.

Interventions

Standard Medical Care (SMC)

Participants will be informed at the end of their assessment appointment that they have been allocated to SMC and that they should follow the advice of their GP and specialist doctor as usual. They will not have access to the self-help booklet used in the trial. As per usual, specialist doctors will prescribe or advise regarding medication as indicated for symptomatic treatment of associated symptoms (eg, insomnia and pain) and comorbid conditions (eg, depressive illness). These patients will start the therapy to which they have been referred after the endpoint of the trial at 12 weeks or more after randomization, when it becomes available. After completion of trial participation, these patients will also receive a copy of the GES booklet.

SMC Plus GES

In addition to receiving SMC, participants in the GES arm will be given a copy of a self-help booklet describing a 6-step

program of graded exercise that should take approximately 12 weeks to complete. A physiotherapist will then join the participant for a 30-minute appointment either face-to-face in the clinic or via telephone/Skype™ within 5 working days of randomization. The physiotherapist will explain how the booklet should be used, explain steps 1 to 4 of the booklet, and answer any questions/concerns of participants. The physiotherapist will provide up to 3 further 20-minute telephone or Skype™ support appointments over the next 8 weeks. These 3 follow-up appointments will take place approximately 1 to 2, 4 to 5, and 7 to 8 weeks after the participant's initial appointment. The physiotherapists will be trained and experienced in delivering GET as a treatment for CFS/ME, and in how to guide and support participants in their use of the booklet without providing additional therapy. The emphasis of guidance/support will be on solutions provided by the booklet and how to apply what is learned, and will follow a support guidance checklist. Contacts with the physiotherapist will be audio-recorded, with informed consent, for training and supervision purposes to ensure that therapists adhere to the guided self-help manual. The GES supervisor will listen to a random sample of the recordings throughout to ensure therapists are maintaining a consistent approach.

The Guided graded Exercise Self-help (GES) booklet is based on the approach of GET developed for the PACE trial [11], which was itself based on effective approaches tested in previous trials [9]. GES is also based upon the recommendations made by NICE in 2007 [7]. Patients with CFS/ME attending clinics at St Bartholomew's and King's College hospitals in London piloted the booklet. Engaging and encouraging participants to undertake their exercise plans using the GES booklet are cornerstones of the guidance and will be its main focus.

The physiotherapist will use established techniques [28] to maximize engagement and adherence throughout. Participants will be encouraged to approach their graded exercise program using the 6 steps described in the booklet: stabilizing a routine, starting regular stretching, deciding on a goal and choosing a type of physical activity (PA), setting their PA baseline, increasing the duration of PA, and finally increasing the intensity of PA. During each session, the therapist will inquire about progress and answer any questions, with a focus on moving forward to the next step. They will recognize achievements and provide feedback to participants on their efforts, with the aim of increasing motivation and self-efficacy. Near the end of the guidance intervention, the physiotherapist will discuss setbacks. If a participant cannot be contacted by telephone or Skype™, an email will be sent in an attempt to reengage them. After the last guidance session, the physiotherapist will rate the participant's CGI (health), their adherence to the GES guided support, and their acceptance of the therapy model.

Departure from Intended Treatment

To measure departure from intended treatment, participants will be asked at follow-up whether they adhered to the booklet and guidance, and how much PA they undertook in the past week. The number of participants who actively withdraw from either intervention will be recorded. The GES booklet is currently only available from specialist doctors and physiotherapists at specific CFS/ME clinics. For the duration of the trial, the GES booklet will not be available on our websites or patient libraries. Participants who are offered face-to-face therapy before completion of their 12 weeks in the trial, due to an appointment becoming available earlier than expected in the service, will complete their follow-up measures prior to that appointment. This will be considered a "protocol deviation."

Assessments and Procedures

Criteria for CFS

The research assessment will include evaluation of the operational criteria for the Oxford and Centers for Disease Control and Prevention (CDC) criteria for CFS. Although not eligibility criteria, these will be used in subgroup analyses [1,2]. To determine both excluding and allowable comorbid psychiatric diagnoses, a standardized psychiatric interview (Structured Clinical Interview for DSM-IV Axis I Disorders; SCID) [29] will be conducted by a trained and supervised research assessor.

Baseline

The following self-rated inventories will be collected at the first assessment (baseline): 11-item Chalder fatigue questionnaire (CFQ), using Likert scoring [30]; SF-36 physical function short form subscale (SF-36 PF) [31]; Hospital Anxiety and Depression Scale (HADS) [32]; Euroqol Questionnaire (EQ-5D) [33]; Work and Social Adjustment Scale (WSAS) [34]; International Physical Activity Questionnaire (IPAQ) [35]; Tampa Scale of Kinesiophobia-Fatigue (TSK-F) [36]; Client Service Receipt Inventory (CSRI) [37]; and Patient Health Questionnaire (PHQ-15) [38]. Participants will be asked when their CFS/ME started; whether they have ever received GET, CBT, or pacing from a therapist; whether they have ever used any listed self-help resources; and whether they are members of a CFS/ME self-help group. Participants will also be asked about their ethnicity, highest education level, current employment status, whether they have had to reduce/stop work due to their CFS/ME, other health problems, and whether they are taking antidepressant medication for any reason.

12-Weeks Post-randomization

The main outcome end-point will be 12 weeks after randomization, before patients begin their service therapy. We chose 12 weeks as this was about the length of the waiting list for therapy at the St Bartholomew's CFS service at the time of application for funding. At the end-point, the following information will be collected via questionnaires sent by mail with a stamped addressed envelope: SF-36 PF, CFQ, self-rated Clinical Global Impression of Change (CGI) [39] (this will be done once for overall health and then a second time specifically for CFS), HADS, EQ-5D, WSAS, IPAQ, CSRI, and PHQ-15. Participants will be asked to describe the following: whether they have used any of 4 listed self-help resources since randomization, including the unpublished GES guide [40-42]; how satisfied they are with the help they received; how closely they followed the GES guide; their current employment status and whether they have had to reduce/stop work due to their CFS/ME; any new health problems not already reported; and whether they are taking antidepressant medication for any reason.

12-Months Post-randomization

The primary purpose of the 12-month follow-up will be to obtain the health-economic assessment (see section below); however, we will also collect data on the primary outcome measures and the CGI so that we can assess longer-term physical functioning, fatigue, and change in overall health and CFS. The following information will be collected via questionnaires sent in the mail with a stamped addressed envelope for return: CFQ, SF-36 PF, CGI, EQ-5D, and CSRI.

Primary Outcomes

We initially planned to use the SF-36 PF as the primary outcome analyzed as an interval variable collected at 12-weeks postrandomization. The SF-36 PF is scored as the sum of responses to 10 items related to functioning on everyday activities from getting dressed to performing physical activities, each of which is coded 0 for "Yes, limited a lot," 5 for "Yes, limited a little" and 10 for "No, not limited at all". This yields a score ranging from 100 for the highest level of perceived physical functioning to 0 for being unable to bathe or dress oneself. The SF-36 PF was to be the sole primary outcome as we were primarily interested in change in physical function.

However, during recruitment we noticed that a significant minority of participants scored close to the mean of the general population (ie, normal physical function) so could be considered recovered even before any intervention [43]. This is because they had substantial reductions in functioning in other domains, such as mental or social activity levels [7].

We therefore added a second primary outcome, the CFQ, which is scored as the sum of responses to 11 items related to physical and mental fatigue, each of which is coded 0 for less than usual," 1 for "no more than usual," 2 for "more than usual" and 3 for "much more than usual," where usual is how they felt the last time they were feeling well. This gives us a symptomatic measure of fatigue. The two primary outcome variables are valid and reliable and have been used in previous CFS trials [9,11]. The ethics committee, Research and Development (R & D), and the trial steering and data monitoring committees approved this change (in June 2013) before any outcome data were formally examined. Because of the change from one to two primary outcomes, we reanalyzed our power calculation and plan to recruit more participants (see section on sample size).

The main secondary outcome measure will be the validated self-rated CGI score, which we will use to measure both change in "CFS" and change in "general health" at the end of treatment, compared with baseline. Each will have 7 possible scores from "very much worse" (score of 7) to "very much better" (score of 1)[39]. Both safety and efficacy can be recorded with this item; we will count scores of 1 and 2 ("very much" and "much" better) as positive outcomes, and scores of 6 and 7 ("very much" and "much" worse) as negative outcomes. Scores of 3-5 ("a little" better, no change, and "a little" worse) will be regarded as no change.

Safety Measures and Reporting

For safety outcomes, we will include serious adverse events (SAEs), serious adverse reactions to trial treatments (SARs), and serious deteriorations (SDs). SAEs will be defined according to usual clinical trial definitions (ie, an event that is fatal, life-threatening, or results in or prolongs hospitalization; an increase in severe and persistent disability or incapacity; self-harm; or any other important condition that may require medical or surgical intervention to prevent the above [10] and will be reported to the appropriate authorities in the standard manner. SARs are SAEs that are considered to be a reaction to any trial therapy or drug prescribed. SDs will be defined as any of the following outcomes: CGI scores of 6 and 7, active withdrawal from the intervention due to worsening, or a reduction on the SF-36 PF scale by 10 or more points. Participants will record any nonserious adverse events (NSAEs) in their follow-up questionnaire. An adverse event is defined as any clinical change, disease, or disorder recorded by the participant, whether or not it is considered to be related to the trial or its treatments. Participants will be asked to record whether they believe the adverse event was "related to following the GET guide." In the event of an adverse event (AE), the center leader will judge the seriousness of the event, and, if judged to be serious, the relationship to a trial supplementary therapy or SMC prescribed treatment, and the expectedness of the event. The trial manager will report all SAEs to the principal investigator (PI) within 24 hours, regardless of the relationship to trial treatment. Reporting of SAEs and SARs will be carried out according to normal regulatory research governance requirements.

After an SAE or SAR, the center leader will make a decision as to whether the participant should be withdrawn from either randomized treatment or from the trial, or if an alteration in their SMC is needed; arrangements will be made for further assessment and management as required. The trial manager will provide the center leader with monthly follow-up reports until resolution. These reports will be communicated to the Data Monitoring and Ethics Committee (DMEC), and other appropriate authorities via the trial manager.

A risk assessment has been undertaken and we have concluded that the therapies are of low risk to participants. NSAEs will be reported en bloc to the DMEC on a regular basis, according to the usual regulatory requirements.

Measures Used for Economic Evaluation

Quality of life and function will be measured using the EQ-5D and the WSAS. The EQ-5D will also be used to generate quality-adjusted life years (QALYs) and linked to costs measured using data collected with the CSRI. The IPAQ will determine PA participation before and after the intervention, and the TSK-F will determine beliefs about exercise at baseline. Participants will be asked about their current employment status and whether they have had to reduce/stop work due to their CFS/ME. The physiotherapist will record the number of contacts and the length of each contact, and during the final guidance session, will measure adherence to the GES guided support. Other service use during the trial will be reported by participants completing the CSRI at follow-up, including use of primary

and secondary care services, use of other self-help approaches such as the Internet, books or voluntary sector support, medication, therapy outside of the trial, complementary healthcare, and care from family/friends. By accessing clinic notes and relevant electronic databases, we will also collect data on how many therapy sessions participants went on to receive after their trial participation up to one year after randomization.

Non-Responders

If a returned form is incomplete, the researcher will contact the patient, usually by telephone, to acquire any missing data. In the event that no outcome data is completed or returned after 2 telephone attempts spaced 1 week apart, the researcher will email or text the participant to ask for answers over the telephone or via email solely for the 2 primary outcomes and the CGI. The researcher will make a file note that the outcome data were collected in this way. If a participant withdraws from the treatment, but not the trial, data will be collected in the usual way. If the participant is not willing to provide all follow-up data, a request will be made to complete only the primary outcome and CGI; if the participant agrees, these will be completed immediately.

Statistical Considerations

Blinding to Outcome Measures

The members of the Trial Steering Committee (TSC), the DMEC, and the trial statistician will be blinded to treatment allocation. The trial manager (TM) and physiotherapists will not be blind to allocation, as they will inform participants of their allocation and deliver the intervention. To further minimize observer bias, outcomes will be self-rated by the participant, and outcome assessments will be coordinated by the TM. The trial statistician will be masked to treatment group until after the main analysis is completed.

Sample Size

Our original sample size was based upon the SF-36 PF as our primary outcome; however, the significance level was reduced to 2.5% to accommodate 2 primary outcomes [31]. A large previous trial of CFS/ME using the SF-36 PF (the PACE trial) indicated a baseline mean score of 37 (SD 15) and an outcome score of 48 (SD 21) following 12 weeks of practitioner-led GET, an 11-point increase [11]. Based on these previous findings, and our estimate that GES will be less effective than GET, the sample size calculations are based on the assumption that a mean difference of 8 (SD 18) points between intervention arms at the 12-week follow-up will be a clinically useful difference on the SF-36 PF scale after 12 weeks [11]. Thus, assuming a significance level (alpha) of 2.5% and power of 80%, we require a minimum of 98 participants in each group. This sample size will be upwardly adjusted to allow for loss to follow-up and other compliance issues. Based upon previous trials, we expect about 10% loss to trial follow-up [17]; therefore, we will recruit 109 patients in each group (a total of 218).

Based on a previous trial of GET, in which the difference between baseline and 12 weeks was 5.4 points on the CFQ [11], we assume that a mean difference of 3 (SD 6) points will represent a clinically useful difference at the 12-week follow-up. Hence, assuming a significance level (alpha) of 2.5% and power of 80%, we require a total of 174 patients, which is less than the 218 to be recruited, so adequate power will be achieved.

Data Entry and Analysis

Data will be double entered by a dedicated data-entry researcher. The analysis and presentation of the trial will be in accordance with CONSORT guidelines including a flow diagram of enrollment, allocation, follow-up, and analysis [26,44]. We plan to use descriptive statistics to compare characteristics of invited individuals who did or did not agree to take part and eligible individuals who were randomized or not randomized (pending ethical approval). We will also examine differences between trial arms in important baseline participant characteristics.

Descriptive Statistics for Primary and Secondary Outcomes

Box plots will be used to assess the data distribution of continuous measures. Descriptive statistics will be broken down by intervention group at baseline and follow-up. Normality of the scales and regression residuals will be explored using diagnostic plots, and if the assumption of normality is violated, the data will be transformed. We will present means and standard deviations for all normally distributed measures, and medians and quartiles for nonnormal measures. Discrete outcomes will be described using both number and percentage.

Missing Data

Item-level missing data on the primary and secondary outcome variables at baseline and follow-up will be imputed using mean replacement (prorating). Prorating will be implemented only when less than 20% of item responses per scale are missing. The reasons for missing baseline and follow-up whole-scale data will be summarized using the CONSORT diagram. We will identify baseline characteristics associated with missing data to allow us to impute data to do sensitivity analyses.

Analysis for Hypothesis 1

Our primary intention-to-treat analysis will compare the SF-36 PF and CFQ at 12 weeks between groups adjusted using multivariable linear regression analyses [45]. Intention-to-treat (ITT) analyses will be conducted on data from all randomized participants with information at follow-up (ie, modified ITT) regardless of any departure from the allocated treatment arm. We will adjust for our stratification factors (depression, center, and severity of disability) as well as baseline values of outcomes and treatment arm.

A secondary analysis will explore the association between treatment arm and having achieved a clinically useful improvement on the SF-36 PF (ie, an 8-point increase) and the CFQ (ie, a 3-point decrease) using chi-squared analysis.

Analysis of the secondary outcome, the CGI, will compare the proportions scoring “much” or “very much” better (1 and 2), the proportions scoring “a little better,” “no change,” or “a little worse” (3 to 5), and the proportions scoring “much” or “very much” worse (6 and 7) across treatment arms, using an ordinal logistic regression adjusting for our stratification variables.

Sensitivity Analysis

Sensitivity analysis will be conducted to assess the impact of missing data on our results. We will estimate whole-scale missing data due to loss to follow-up using multiple imputation by chained equation. This will allow us to conduct a strict ITT for all respondents who took part at baseline. Following recent guidelines, we will also conduct a sensitivity analysis that will take into account the partially nested design of the study and, therefore, assess the potential impact of the "therapist effect" on our results [46]. Further analysis will be conducted to adjust for potential confounders, including sex and age.

A per-protocol analysis will serve as a further sensitivity analysis to investigate the robustness of the conclusions of the primary analysis, following departures from the randomized intervention policies. This will exclude those participants in the control arm who used a GET self-help approach. Subgroup analyses including only those meeting the Oxford or CDC criteria for CFS will also be undertaken. We will analyze moderators of improvement, such as these criteria, but also depression and severity of physical function and fatigue. These subgroup analyses are exploratory and will be interpreted with due caution [47].

Analysis for Hypotheses 2 and 3

Chi square will be used to describe any difference in satisfaction (ie, satisfied vs nonsatisfied) across treatment arms and any differences in SAEs, SARs, or serious deterioration (1+ vs none) across treatment arms.

The above plan is what we intend to do; however, the final analyses reported may differ from those planned, allowing for *post hoc* analysis where it is indicated [48]. We will report alternative methods if statistical models do not converge, and omit planned analyses that are superseded, redundant, or no longer of interest. We will report any changes in consequent papers.

Economic Evaluation

The economic analysis will take a health and social care perspective. Service use will be combined with appropriate unit costs (eg, from Kent University and NHS Reference Costs) to generate service costs. QALYs gained over the period from baseline to 12-week follow-up will be generated using area-under-the-curve methods from the EQ-5D (using published tariffs from the University of York) combined with costs in the cost-effectiveness analysis. If the intervention group has lower costs and better outcomes than the control group, then the intervention will be seen as "dominant." If the intervention group has higher costs and better outcomes, we will use incremental cost-effectiveness ratios to identify the extra cost incurred to achieve one extra QALY. Uncertainty around cost-effectiveness estimates will be explored using cost-effectiveness planes (produced from outcome-cost combinations from 1000 bootstrapped resamples). Interpretation will be aided using cost-effectiveness acceptability curves derived using the net-benefit approach with values between £0 and £100,000, placed on a QALY gain so as to include the threshold used by NICE (2007) [7]. We will also conduct similar analyses using costs and the primary outcome measure. However, QALYs are the main measure for the economic evaluation given that thresholds for cost-effectiveness used by NICE exist.

12-Week Follow-Up

The main outcomes, including QALYs, will be measured over the 12-week period from baseline assessment to follow-up. We would expect to see a change in the EQ-5D (which provides us with QALY information) and the WSAS over this time. We will also measure the intervention costs and any short-term impact on the use of other services through the CSRI. We recognize that longer-term impacts, which we are unable to measure may also be important. We will measure serious deterioration using a composite measure including the CGI ("much" or "very much worse"), those who actively withdraw from their intervention, or those whose SF-36 PF score falls by 10 or more points.

12-Month Follow-Up

We will go on to measure how many appointments each participant has with an SMC doctor and with a therapist (and which therapist: psychologist, physiotherapist, occupational therapist, or group therapy) after their trial participation up to 12 months from randomization. We will estimate the costs of the interventions and compare between the groups.

Data Protection

Participants will be allocated a unique 8-digit identification number made up of a center number, an individual patient number, and patient initials. This number is assigned to the patient and is used on assessment forms prior to transfer of data, so that they are anonymized at source. A list of names and corresponding identification numbers will be kept separately and securely on an encrypted university server. All guided support sessions will be audio-recorded if consent is given, and they will be stored on an encrypted university server.

Data Monitoring

The DMEC will receive notice of SAEs and SARs for the sample as a whole and per treatment arm. If the incidence of SAEs of a similar type are greater than would be expected in this population, the DMEC will be able to retrieve data according to trial arm, to determine any evidence of excess in either arm. NSAEs will be included in the safety reporting of the completed trial. Suspected unexpected serious adverse reactions (SUSARs) will be reported separately.

Independent Scrutiny

At the end of the trial, two independent scrutineers will be appointed to consider whether any AE is an SAE and whether any SAE is an SAR. These figures will be reported.

Compliance

The trial will be conducted in compliance with the Declaration of Helsinki, the trial protocol, Medical Research Council Good Clinical Practice (GCP) guidance, the Data Protection Act (1998), the Multi-centre Research Ethics Committee (MREC), and Local Research Ethics Committees (LREC) approvals and other regulatory requirements, as appropriate. The final trial

publication will include all items recommended under CONSORT [49].

Qualitative Study

Purpose

We will undertake a nested qualitative study with a subsample of participants to ascertain patients' views and experiences of GES, specifically looking for differences in perceptions and experiences between those who improved and worsened with GES.

Both our patient representatives and the TSC suggested using the trial to better understand why patients vary in their responses to graded exercise therapy (GET), particularly by examining engagement and other barriers/facilitators to successful treatment. The best way to gather this knowledge is to undertake a small qualitative study, stratified by both good and poor outcomes. We will conduct one-on-one interviews with participants who have taken part in the active arm of the trial to investigate variations in participant attitudes to, and experiences of, GES. This study will be nested within the time-frame for the main trial.

Background Issues

A recent meta-synthesis of qualitative studies uncovered various ways in which people with CFS/ME interpret and experience their illness and their treatments [50]. Themes included wide variability in symptoms, amount of perceived control, and theories about causation and best coping strategies (eg, reducing activities, listening to the body, and balancing activities). Perspectives of patients are also known to change with treatment experience. For instance, if beliefs about the need to avoid exercise and less helpful thought patterns can be addressed (eg, catastrophic thinking), then improvements in fatigue may follow [51]. At the same time, some patient organizations believe that one particular treatment, graded exercise therapy (GET), is harmful to CFS/ME patients [12]. Qualitative research can provide a deeper understanding of the way that participants approach, experience, and give meaning to interventions like GES [52]. There is no published, qualitative research that investigates variation in participant attitudes to, and experiences of, GET in a randomized controlled trial. Yet, the evidence is that patients who benefit from such interventions are likely to approach the intervention differently than those who do not [53]. Our preliminary (unpublished) analysis of free-text feedback from GET participants in the PACE trial [11] suggested different categories of participants. For instance, people differed in their appraisals of GET from positive to negative, and whether they attended more to the learning, support, treatment, and/or contextual issues outside of the trial. However, we do not yet have sufficient data to examine the significance of different styles of patient engagement with GET.

Research Questions for the Qualitative Study

The following two research questions will be investigated in the qualitative study: (1) Are there any differences in treatment perceptions and experiences between those trial participants who improved and those who worsened during use of guided self-help based on GET? and (2) What are the implications for the way patients understand "getting better?"

Recruitment and Sampling Strategy

We aim to recruit up to 20 participants, all of whom will have received GES. Participants will be stratified into 2 similar-sized groups of either improvement or deterioration (CGI score at 12-week follow-up assessment of "much" or "very much" better versus "much," or "very much" worse) for comparison [39]. We will seek written informed consent from these 20 participants. Participants will have completed the 12-week follow-up assessment, and will be recruited at least one month later to allow time for them to reflect on their GES and trial experience.

Participant Involvement

Participants will undertake a one-off semistructured interview, either face-to-face, by telephone, or by Skype™, depending on their preference.

Data Collection

Qualitative semistructured interviews, digital audio-recorded, with fully informed consent, will be conducted with participants. An experienced qualitative researcher will conduct the interviews, using a semistructured approach [54]. By ensuring the same topics are covered in each interview, we will collect comparable data about participants' experiences of the trial and treatment within each group. In addition, the semistructured approach will allow greater flexibility for participants to highlight their specific concerns, meanings, and priorities, even if not anticipated by the researchers. Topics will include before and after trial well-being, expectations of treatment, understanding of "baseline" and "recovery," the meaning of exercise, barriers and facilitators to treatment, and any outside influences on trial participation. Thus, we will use an approach suited to collecting a wide range of experiences in each group. We will use face-to-face interviews to collect people's experiences (eg, in people's homes, or a university interview room). We will also use less conventional ways to include the perspectives of people who may have trouble participating; for example, recording of interviews over the phone, or the use of Skype™ video calls for interviews. Sample questions are provided in Multimedia Appendix 1.

Data Management and Analysis

The audio-recordings from the interviews will be professionally transcribed (a confidentiality agreement will be in place). The transcription will be reviewed against the audio by the researcher for errors and to remove any identifying information, and then returned to the participant to check accuracy and add any clarifying points at the end of the interview, with a deadline of one month to reply.

Thematic analysis (ie, "identifying, analyzing, and reporting patterns within data") is a basic building block of all kinds of qualitative analysis [55], and will be the approach used for analysis in this study. Data will be inputted and coded in the qualitative data analysis software environment, NVivo. NVivo will aid the coding of themes, organization, and searching of all interviews in both patient outcome categories (improvement

vs worsening). The software will enable the comparison of themes across the full range of data (constant comparison, ie, comparing all bits of similar data with each other) [56] so more robust conclusions can be drawn.

While the researcher will drive the analysis, all investigators will be involved in group analytical sessions, debating and clarifying themes, and drafting of reports to arrive at the final analysis.

Patient and Public Involvement

Patients were significantly involved in the design and piloting of the GES booklet before the trial started. Two patient representatives have also advised us in design of this trial and in the application and amendments to this trial. A patient representative is a member of the TMC, which will meet twice yearly. This individual will therefore be intimately involved in all aspects of this trial, so that we can ensure that this research reflects the needs and views of the patient group. A representative of the Association for Young People with ME will sit on the TSC.

Ethics and Dissemination

The study was approved on November 23, 2011 (reference 11/LO/1572) by NRES Committee London, London Bridge. Four favorable opinions were provided on May 8, 2012, May 31, 2012, June 27, 2012, and June 20, 2013, for amendments to the study protocol and documents. A fifth amendment, requesting the addition of a nested qualitative study was rejected on 2014 September 1, with the suggestion it should be submitted as a separate study. The qualitative study received a favorable ethical opinion on January 9, 2015 (reference 15/WM/0007) by NRES Committee West Midlands, The Black Country. All patients involved in the study provided informed consent to take part in the study.

The results of the GETSET study will be disseminated to the scientific community, media, relevant charities, and general public. Results will be published in peer-reviewed international journals and will be presented at national and international conferences and symposiums.

Results

The trial has finished recruiting (first randomization: May 15, 2013; last randomization: December 24, 2014). Follow-up for the main analysis was completed in April 2014 and long-term follow-up in March 2016. Data analysis are underway and the first results are expected to be submitted for publication later this year.

Discussion

CFS/ME is a relatively common and frequently disabling condition with limited treatment options of proved efficacy available within the NHS. GET is recommended, but access to it is limited, with patients often spending many months waiting for rehabilitative therapy with no help given during that time. The longer someone has CFS/ME, the worse the prognosis [6].

Guided exercise self-help (GES) has never been tested in a randomized controlled trial for CFS/ME. It is important for people with CFS and the NHS to know whether GES is more effective, and cost-effective, when used with SMC, than when SMC is used alone.

If this trial shows GES to be acceptable and safe, and shows a clinically useful difference between arms, then the GES booklet will be made available on the Internet and through other media as a practitioner resource, with the knowledge that it is an acceptable, safe, and effective treatment when supported by advice from a trained therapist. If found to be cost-effective, then it could be recommended for commissioners of services. It could be used as a first line of treatment while patients are waiting for face-to-face specialist practitioner-delivered therapies, such as GET and CBT. Guided self-help exercise could become the first step in a stepped-care approach for CFS/ME in the NHS, by training current physiotherapists to deliver it.

The next trial would be to test this intervention in primary care, which could immediately follow this trial. The secondary care trial is necessary first, to ensure this intervention is effective in those with properly diagnosed CFS/ME, before testing it in those at the primary care level, where the diagnosis is not so well-established [57].

If shown to be an effective treatment, this policy of providing a guided self-help approach to initially stabilize and then increase PA in patients with CFS/ME could also be tested for patients with many other chronic disabling conditions known to respond to practitioner-delivered graded exercise approaches, including arthritis, chronic obstructive airways disease, and diabetes mellitus [58].

Acknowledgments

This paper presents independent research funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number PB-PG-0610-22060). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health. This trial was sponsored by Queen Mary, University of London. This study was supported by the United Kingdom Clinical Research Collaboration-registered King's Clinical Trials Unit at King's Health Partners, which is partly funded by the NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London and the NIHR Evaluation, Trials and Studies Coordinating Centre. The members of our TSC and DMEC are Christopher Williams, Astrid Fletcher, Charlotte Feinman, Irwin Nazareth, Alastair Miller, Rona Moss-Morris, and a patient representative.

Janice Thomas (Queen Mary University of London) was the original statistician on the trial.

Authors' Contributions

PDW was the PI and LVC was the trial manager. PDW and LVC conceived the study, participated in the trial design and coordination, and drafted the manuscript. DR and AC designed the qualitative methodology, which was conducted by AC and supervised by DR. FP was involved in the design of the statistical methodology. PM designed the economic evaluation. MVW participated in the trial design and coordination as center leader.

Conflicts of Interest

PDW does voluntary and paid work for the UK government and a reinsurance company.

Multimedia Appendix 1

Sample questions.

[PDF File (Adobe PDF File), 29KB - resprot_v5i2e70_app1.pdf]

References

1. Reeves WC, Lloyd A, Vernon SD, Klimas N, Jason LA, Bleijenberg G, International Chronic Fatigue Syndrome Study Group. Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution. BMC Health Serv Res 2003 Dec 31;3(1):25 [FREE Full text] [doi: 10.1186/1472-6963-3-25] [Medline: 14702202]
2. Sharpe MC, Archard LC, Banatvala JE, Borysiewicz LK, Clare AW, David A, et al. A report--chronic fatigue syndrome: Guidelines for research. J R Soc Med 1991 Feb;84(2):118-121 [FREE Full text] [Medline: 1999813]
3. Wessely S, Hotopf M, Sharpe M. Chronic Fatigue and its Syndromes. Oxford: Oxford University Press; 1998.
4. Department of Health, London, UK. 2002. Report of the Working Party on CFS/ME to the Chief Medical Officer for England and Wales URL: http://www.erythos.com/gibsonenquiry/docs/cmoreport.pdf [accessed 2016-03-24] [WebCite Cache ID 6gFDH7Xzk]
5. Prins JB, van der Meer JW, Bleijenberg G. Chronic fatigue syndrome. Lancet 2006 Jan 28;367(9507):346-355. [doi: 10.1016/S0140-6736(06)68073-2] [Medline: 16443043]
6. Cairns R, Hotopf M. A systematic review describing the prognosis of chronic fatigue syndrome. Occup Med 2005;55(1):20-31. [doi: 10.1093/occmed/kqi013]
7. National Institute for Health and Clinical Excellence. Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (or Encephalopathy): Diagnosis and Management of CFS/ME in Adults and Children. Clinical Guideline CG53 URL: http://www.nice.org.uk/guidance/CG53 [accessed 2015-12-21] [WebCite Cache ID 6dwTCJd0a]
8. Castell BD, Kazantzis N, Moss-Morris R. Cognitive behavioral therapy and graded exercise for chronic fatigue syndrome: A meta-analysis. Clin Psychol Sci Pract 2011;18(4):311-324. [doi: 10.1111/j.1468-2850.2011.01262.x]
9. Larun L, Brurberg KG, Odgaard-Jensen J, Price JR. Exercise therapy for chronic fatigue syndrome. Cochrane Database Syst Rev 2016 Feb;Issue 2:CD003200. [doi: 10.1002/14651858.CD003200.pub4] [Medline: 26852189]
10. White PD, Sharpe MC, Chalder T, DeCesare JC, Walwyn R, PACE Trial Group. Protocol for the PACE trial: A randomised controlled trial of adaptive pacing, cognitive behaviour therapy, and graded exercise, as supplements to standardised specialist medical care versus standardised specialist medical care alone for patients with the chronic fatigue syndrome/myalgic encephalomyelitis or encephalopathy. BMC Neurol 2007 Mar;7:6 [FREE Full text] [doi: 10.1186/1471-2377-7-6] [Medline: 17397525]
11. White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, PACE trial management group. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): A randomised trial. Lancet 2011 Mar 5;377(9768):823-836 [FREE Full text] [doi: 10.1016/S0140-6736(11)60096-2] [Medline: 21334061]
12. The ME Association. 2010. Managing My M.E. What People with CFS/ME and their Carers Want from the UK's Health and Social Services URL: http://www.meassociation.org.uk/managing-my-me-me-association-publish-results-of-huge-survey-report/ [accessed 2015-12-21] [WebCite Cache ID 6dwUXO0rH]
13. Collin SM, Sterne JA, Hollingworth W, May MT, Crawley E. Equity of access to specialist chronic fatigue syndrome (CFS/ME) services in England (2008-2010): A national survey and cross-sectional study. BMJ Open 2012;2(4) [FREE Full text] [doi: 10.1136/bmjopen-2012-001417] [Medline: 22899647]
14. Chalder T, Wallace P, Wessely S. Self-help treatment of chronic fatigue in the community: A randomized trial. Br J Health Psychol 1997;2(3):189-197. [doi: 10.1111/j.2044-8287.1997.tb00535.x]
15. Chalder T. Coping with Chronic Fatigue. London: Sheldon Press; 1995.
16. Ridsdale L, Darbishire L, Seed PT. Is graded exercise better than cognitive behaviour therapy for fatigue? A UK randomized trial in primary care. Psychol Med 2004 Jan;34(1):37-49. [Medline: 14971625]

17. Knoop H, van der Meer JW, Bleijenberg G. Guided self-instructions for people with chronic fatigue syndrome: Randomised controlled trial. Br J Psychiatry 2008 Oct;193(4):340-341 [FREE Full text] [doi: 10.1192/bjp.bp.108.051292] [Medline: 18827302]
18. Cuijpers P. Bibliotherapy in unipolar depression: A meta-analysis. J Behav Ther Exp Psychiatry 1997 Jun;28(2):139-147. [Medline: 9194011]
19. den Boer PC, Wiersma D, Van Den Bosch RJ. Why is self-help neglected in the treatment of emotional disorders? Psychol Med 2004 Aug;34(6):959-971. [Medline: 15554567]
20. Gould RA, Clum GA. A meta-analysis of self-help treatment approaches. Clin Psychol Rev 1993 Jan;13(2):169-186. [doi: 10.1016/0272-7358(93)90039-O]
21. Scogin F, Bynum J, Stephens G, Calhoun S. Efficacy of self-administered treatment programs: Meta-analytic review. Prof Psychol Res Pr 1990;21(1):42-47.
22. Barlow J, Wright C, Sheasby J, Turner A, Hainsworth J. Self-management approaches for people with chronic conditions: A review. Patient Educ Couns 2002;48(2):177-187. [Medline: 12401421]
23. Newman S, Steed L, Mulligan K. Self-management interventions for chronic illness. Lancet 2004 Oct;364(9444):1523-1537. [doi: 10.1016/S0140-6736(04)17277-2] [Medline: 15500899]
24. Jason LA, Ferrari JR, Taylor RR, Slavich SP, Stenzel CL. A national assessment of the service, support, and housing preferences by persons with chronic fatigue syndrome. Toward a comprehensive rehabilitation program. Eval Health Prof 1996 Jun;19(2):194-207. [Medline: 10186910]
25. Action for M.E. M.E. 2008: What progress?. 2008. URL: https://www.pdffiller.com/en/project/48428381.htm?form_id=37188630 [accessed 2016-03-21] [WebCite Cache ID 6dwU7cPrxon]
26. Zwarenstein M, Treweek S, Gagnier JJ, Altman DG, Tunis S, Haynes B, et al. Improving the reporting of pragmatic trials: An extension of the CONSORT statement. BMJ 2008 Dec 30;337(nov11 2):a2390-a2390. [doi: 10.1136/bmj.a2390]
27. Davasahayam A, Lawn T, Murphy M, White PD. Alternative diagnoses to chronic fatigue syndrome in referrals to a specialist service: Service evaluation survey. JRSM Short Report 2012;3(1):4. [Medline: 22299071]
28. Hunt P, Hillsdon M. Changing Eating and Exercise Behaviour. Oxford, UK: Blackwell Science; 1996.
29. First MB, Spitzer RL, Gibbon M, Williams J. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition with Psychotic Screen (SCID-I/P W/ PSY SCREEN). New York: Biometrics Research, New York State Psychiatric Institute; 2002.
30. Chalder T, Berelowitz G, Hirsch S. Development of a fatigue scale. J Psychosom Res 1993;37(2):147-153. [doi: 10.1016/0022-3999(93)90081-P]
31. McHorney CA, Ware JE, Raczek AE. The MOS 36-item short form health survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993;31(3):247-263. [Medline: 8450681]
32. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatrica Scandinavica 1983;67(6):361-370. [doi: 10.1111/j.1600-0447.1983.tb09716.x]
33. The EuroQOL group. The EuroQOL - a new facility for the measurement of health-related quality of life. Health Policy 1990;16(3):199-208. [Medline: 10109801]
34. Mundt JC, Marks IM, Shear MK, Greist JH. The Work and Social Adjustment Scale: a simple measure of impairment in functioning. Br J Psychiatry 2002;180(5):461-464. [doi: 10.1192/bjp.180.5.461] [Medline: 11983645]
35. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003;35(8):1381-1395. [Medline: 12900694]
36. Silver A, Haeney M, Vijayadurai P, Wilks D, Pattrick M, Main CJ. The role of fear of physical movement and activity in chronic fatigue syndrome. J Psychosom Res 2002 Jun;52(6):485-493. [Medline: 12069873]
37. Beecham J, Knapp M. Costing psychiatric interventions. In: Thornicroft G, editor. Measuring Mental Health Needs, 2nd edition. London: Gaskell; 2001:200-224.
38. Kroenke K, Spitzer RL, Williams JB. The PHQ-15: Validity of a new measure for evaluating the severity of somatic symptoms. Psychosomatic Medicine 2002;64(2):258-266. [Medline: 11914441]
39. Guy W. ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: National Institute of Mental Health; 1976:218-222.
40. Chalder T. Coping with Chronic Fatigue. London: Sheldon Press; 1995.
41. Burgess M, Chalder T. Overcoming Chronic Fatigue. London: Robinson; 2005.
42. Campling F, Sharpe M. Chronic Fatigue Syndrome (CFS/ME), 2nd edition. Oxford: Oxford University Press; 2008.
43. Bowling A, Bond M, Jenkinson C, Lamping DL. Short Form 36 (SF-36) Health Survey questionnaire: Which normative data should be used? Comparisons between the norms provided by the Omnibus Survey in Britain, the Health Survey for England and the Oxford Healthy Life Survey. J Public Health Med 1999 Sep;21(3):255-270 [FREE Full text] [Medline: 10528952]
44. Moher D, Schulz KF, Altman DG. The CONSORT statement: Revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 2001 Apr 14;357(9263):1191-1194. [Medline: 11323066]

45. The European Agency for the Evaluation of Medicinal Products. EMEA. 2003 May 22. Points to Consider on Adjustment for Baseline Covariates URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003639.pdf [accessed 2016-03-29] [WebCite Cache ID 6dwTjb4fHon]
46. Baldwin SA, Bauer DJ, Stice E, Rohde P. Evaluating models for partially clustered designs. Psychol Methods 2011 Jun;16(2):149-165. [Medline: 21517179]
47. Brookes ST, Whitley E, Peters TJ, Mulheran PA, Egger M, Davey SG. Subgroup analyses in randomised controlled trials: Quantifying the risks of false-positives and false-negatives. Health Technol Assess 2001;5(33):1-56 [FREE Full text] [Medline: 11701102]
48. Finfer S, Bellomo R. Why publish statistical analysis plans? Crit Care Resusc 2009;11(1):5-6. [Medline: 19281437]
49. Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P, CONSORT group. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: Explanation and elaboration. Ann Int Med 2008;148(4):295-309. [doi: 10.7326/0003-4819-148-4-200802190-00008]
50. Anderson VR, Jason LA, Hlavaty LE, Porter N, Cudia J. A review and meta-synthesis of qualitative studies on myalgic encephalomyelitis/chronic fatigue syndrome. Patient Educ Couns 2012;86(2):147-155. [Medline: 21571484]
51. Deale A, Chalder T, Wessely S. Illness beliefs and treatment outcome in chronic fatigue syndrome. J Psychosom Res 1998 Jul;45(1):77-83. [Medline: 9720857]
52. Chew-Graham CA, Cahill G, Dowrick C, Wearden A, Peters S. Using multiple sources of knowledge to reach clinical understanding of chronic fatigue syndrome. Ann Fam Med 2008;6(4):340-348 [FREE Full text] [doi: 10.1370/afm.867] [Medline: 18626034]
53. Wearden AJ, Emsley R. Mediators of the effects on fatigue of pragmatic rehabilitation for chronic fatigue syndrome. J Consult Clin Psychol 2013 Oct;81(5):831-838. [doi: 10.1037/a0033561] [Medline: 23796316]
54. Minichiello V, Aroni R, Timewell E. In-depth Interviewing: Principles, Techniques, Analysis. Melbourne: Longman Cheshire; 1995.
55. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006;3(2):77-101. [doi: 10.1191/1478088706qp063oa]
56. Cutcliffe JR. Adapt or adopt: Developing and transgressing the methodological boundaries of grounded theory. J Adv Nurs 2005;51(4):421-428. [doi: 10.1111/j.1365-2648.2005.03514.x]
57. Darbishire L, Ridsdale L, Seed PT. Distinguishing patients with chronic fatigue from those with chronic fatigue syndrome: A diagnostic study in UK primary care. Br J Gen Pract 2003;53(491):441-445.
58. Durstine J. ACSM's Exercise Management for Persons with Chronic Diseases and Disabilities. Champaign, IL: Human Kinetics; 2009.

Abbreviations

CBT: cognitive behavior therapy
CFS: chronic fatigue syndrome
CGI: Clinical Global Impression change score
CFQ: Chalder Fatigue Questionnaire
CSRI: Client Service Receipt Inventory
DMEC: data monitoring and ethics committee
EQ-5D: Euroqol Questionnaire
GES: guided graded exercise self-help
GET: graded exercise therapy
HADS: Hospital Anxiety and Depression Scale
IPAQ: International Physical Activity Questionnaire
ITT: intention to treat
ME: myalgic encephalopathy/encephalomyelitis
NICE: National Institute for Health and Clinical Excellence
NHS: National Health Service
NRES: National Research Ethics Service
PA: physical activity
PHQ-15: Patient Health Questionnaire (15 questions)
PI: principal investigator
QALY: quality-adjusted life years
SAE: serious adverse event
SAR: serious adverse reaction
SCID: Structured Clinical Interview for DSM-IV Axis I Disorders
SF-36 PF: Short Form 36-Questionnaire physical functioning subscale
SMC: specialist medical care

TM: trial manager
TMG: Trial Management Group
TSC: trial steering committee
TSK-F: Tampa Scale of Kinesiophobia-Fatigue
WSAS: Work and Social Adjustment Scale

Edited by G Eysenbach; submitted 30.11.15; peer-reviewed by A Wearden; comments to author 20.12.15; revised version received 29.12.15; accepted 03.01.16; published 08.06.16.

Please cite as:
Clark LV, McCrone P, Ridge D, Cheshire A, Vergara-Williamson M, Pesola F, White PD
Graded Exercise Therapy Guided Self-Help Trial for Patients with Chronic Fatigue Syndrome (GETSET): Protocol for a Randomized Controlled Trial and Interview Study
JMIR Res Protoc 2016;5(2):e70
URL: http://www.researchprotocols.org/2016/2/e70/
doi:10.2196/resprot.5395
PMID:27278762

Protocol

A Web-Based Psychoeducational Intervention Program for Depression and Anxiety in an Adult Community in Selangor, Malaysia: Protocol of a Randomized Controlled Trial

Siti Fatimah Kader Maideen[1*], MPH; Sherina Mohd-Sidik[1*], PhD; Lekhraj Rampal[1*], PhD; Firdaus Mukhtar[1], PhD; Normala Ibrahim[1], PhD; Cheng-Kar Phang[1], MD; Kit-Aun Tan[1], PhD; Rozali Ahmad[2], MPH

[1]Universiti Putra Malaysia, Selangor, Malaysia

[2]Ministry of Defence, Kuala Lumpur, Malaysia

[*]these authors contributed equally

Corresponding Author:
Sherina Mohd-Sidik, PhD
Universiti Putra Malaysia
Selangor, 43400
Malaysia
Phone: 60 89472530
Fax: 60 89472541
Email: sherina@upm.edu.my

Abstract

Background: Mental disorders are a major public health problem and are debilitating in many nations throughout the world. Many individuals either do not or are not able to access treatment. The Internet can be a medium to convey to the community accessible evidenced-based interventions to reduce these burdens.

Objective: The objective of this study is to investigate the effectiveness of 4 weeks of a Web-based psychoeducational intervention program for depressive and anxiety symptoms in the community of Selangor, Malaysia.

Methods: A two-arm randomized controlled trial of a single-blind study will be conducted to meet the objective of this study. We aim to recruit 84 participants each for the intervention and control groups. The recruitment will be from participants who participated in the first phase of this research. The primary outcomes of this study are depressive and anxiety scores, which will be assessed using the Patient Health Questionnaire 9 and Generalized Anxiety Disorder 7, respectively. The secondary outcome includes mental health literacy of the participants, which will be assessed using the self-developed and adapted Mental Health Literacy Questionnaire. The psychoeducational intervention program consists of four sessions, which will be accessed each week. The depressive and anxiety symptoms will be compared between participants who participated in the psychoeducational program compared with the control group. Depressive and anxiety scores and mental health literacy will be assessed at week 1 and at follow-ups at week 5 and week 12, respectively.

Results: The psychoeducational intervention program consists of four sessions, which will be accessed at each week. The depressive and anxiety symptoms will be compared between the intervention and control groups using a series of mixed ANOVAs. Depressive and anxiety scores and mental health literacy will be assessed at week 1 and at two follow-ups at week 5 and week 12, respectively.

Conclusions: To our knowledge, this study will be the first randomized controlled trial of a Web-based psychoeducational intervention program for depression and anxiety in an adult community in Malaysia. The results from this study will determine the effectiveness of a psychoeducational intervention program in the management of depression and anxiety among adults in the community. If proven to be effective, the intervention can serve as a new modality to manage and reduce the burden of these disorders in the community.

ClinicalTrial: International Standard Randomized Controlled Trial Number (ISRCTN): 39656144; http://www.isrctn.com/ISRCTN39656144 (Archived by WebCite at http://www.webcitation.org/6hSVhV71K)

(JMIR Res Protoc 2016;5(2):e112) doi:10.2196/resprot.4622

KEYWORDS

Web-based intervention; randomized controlled trial; depression; anxiety; psychoeducation; community; Malaysia

Introduction

Mental disorders are a major global public health problem and have a debilitating effect [1]. The burden and disability due to mental disorders are huge and yet many are still untreated and do not receive professional care [2]. Although mental disorders cause approximately 60% of unavertable burden, only a limited percentage of people receive effective treatment [3]. It is estimated that 60% of depressed individuals are not being treated [4]. This is particularly for those patients seeking cognitive behavioral therapy (CBT), which is difficult to obtain due to the insufficient mental health professionals in CBT [5] and lack of services in some geographical locations [6]. Furthermore, the stigma attached to mental health problems [7,8] and discrimination toward mental illness [7] causes many individuals to seek confidential services that assure anonymity.

Lack of psychological treatment and poor compliance with medications [8], cost of treatment, limited mobility due to illnesses [6], and lack of transportation are factors that favor the Internet as a possible medium to deliver interventions to cope with these barriers. Easy access to treatment [6] and the convenience, anonymous accessibility, and programs tailored to individuals' needs as well as information that can be updated over time are some of the advantages of interventions delivered through the Internet as compared to the conventional method [5]. In addition to reducing the cost and time of travelling, participants are also able to access the resources at home and as often as they like [9].

Many patients report an inclination for self-help treatments. The Internet can be a medium for delivering such services and evidence shows that automated, professionally developed self-help psychological interventions can be effective [10]. Internet programs without the input of professionals can still be effective [10]. Internet interventions have been shown to reduce depression, anxiety, panic disorder, posttraumatic disorders, eating disorders, and insomnia [5]. Prevention and treatment of mental disorders, especially depression and anxiety disorders, through the Internet are increasing [10]. Several Internet-based interventions were found to reduce depression and anxiety symptoms [6,8,10-13].

A systematic review of the role of the Internet in managing depression and anxiety showed that the Internet is used as a source of information often among depressed and anxious patients [8]. Internet-based CBT programs significantly reduce the severity of generalized anxiety disorder (GAD), panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, and social anxiety disorder. The study also demonstrated that confidence of participants in managing their problems is also increased [6].

A study by Straten et al [14] of 213 participants found that self-help interventions are effective in reducing the symptoms of depression and anxiety. The study also found that those with severe baseline scores and those who completed the entire session benefit most from the program. In another study, guided self-help treatment had similar effects as face-to-face psychotherapy for the treatment of depression and anxiety [15].

A variety of psychological interventions are available for treating and managing depression and anxiety, one of them being psychoeducation. Psychoeducational interventions are educational interventions offered to individuals with psychological or physical illnesses, which are available in both active and passive forms [16].

A meta-analysis on depression, anxiety, and psychological distress showed that brief, passive psychoeducational interventions are useful to reduce depression and psychological distress [16]. Passive psychoeducational interventions are relatively cheap, easy to implement, and can be done by nonprofessionals [16]. Brief intervention programs are shown to yield positive results [17].

In another review on psychological therapies for mood disorders in adults, it was found that psychoeducation is effective in treating depression [18]. Patients with mild symptoms of depression benefit more from psychoeducation and were found to have better quality of life [19]. The study also showed that group psychoeducation is effective in the short term in reducing the scores of depression. Significant reduction in depressive symptoms through a brief mailed intervention was also demonstrated in a study by Geisner and colleagues [20]. It has also been shown that psychoeducation is effective in reducing mild-to-moderate depression [21].

A study by Mackinnon and colleagues [17] comparing the outcome of CBT and a depression information website showed a reduction in depressive symptoms in both intervention groups compared to the control group. The study also found that the effect persisted at 12 months of follow-up.

A study comparing the effectiveness of two Internet interventions found that both CBT and psychoeducation reduce depressive symptoms in the intervention group as compared to the control group [11]. The information site for depression was also found to improve the participants' knowledge on their medical, psychological, and preference of lifestyle treatments.

Due to the importance and significance of self-management to reduce depression and anxiety, we aim to investigate the effectiveness of a 4-week Web-based psychoeducational intervention program for depressive and anxiety symptoms in the community of Selangor, Malaysia. As far as we know, there is currently no available published data on Internet-based management in Malaysia on these disorders. Therefore, this study was designed to evaluate the effectiveness and applicability of a Web-based psychoeducational intervention program in our population.

Methods

Study Design

A two-arm parallel randomized controlled trial (RCT) of a single-blind study will be conducted to compare 4 weeks of a

Web-based psychoeducational intervention program versus a waitlist control group. This study (phase 2) is a continuation of a preliminary study (phase 1), which consisted of a cross-sectional survey to detect depression and anxiety among adults in community households in the state of Selangor, Malaysia. Selangor is one of the 13 states in Malaysia, with the highest level of urbanization. In the previous study, the cross-sectional study was conducted in three of nine districts in Selangor, namely Hulu Langat, Klang, and Sepang. The study population of this study is only representative of Selangor.

Inclusion and Exclusion Criteria

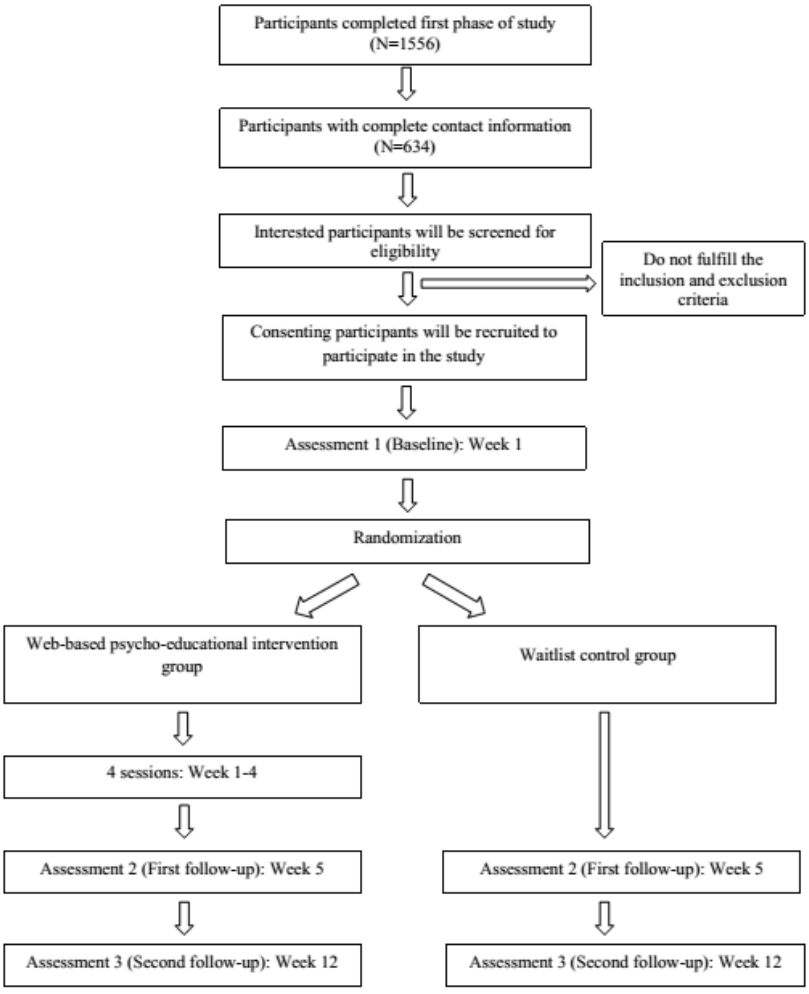
Participants who participated in the first phase of this study will be invited to participate in this study. The inclusion criteria of this study are: (1) participants who have participated in the first phase of this study and who are still living in Selangor, (2) have access to a computer and have an Internet connection, and (3) are Internet-literate. Potential participants will be excluded if they are currently receiving any psychotherapy for diagnosed psychiatric disorders.

Recruitment

A total of 1556 participants participated in the first phase of this study, entitled "Contributing Factors of Common Mental Health Disorders in Selangor." Out of these, 634 participants provided complete contact information. This serves as the sampling frame in this study. A team of trained enumerators will visit the participants' households to brief them about the study. Their personal particulars will be updated and their Internet literacy will be checked.

Eligible participants will be invited to participate in the study (second phase) through a phone call by a trained research assistant. They will be briefed about the study again. A respondent information sheet containing detailed information about the study, website log-in information, and a consent form will be emailed to the participants. After consenting to participate in the study, the participants will complete the baseline online assessment and then will be randomly allocated to either the intervention or the control group (Figure 1).

Figure 1. Flowchart of study design.



Randomization

A list of eligible participants who consented to participate in the study will be numbered. Using a random number table, the participants will be randomly allocated to either the intervention or the control group. This study is a single-blinded trial in which the participants will not know whether they are in the intervention or the control group. However, the researcher-in-charge will be aware of the group allocation.

Intervention

Psychoeducational Intervention Program ("Komuniti Sihat")

"Komuniti Sihat," which means "A Healthy Community," is a brief Web-based psychoeducational intervention program. It was developed based on the findings from the first phase of this study, which explored the predictors of depression [22] and anxiety in the community of Selangor, Malaysia. The predictors of depression and anxiety were the presence of chronic diseases, serious problems at work, serious financial constraint, high perceived stress, domestic violence, low self-esteem, and unhappy relationships with children, spouse, and family. These predictors were incorporated in the program.

The intervention program consists of four sessions, with each session accessed each week. The first session includes a description of depression and anxiety, facts and myths, causes, symptoms, available treatments, self-help tips, and contact information for help. The second session involves some CBT and positive psychology. This session includes: what we need to understand, why we need to change our thinking, what we need to do, ways to think positive, ways to solve problems, relaxation techniques, and general ways to achieve good mental health. The third and fourth sessions are mainly to address stressful life events based on the findings from the first phase of the study. The third session is on techniques on how to deal with chronic diseases, stress, low self-esteem, and domestic violence, whereas the fourth session deals with issues of unhappy relationships with spouse and children, financial constraints, and problems at work.

A pilot study was carried out among 40 participants before data collection in February 2014. Errors and mistakes in the program were identified through comments obtained from the participants and were corrected accordingly. The content of this program was also reviewed by a group of expert panels, including a family medicine specialist, two psychiatrists, two clinical psychologists, a public health physician, an epidemiologist, and a biostatistician. The content of the program was revised and refined based on the comments and suggestions received from the expert panel and were also modified to meet our target population. The development of the program, process of reviewing, amendments, and completion of the program took 8 months to complete.

The four-session program is delivered online on a weekly basis. It takes approximately 15 to 20 minutes to complete each session. The participants will be taught on how to log on and use the website during the first visit to their respective households. Participants' email addresses will be registered by an information technology technician based on the allocation group. Thereafter, the participants will log on to the website [23], using their email addresses and passwords, and complete the assessments and sessions on their own. Participants in the intervention group are allowed to view the full content on the website and use the program as frequently and as long as they want. The researchers can monitor each participant's detailed log-in information in the back-end system.

Emails and Text Messages

Before commencement of the program, the participants will be notified of the dates for each session through email, which will also be provided in the website log-in information site. Participants will receive notification of the commencement of each session every Monday via email and a phone call and they will be given 7 days to complete the session. First reminders via text messages will be sent every Wednesday to alert the participants to log in and complete the session. For those who do not complete the session, a second and third reminder through phone calls will be done on Fridays and Sundays. These reminders are important to enhance the compliance of the participants to the program.

Waitlist Control Group

Participants allocated to the control group will be blocked from the content of the intervention program. They will only be allowed to do the assessments. After the 12-week follow-up assessment, the participants in the control group will be offered to join the intervention program if they are interested and this is purely on a voluntary basis.

Outcome Measures

Primary Outcome Measure

The primary outcome of this study will be the change in depressive and anxiety symptoms. This is defined by a change in the sum score on the Patient Health Questionnaire 9 (PHQ-9) and Generalized Anxiety Disorder 7 (GAD-7) between the baseline and follow-up assessments at weeks 5 and 12.

Secondary Outcome Measure

The secondary outcome of this study will be the change in the mental health literacy score. This is defined by a change in the total score on the Mental Health Literacy Questionnaire (MHLQ) between the baseline and follow-up assessments at weeks 5 and 12 (Table 1).

Table 1. Overview of measurements.

Instrument	Aim	Time of measurement		
		T_0 (Baseline)	T_1 (Posttest at week 5)	T_2 (Follow-up at week 12)
Sociodemographics	Characteristics of participant	Yes		
PHQ-9	Symptoms of depression	Yes	Yes	Yes
GAD-7	Symptoms of anxiety	Yes	Yes	Yes
MHLQ	Mental health literacy	Yes	Yes	Yes

Instruments

Patient Health Questionnaire 9

The PHQ-9 is used to measure the severity of depression based on the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition; *DSM-IV*) criteria. It consists of nine items, each item rated on a scale from 0 to 3, and a total score range from 0 to 27. Both the validated English [24] and Malay [25] versions of the questionnaire are used in this study.

Generalized Anxiety Disorder 7

The GAD-7 is used to measure the severity of anxiety based on the *DSM-IV* criteria. The seven items are each scored from 0 to 3, with an overall range score of 0 to 21. Both the validated English [26] and Malay [27] versions of the questionnaire are used in the study.

Mental Health Literacy Questionnaire

Some studies uses case vignettes to measure the knowledge of participants on mental health illness, such as depression, anxiety, and schizophrenia. However, the education level of a community in a developing country such as Malaysia is lower compared to developed countries. Because of this, we are unable to use case vignettes and specific facts to assess the mental health knowledge of the participants. Therefore, we had to create items measuring knowledge based on a local context, taking into account cultural-specific issues.

To assess the knowledge on depression and anxiety, eight items were developed based on the content of the psychoeducational intervention program (general knowledge on mental health). Another four items were adapted from the MHLQ from the domain of knowledge and capability [28] and were modified based on the suitability of the items measuring depression and anxiety in this study. In total, 12 items were used to assess the participant's knowledge on depression and anxiety. The items are coded as yes and no. The items will be summed, with a total score ranging from 0 to 12. Both English and Malay versions of the questionnaire are used in this study.

Sample Size

The sample size for this study was calculated using a formula by Lemeshow et al [29]: $n=(2\sigma^2[Z_{1-\alpha/2}+Z_{1-\beta}]^2)/([\mu_1-\mu_2]^2)$.

Using a power of 80%, a confidence interval of 95%, a pooled standard deviation of 9.865, and a baseline and posttest mean score of 21.1 and 16.2, respectively, in the intervention group [11], the calculated sample size was estimated to be 64 participants. Taking into consideration a 30% dropout rate [30], the final sample size calculated was 84 participants in each group.

Statistical Analysis

Data will be analyzed using IBM SPSS version 21.0 software. Differences between sociodemographic characteristics for the intervention and control groups will be tested using chi-square and *t* tests. A mixed between-within subjects ANOVA will be employed to compare the mean difference of the psychoeducation intervention program between the two groups at pretest, posttest (week 5), and at 2-months of follow-up (week 12). The magnitude effect size of the intervention program will be calculated using Cohen's formula. Analyses will be conducted based on the intention-to-treat principle and for all completers.

Trial

The trial will be conducted using the Internet as a medium of implementation of the psychoeducation intervention program. The planning of the study started on March 1, 2013, and data collection is expected to be complete on August 14, 2014. At the point of submitting this paper for publication, data analysis had not yet been completed.

Ethics Approval and Registration

This study was approved by the University Research Ethics Committee of Universiti Putra Malaysia on August 14, 2013 (Reference No: UPM/TNCPI/RMC/1.4.18.1 JKEUPM). The study is registered in the Malaysian National Medical Research Registry (NMRR-14-698-21864) and in the ISRCTN registry (ISRCTN39656144). Consent will be obtained from all the participants who are willing to participate in the study.

Results

By the time the manuscript was submitted to the journal, data collection was completed. The results are expected to be published in late 2015 or early 2016.

Discussion

This RCT study protocol is aimed to investigate the effectiveness of a Web-based psychoeducational intervention for depressive and anxiety symptoms for the adult community in Selangor, Malaysia. Self-management through the Internet offers the opportunity to reach and treat the community who may suffer from mild-to-moderate depression and anxiety, and for those who are reluctant to seek for assistance from medical professionals. In addition, it can serve as an appealing modality for quick help to manage these problems. Web-based programs

can provide the advantage of disclosing certain information better than face-to-face interviews. Moreover, information can be accessed 24/7 and is available to a wider community. This can be very useful when an immediate need is required for information on management.

To our knowledge, Internet-based management for both depression and anxiety in the community has not been studied in Malaysia. This study could give an insight on the effectiveness and applicability of a Web-based psychoeducation program in the current population. The strength of this study is that the psychoeducational intervention program is developed based on the predictors of depression [22] and anxiety in our own population. The program aims to address the predictors that contribute to depression and anxiety in our community. This brief Web-based program will enable the community to use easy, user-friendly, valid, and reliable tools for assessing their mental health status.

Second, the availability of the program in both English and Malay languages is an additional plus point. Participants can choose their preference language to complete the sessions. Third, the assessments are available in both languages and have been validated in our population. Fourth, the intervention program was designed to be as brief as possible to increase the acceptability of the program versus other lengthier interventions, which could further increase the dropout rates.

Nevertheless, there are some limitations in this study. One potential limitation of this study is the nature of a Web-based program itself. The Web-based program will be restricted only to those who are literate and who have access to the Internet. Although its use will be limited to people who are computer literate and who have access to the Internet, this population is increasing significantly in Malaysia. Therefore, a great number of people will be able to access this Web-based assessment and intervention program, and use it for assessment of their own mental health and seek help when required. A second limitation is assurance cannot be made that the selected participants will complete the study by themselves. However, by having a specific username and password to log in to the system, this problem would be minimized. Another potential limitation is the short duration of follow-up to assess the effect of the intervention program. However, studies have shown that effectiveness can be shown even with shorter durations [19].

The Web-based psychoeducation program could serve as a new modality to manage mild-to-moderate depression and anxiety. Our study aims to provide better recognition and management of depressive and anxiety symptoms. It also aims to educate and create awareness about depression and anxiety in the community. Depression and anxiety are the most common mental health disorders. There is a need to develop simple, brief, and effective interventions tailored to the needs of the community to reduce the burden of these disorders.

Acknowledgments

We would like to thank the government of Malaysia for funding this study and the research assistants who were involved in the website development and participant recruitment. This research was funded by the E-science Fund Ministry of Science and Technology Malaysia (MOSTI) under the project grant number of 06-01-04-SF1587 to SMS.

Conflicts of Interest

None declared.

References

1. Kessler R, Aguilar-Gaxiola S, Alonso J, Chatterji S, Lee S, Ormel J, et al. The global burden of mental disorders: an update from the WHO World Mental Health (WMH) surveys. Epidemiol Psychiatr Soc 2009;18(1):23-33 [FREE Full text] [Medline: 19378696]
2. Wittchen H, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jönsson B, et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur Neuropsychopharmacol 2011 Sep;21(9):655-679. [doi: 10.1016/j.euroneuro.2011.07.018] [Medline: 21896369]
3. Andrews G, Issakidis C, Sanderson K, Corry J, Lapsley H. Utilising survey data to inform public policy: comparison of the cost-effectiveness of treatment of ten mental disorders. Brit J Psychiat 2004 Jun 01;184(6):526-533. [doi: 10.1192/bjp.184.6.526]
4. Kohn R, Saxena S, Levav I, Saraceno B. The treatment gap in mental health care. Bull World Health Organ 2004 Nov;82(11):858-866 [FREE Full text] [Medline: 15640922]
5. Griffiths K, Christensen H. Review of randomised controlled trials of Internet interventions for mental disorders and related conditions. Clin Psychol 2006;10(1):16-29. [doi: 10.1080/13284200500378696]
6. Klein B, Meyer D, Austin D, Kyrios M. Anxiety online: a virtual clinic: preliminary outcomes following completion of five fully automated treatment programs for anxiety disorders and symptoms. J Med Internet Res 2011;13(4):e89 [FREE Full text] [doi: 10.2196/jmir.1918] [Medline: 22057287]
7. Siu BW, Chow KK, Lam LC, Chan W, Tang VW, Chui WW. A questionnaire survey on attitudes and understanding towards mental disorders. East Asian Arch Psychiatry 2012 Mar;22(1):18-24 [FREE Full text] [Medline: 22447801]
8. Wade AG. Use of the internet to assist in the treatment of depression and anxiety: a systematic review. Prim Care Companion J Clin Psychiatry 2010;12(4). [doi: 10.4088/PCC.09r00876blu]

9. Ebert DD, Lehr D, Baumeister H, Boß L, Riper H, Cuijpers P, et al. GET.ON Mood Enhancer: efficacy of Internet-based guided self-help compared to psychoeducation for depression: an investigator-blinded randomised controlled trial. Trials 2014;15:39 [FREE Full text] [doi: 10.1186/1745-6215-15-39] [Medline: 24476555]
10. Griffiths K, Farrer L, Christensen H. The efficacy of internet interventions for depression and anxiety disorders: a review of randomised controlled trials. Med J Aust 2010 Jun 7;192(11 Suppl):S4-S11. [Medline: 20528707]
11. Christensen H, Griffiths K, Jorm AF. Delivering interventions for depression by using the internet: randomised controlled trial. BMJ 2004 Jan 31;328(7434):265 [FREE Full text] [doi: 10.1136/bmj.37945.566632.EE] [Medline: 14742346]
12. Spek V, Cuijpers P, Nyklícek I, Riper H, Keyzer J, Pop V. Internet-based cognitive behaviour therapy for symptoms of depression and anxiety: a meta-analysis. Psychol Med 2007 Mar;37(3):319-328. [doi: 10.1017/S0033291706008944] [Medline: 17112400]
13. Andersson G, Cuijpers P, Carlbring P, Linderfors N. ffects of Internet-delivered cognitive behaviour therapy for anxiety and mood disorders. Psychiatry 2007;2:9-14.
14. van Straten A, Cuijpers P, Smits N. Effectiveness of a web-based self-help intervention for symptoms of depression, anxiety, and stress: randomized controlled trial. J Med Internet Res 2008;10(1):e7 [FREE Full text] [doi: 10.2196/jmir.954] [Medline: 18364344]
15. Cuijpers P, Donker T, van Straten A, Li J, Andersson G. Is guided self-help as effective as face-to-face psychotherapy for depression and anxiety disorders? A systematic review and meta-analysis of comparative outcome studies. Psychol Med 2010 Dec;40(12):1943-1957. [doi: 10.1017/S0033291710000772] [Medline: 20406528]
16. Donker T, Griffiths K, Cuijpers P, Christensen H. Psychoeducation for depression, anxiety and psychological distress: a meta-analysis. BMC Med 2009;7(79). [doi: 10.1186/17417015779]
17. Mackinnon A, Griffiths K, Christensen H. Comparative randomised trial of online cognitive behavioural therapy and an information website for depression: 12 month outcomes. Br J psychiatry 2008;192(2):130-134. [doi: 10.1192/bjp.bp.106.032078]
18. Hollon S, Ponniah K. A review of empirically supported psychological therapies for mood disorders in adults. Depress Anxiety 2010 Oct;27(10):891-932 [FREE Full text] [doi: 10.1002/da.20741] [Medline: 20830696]
19. Casañas R, Catalán R, Luis J, Real J, Valero S, Casas M. ffectiveness of a psycho-educational group program for major depression in primary care: a randomized controlled trial. BMC Psychiatry 2012 2012;12(230). [doi: 10.1186/1471-244X-12-230]
20. Geisner I, Neighbors C, Larimer ME. A randomized clinical trial of a brief, mailed intervention for symptoms of depression. J Consult Clin Psychol 2006 Apr;74(2):393-939. [doi: 10.1037/0022-006X.74.2.393] [Medline: 16649884]
21. Cuijpers P, Donker T, Johansson R, Mohr D, van Straten A, Andersson G. Self-guided psychological treatment for depressive symptoms: a meta-analysis. PLoS One 2011;6(6):e21274 [FREE Full text] [doi: 10.1371/journal.pone.0021274] [Medline: 21712998]
22. Kader MS, Mohd SS, Rampal L, Mukhtar F. Prevalence, associated factors and predictors of depression among adults in the community of Selangor, Malaysia. Plos One 2014;9(4):e95395. [doi: 10.1371/journal.pone.0095395]
23. Universiti Putra Malaysia. Komuniti Sihat [A healthy community]. 2014. URL: http:\www.komunitisihat.com [WebCite Cache ID 6hnM5hQF8]
24. Kroenke K, Spitzer R, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001 Sep;16(9):606-613 [FREE Full text] [Medline: 11556941]
25. Sherina M, Arroll B, Goodyear-Smith F. Criterion validity of the PHQ-9 (Malay version) in a primary care clinic in Malaysia. Med J Malaysia 2012 Jun;67(3):309-315 [FREE Full text] [Medline: 23082424]
26. Spitzer R, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006 May 22;166(10):1092-1097. [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
27. Mohd SS, Arroll B, Goodyear-Smith F. Validation of the GAD-7 (Malay version) among women attending a primary care clinic in Malaysia. J Prim Health Care 2012;4(1):5-11.
28. Davis C, Massey O, Smith R, Armstrong M, Vergon K, McNeish R. Refinement of an Instrument to Measure Mental Health Literacy and Examination of Interventions to Enhance Mental Health Literacy (Agency for Health Care Administration). Tampa, FL: Louis de la Parte Florida Mental Health Institute; 2008.
29. Lemeshow S, Hosmer D, Klar J, Lwanga S. Adequacy of Sample Size in Health Studies. Hoboken, NJ: Wiley; 1990.
30. Melville K, Casey L, Kavanagh DJ. Dropout from Internet-based treatment for psychological disorders. Br J Clin Psychol 2010 Nov;49(Pt 4):455-471. [doi: 10.1348/014466509X472138] [Medline: 19799804]

Abbreviations

CBT: cognitive behavioral therapy
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)
GAD: generalized anxiety disorder
GAD-7: Generalized Anxiety Disorder 7
MHLQ: Mental Health Literacy Questionnaire

PHQ-9: Patient Health Questionnaire 9
RCT: randomized controlled trial

Edited by G Eysenbach; submitted 06.05.15; peer-reviewed by H Jin; comments to author 05.01.16; revised version received 01.02.16; accepted 01.02.16; published 21.06.16.

Please cite as:
Kader Maideen SF, Mohd-Sidik S, Rampal L, Mukhtar F, Ibrahim N, Phang CK, Tan KA, Ahmad R
A Web-Based Psychoeducational Intervention Program for Depression and Anxiety in an Adult Community in Selangor, Malaysia: Protocol of a Randomized Controlled Trial
JMIR Res Protoc 2016;5(2):e112
URL: http://www.researchprotocols.org/2016/2/e112/
doi:10.2196/resprot.4622
PMID:27329333

Protocol

Use of Subperiosteal Drain Versus Subdural Drain in Chronic Subdural Hematomas Treated With Burr-Hole Trepanation: Study Protocol for a Randomized Controlled Trial

Jehuda Soleman[1,2], MD; Katharina Lutz[1], MD; Sabine Schaedelin[3], MSc; Luigi Mariani[2], MD; Javier Fandino[1], MD

[1]Department of Neurosurgery, Kantonsspital Aarau, Aarau, Switzerland, Aarau, Switzerland

[2]Department of Neurosurgery, University Hospital Basel, Basel, Switzerland, Basel, Switzerland

[3]Clinical Trial Unit, University Hospital of Basel, Basel, Switzerland, Basel, Switzerland

Corresponding Author:
Jehuda Soleman, MD
Department of Neurosurgery, University Hospital Basel, Basel, Switzerland
Spitalstrasse 21
Basel,
Switzerland
Phone: 41 62 2654141
Fax: 41 62 2654141
Email: jehuda.soleman@gmail.com

Abstract

Background: Chronic subdural hematoma (cSDH) is one of the most frequent neurosurgical conditions affecting elderly people and is associated with substantial morbidity and mortality. The use of a subdural drain (SDD) after burr-hole trepanation for cSDH was proven to reduce recurrence and mortality at 6 months. To date in neurosurgery practice, evidence-based guidelines on whether an SDD or subperiosteal drain (SPD) should be used do not exist. Currently both methods are being practiced depending on the institute and/or the practicing neurosurgeon.

Objective: The aim of this study is to compare the reoperation rates after burr-hole trepanation and insertion of an SPD or SDD in patients with cSDH.

Methods: This is a prospective, noninferiority, multicenter, randomized controlled trial designed to include 220 patients over the age of 18 years presenting with a symptomatic cSDH verified on cranial computed tomography or magnetic resonance imaging who are to undergo surgical evacuation with burr-hole trepanation. After informed consent is obtained, patients are randomly allocated to an SPD or SDD group. The primary endpoint is recurrence indicating a reoperation within 12 months.

Results: This research is investigator-initiated and has received ethics approval. Patient recruitment started in April 2013, and we expect all study-related activities to be completed by the end of 2016 or beginning of 2017.

Conclusions: To date, evidence-based recommendations concerning the operative treatment of cSDH are sparse. Results of this research are expected to have applications in evidence-based practice for the increasing number of patients suffering from cSDH and possibly lead to more efficient treatment of this disease with fewer postoperative complications.

Trial Registration: ClinicalTrials.gov NCT01869855; https://clinicaltrials.gov/ct2/show/NCT01869855 (Archived by WebCite at http://www.webcitation.org/6fNK4Jlxk)

(JMIR Res Protoc 2016;5(2):e38) doi:10.2196/resprot.5339

KEYWORDS

chronic subdural hematoma; drain; hematoma; recurrent hematoma; burr-hole trepanation

Introduction

Background

Chronic subdural hematoma (cSDH) is one of the most frequent neurosurgical conditions affecting elderly people and is associated with substantial morbidity and mortality [1-3]. Its incidence is reported to be 1.7-13.1 per 100,000 inhabitants per year, but the incidence has been steadily increasing due to prolonged life expectancy [4-6]. Surgical treatment is recommended in patients with neurological symptoms. In the

only evidence-based review of the different surgical treatment modalities of cSDH, Weigel et al concluded that burr-hole craniostomy with irrigation and drainage has the best cure-to-complication ratio [7]. Recurrence is the most common complication following surgical treatment of cSDH with a rate of 0%-30% [3,4,8]. A randomized controlled study by Santarius et al showed reduced recurrence and mortality placing a subdural drain (SDD) compared to not placing a drain after burr-hole evacuation of cSDH [2]. Gazzeri et al and Zumofen et al used a closed subperiosteal drain (SPD) instead of the more commonly used SDD, and the method showed equal or superior results in outcome, complications, and postoperative symptoms compared to previous studies [9,10]. Since the SPD is not positioned in direct contact to cortical structures, bridging veins, or hematoma membranes, it is considered safer and might be favorable to an SDD. In a retrospective study, Bellut et al compared 48 patients treated with SPD to 65 patients treated with SDD and found lower mortality rates and fewer serious complications in the group treated with SPD with no difference in recurrence rate of cSDH [5]. However, none of the results showed a significant difference, and it was concluded that further randomized studies with a larger patient cohort are needed [5]. In a recently published prospective randomized study, Kaliaperumal et al concluded that the recurrence rate after placing an SPD is equal to that following placement of an SDD, with the modified Rankin scale (mRS) of the patients in the SPD group being significantly better after 6 months [11]. However, the results may have been biased since the preoperative mRS in the SPD group was inferior to those in the SDD group. In addition, the number of patients studied was small (25 per group), and the overall recurrence rate was 0%, with very low morbidity and mortality rates compared to the literature. Due to these biases the authors recommend further prospective and randomized studies with larger patient cohorts [11].

At the time of this writing, evidence-based guidelines on which method should be used in cSDH do not exist, and both SDDs and SPDs are being used depending on the institute and/or the practicing neurosurgeon.

Aims and Objectives

The primary objective of our study is to investigate in a randomized controlled fashion whether the recurrence rate after insertion of an SPD is noninferior compared to the insertion of an SDD in patients undergoing surgical evacuation of a cSDH with burr-hole trepanation. The secondary objective of the study is to assess whether the insertion of an SPD leads to fewer operative complications, a lower mortality, and a better outcome.

Methods

Trial Design

This is a prospective, multicenter, noninferiority, randomized controlled study. Eligible participants are block-randomized in a 1:1 allocation ratio to one of two arms: an intervention arm, insertion of an SPD and a control arm, insertion of an SDD.

Study Setting and Selection Criteria

Patients will be recruited from the departments of neurosurgery at Kantonsspital Aarau and University Hospital of Basel in Switzerland. Both centers are major trauma and neurosurgical referral centers. Eligible participants are female or male over the age of 18 years presenting to one of the centers with a symptomatic cSDH diagnosed by computed tomography (CT) and/or magnetic resonance imaging (MRI). Exclusion criteria are as follows: (1) surgeon decides to perform a craniotomy based on any intraoperative condition (eg, acute hematoma), (2) cSDH is caused by an underlying condition (eg, overdrainage of a ventriculoperitoneal shunt), and (3) no informed consent.

Informed Consent

Written informed consent of the patient or relative must be obtained by a member of the neurosurgical staff prior to randomization. The neurosurgical staff members undergo a trial-specific training making them eligible to include patients in the trial. A written information sheet is given to the patient or relative and as much time as necessary is allowed to discuss the options. If the patient is unable to give consent due to the nature of the hemorrhage, a personal representative is approached to give consent on behalf of the patient. If the patient is unable to consent and a relative or representative of the patient is not available, an independent doctor can consent on behalf of the patient. In such a case, consent by the patient or representative must be sought at a later time or the patient will be excluded from the study. The consent forms (written in German) are filed with the trial documentation.

Randomization

Randomization with blocks of 30 in an allocation ratio of 1:1 will be performed by the investigators using the Web-based randomization software Random Allocation version 1.0. Instructions on which drain should be implanted are kept in sealed envelopes labeled with sequential study numbers and opened at surgery before the insertion of the drain. The nature of this intervention does not allow for masking of treatment allocation. However, data is encoded and clinicians are masked to outcomes when possible.

Trial Interventions

All patients undergo surgical evacuation of a symptomatic cSDH with two burr-hole trepanations; an SPD or SDD is then inserted without suction according to the arm of the study to which the patient has been randomized. The surgical procedure is standardized for both institutions and consists of supine positioning of the patients on a horseshoe headrest. The frontal and parietal areas of the head are shaved, and patient is draped. After skin incision, two 13 mm burr-holes about 7 to 8 cm apart are drilled over the maximum width of the hematoma. The dura mater is opened with a cruciate incision and coagulated. The subdural hematoma is then washed out with warm saline with or without a Nelathon catheter. Once the surgeon completes the irrigation and is ready for drain insertion, the randomization envelope is opened and the assigned drain (subdural or subperiosteal) is inserted. The SDD is inserted from the parietal burr-hole in frontal direction under visual control. The SPD is inserted subgalealy and placed over both burr-holes. In case of

a subperiosteal insertion, the burr-holes should not be sealed off with any kind of material (eg, PDS-Folie, Spongostan) so that a communication between the subdural space and the SPD is maintained. Bilateral hematomas are treated as one case; both sides receive the same treatment. Patients with crossover treatment (ie, a patient is randomized to SDD but the surgeon feels it is unsafe to insert an SDD because the brain might be injured and inserts an SPD) will be noted in the case report form and will not be excluded from the study. If the surgeon decides intraoperatively to perform a craniotomy (eg, due to clotted hemorrhage which does not evacuate with burr-hole trepanation), the patient will be excluded from the trial.

Data Collection

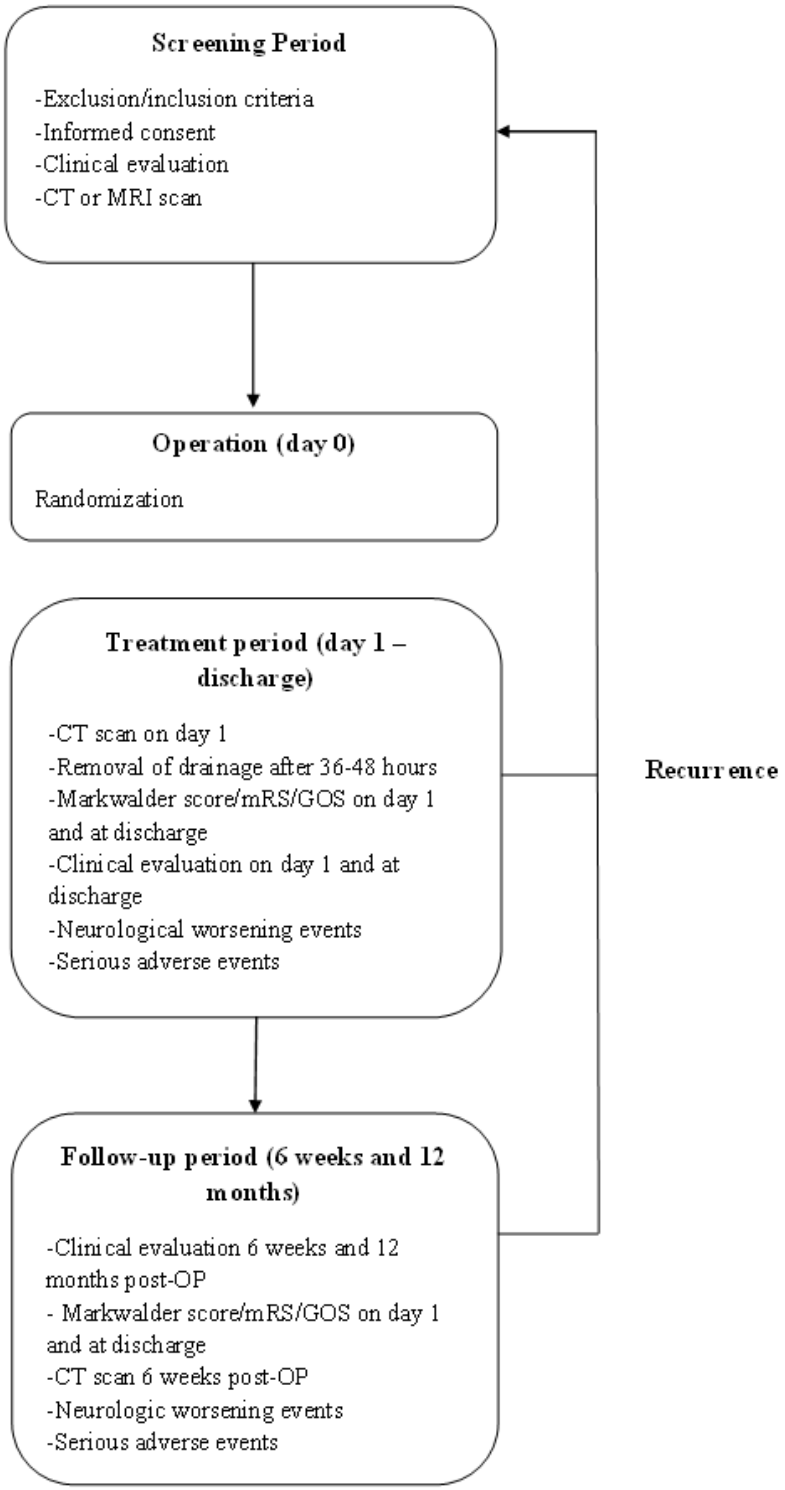
To preserve confidentiality all patients are allocated a unique study identifier during the recruitment process that is used on all data collection forms. All study documentation is held in secure offices, and the study researchers operate according to a signed code of confidentiality. All data are entered into a password-secured database by the data managers.

Participant Timeline

1. Patient admission.
2. Clinical evaluation and cranial CT (if none exists).
3. Obtain informed consent.
4. If the patient is treated with vitamin K antagonist, preoperative reversal using Beriplex and Konakion is done aiming for a preoperative international normalized ratio of 1.3. In patients treated with Aspirin Cardio or Plavix, the medications should be discontinued and surgery postponed for 5 to 7 days if possible. If emergency surgery is indicated, the Aspirin Cardio or Plavix should be discontinued preoperatively and for 2 to 6 weeks postoperatively depending on the indication for treatment (see step 12).
5. Surgical evacuation of the cSDH with burr-hole trepanation.
6. Randomization: SDD group versus SPD group.
7. Monitoring in the intermediate or intensive care unit.
8. Cranial CT and clinical evaluation 24 hours postoperative.
9. Low-weight molecular heparin in prophylactic dosage is given postoperatively with mobilization of the patient (with the drainage pinched off) after 24 to 48 hours.
10. Drain removal after 36 to 48 hours.
11. Patient discharge after clinical evaluation on postoperative day 5 or later.
12. Resumption of Aspirin Cardio or Plavix no earlier than 2 weeks postoperatively for patients with secondary prophylaxis and 6 weeks postoperatively for patients with primary prophylaxis. Resumption of Marcoumar should be no earlier than 6 weeks postoperatively.
13. Clinical evaluation and cranial CT at the outpatient clinic 6 weeks postoperatively (±2 weeks).
14. Clinical evaluation at the outpatient clinic 12 months postoperatively (±4 weeks).

See Multimedia Appendix 1 for a time schedule of enrollment, interventions, assessments, and visits for participants. The flow diagram (Figure 1) illustrates the key steps of the trial.

Figure 1. Study workflow mRS: modified Rankin Scale, GOS: Glasgow Outcome Scale, CT: computer tomography, MRI: magnetic resonance imaging.



Serious Adverse Events

Serious adverse events (SAEs) are recorded on the SAE form and include any of the following outcomes: death, life threatening events, requirement for a new hospitalization or prolongation of existing hospitalization, recurrent event, or persistent or significant disability caused by the surgical treatment. All SAEs will be reported to the local ethics committee, Ethikkommission Nordwest- und Zentralschweiz (EKNZ), within 7 days.

Outcomes

The primary outcome measure is recurrence needing revision surgery within 12 months postoperatively. Secondary outcome

measures include: (1) complication (morbidity) within 12 months postoperatively; (2) mortality within 12 months postoperatively; (3) Markwalder Scale, mRS, and Glasgow Outcome Score; and (4) radiological characteristics of postoperative CT images at 24 hours and 6 weeks. On axial CT scans, the midline shift is measured in millimeters at the level of the foramina of Monro and the thickness of the hematoma at the thickest area.

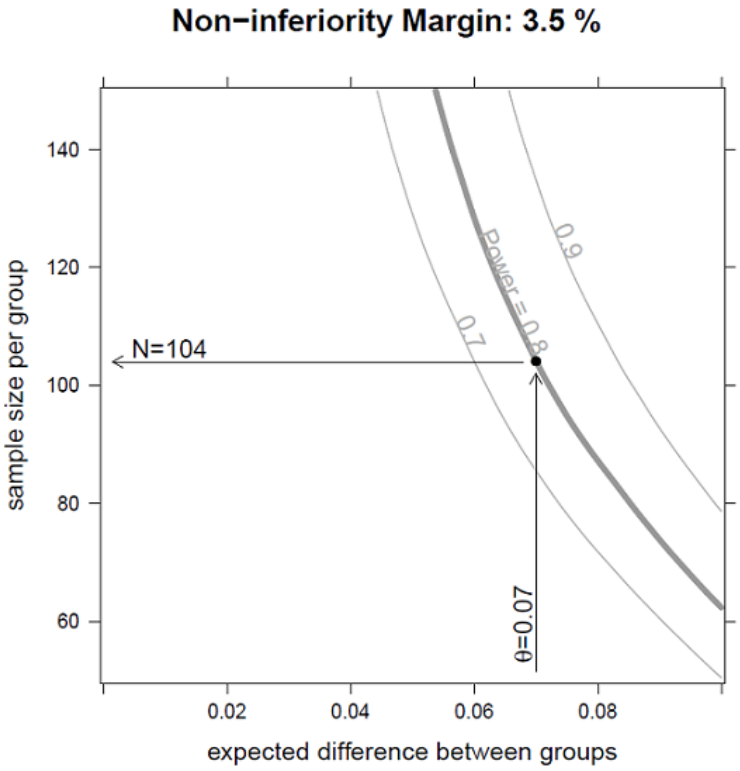
Sample Size

Initially the study was planned as a superiority study to show a significant difference in the recurrence rate of cSDH between insertion of an SPD and an SDD. When estimating the sample size, a difference in the recurrence rate of 10% in the SDD group versus 20% in the SDP group was assumed (based on Bellut et al and Santarius et al [2,5]), leading to the estimate of 150 patients in each group. New studies [12] and the blind data review of the first 56 patients (both groups pooled) suggested a lower recurrence rate of 7%. Therefore the sample size was reviewed. At the same time, the study design was changed from a superiority to a noninferiority design, and a noninferiority margin of 3.5% was defined.

We reestimated the recurrence rates in a blinded manner based on the overall recurrence rate. Since no hypothesis test was performed, no *P* value adjustment to control type I error was needed. Data from all patients who had a follow-up visit could be used for the sample size review. When reestimating the recurrence rates, it was assumed that the probability of being in one group or the other (SDD vs SPD) for patients who had a follow-up visit would be equal. As stated the reestimated recurrence rate was 7%, which was the expected difference between the SDD group and SPD group (3.5%−10.5%=7%). Using the reestimated recurrence rates, the sample size N was reestimated using a resampling procedure. Each sample size, $N_{i=1;...;101}=50;...;150$, was evaluated by sampling 9999 times N_i individual samples based on the assumptions described above. Confidence intervals (CIs) for the difference between proportions were calculated using a continuity-corrected modification of the Wilson score method. Sample size was set to ensure with 80% power (1–β=0.8) (ie, in 80 of 100 hypothetical repetitions of the study) the estimation of a 95% CI, which is entirely below the predefined noninferiority margin of 3.5%.

For this study, a total of 220 patients should be randomized to ensure 208 evaluable patients (110 patients randomized per study arm) (Figure 2) considering an overall drop-out rate of 5% after randomization (eg, death, lost to follow-up).

Figure 2. Sample size calculations.



Statistical Analysis

Analysis will be done on an intention-to-treat basis. Given the possibility of a proportion of crossovers, a secondary sensitivity per-protocol analysis will be undertaken. The statistical analysis for the primary outcome measure will be done in a noninferiority design with 95% CI and a noninferiority margin of 3.5% between the groups, while the secondary measures will be analyzed in a superiority design, where a *P* value of less than .05 is considered statistically significant.

Patient data will be prospectively collected and registered on case report forms. Age; sex; date of trauma; blood thinners; medical history; GCS and neurological condition at admission; hematoma size; side; and the existence of brain herniation, hydrocephalus, and midline shift are documented as basic

characteristics. Clinical outcome variables (24 hours postoperative, at discharge, 6 weeks postoperative, and 12 months postoperative): Glasgow Coma Scale and (improvement of) neurological condition, mRS, Glasgow Outcome Score, Markwalder score, recurrence needing reoperation, complications (eg, infection, epilepsy, aphasia, paresis), hospitalization time, and mortality. Radiological outcome variables (24 hours postoperative and 6 weeks postoperative): hematoma size, midline shift, and rebleed seen on cranial CT. Intraoperative variables: elective or emergency procedure, type of hematoma (chronic, acute, subacute), drain type, crossover, number of membranes, and existing communication between the two burr-holes.

Monitoring

The trial master folder and case report form data for each participant will be inspected by a monitor at yearly intervals throughout the study to verify the completeness, consistency, and accuracy of the data. The existence and integrity of the informed consent forms signed by the patient or legal representative will be monitored as well. The study monitoring is provided by Kammermann Monitoring Service, Zug, Switzerland.

A strict confidential yearly interim analysis is done by a statistician (Clinical Trial Unit, Basel, Switzerland) for the recurrence rate (primary outcome measure) and morbidity (secondary outcome measure). The trial will be stopped if the intervention arm (SPD) shows a significant noninferiority margin of 3.5% compared to the treatment arm (SDD) or if recruitment rates are unexpectedly low.

Ethical Issues

This study was approved by the local ethics committee (EKNZ, Basel, Switzerland, AG2013/001). The trial is conducted within the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice guidelines and the principles of the Declaration of Helsinki and is registered in the clinical study database ClinicalTrials.gov (NCT01869855).

Results

The study is a currently ongoing study in two neurosurgical centers: Kantonsspital Aarau and University Hospital of Basel. Enrollment began in April 2013. We expect all study-related activities to be completed by the end of 2016 or beginning of 2017.

Discussion

To date, evidence-based recommendations concerning the operative and postoperative treatment of cSDH are sparse. Most recommendations are based on observational or retrospective studies and some meta-analyses leading to class II or III recommendations [3]. For the surgical management of cSDH only one randomized controlled trial (RCT) exists, providing grade I evidence and showing that the intraoperative insertion of a drain after the completion of a burr-hole trepanation reduces the recurrence rates of cSDH significantly [2]. Further RCTs investigating and scrutinizing the standard treatment of cSDH are warranted, first and foremost due to the fact of a steady increase in the incidence of cSDH as a result of prolonged life expectancy [2,3]. With this multicenter RCT, we intend to provide grade I evidence (and class I recommendations) to an additional aspect in the surgical treatment of cSDH, namely the ideal and safest localization of an intraoperative drain. In our opinion this RCT will have great impact on the surgical management of patients presenting with this frequent condition. We hope that this clinical study will contribute to the important goal of evidence-based treatment of cSDH.

Acknowledgments

The study is financially supported by the Forschungsfond des Kantonsspital Aarau.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Visit assessment schedule.

[PDF File (Adobe PDF File), 31KB - resprot_v5i2e38_app1.pdf]

References

1. Markwalder T, Steinsiepe K, Rohner M, Reichenbach W, Markwalder H. The course of chronic subdural hematomas after burr-hole craniostomy and closed-system drainage. J Neurosurg 1981 Sep;55(3):390-396. [doi: 10.3171/jns.1981.55.3.0390] [Medline: 7264730]
2. Santarius T, Kirkpatrick P, Ganesan D, Chia H, Jalloh I, Smielewski P, et al. Use of drains versus no drains after burr-hole evacuation of chronic subdural haematoma: a randomised controlled trial. Lancet 2009 Sep 26;374(9695):1067-1073. [doi: 10.1016/S0140-6736(09)61115-6] [Medline: 19782872]
3. Soleman J, Taussky P, Fandino J, Muroi C. Evidence-Based Treatment of Chronic Subdural Hematoma. In: Sadaka F, editor. Traumatic Brain Injury. Rijeca, Croatia: InTech; 2014.

4. Baechli H, Nordmann A, Bucher H, Gratzl O. Demographics and prevalent risk factors of chronic subdural haematoma: results of a large single-center cohort study. Neurosurg Rev 2004 Oct;27(4):263-266. [doi: 10.1007/s10143-004-0337-6] [Medline: 15148652]
5. Bellut D, Woernle C, Burkhardt J, Kockro R, Bertalanffy H, Krayenbühl N. Subdural drainage versus subperiosteal drainage in burr-hole trepanation for symptomatic chronic subdural hematomas. World Neurosurg 2012 Jan;77(1):111-118. [doi: 10.1016/j.wneu.2011.05.036] [Medline: 22154148]
6. Taussky P, Fandino J, Landolt H. Number of burr holes as independent predictor of postoperative recurrence in chronic subdural haematoma. Br J Neurosurg 2008 Apr;22(2):279-282. [doi: 10.1080/02688690701818885] [Medline: 18348026]
7. Weigel R, Schmiedek P, Krauss JK. Outcome of contemporary surgery for chronic subdural haematoma: evidence based review. J Neurol Neurosurg Psychiatry 2003 Jul;74(7):937-943 [FREE Full text] [Medline: 12810784]
8. Gelabert-González M, Iglesias-Pais M, García-Allut A, Martínez-Rumbo R. Chronic subdural haematoma: surgical treatment and outcome in 1000 cases. Clin Neurol Neurosurg 2005 Apr;107(3):223-229. [doi: 10.1016/j.clineuro.2004.09.015] [Medline: 15823679]
9. Gazzeri R, Galarza M, Neroni M, Canova A, Refice G, Esposito S. Continuous subgaleal suction drainage for the treatment of chronic subdural haematoma. Acta Neurochir (Wien) 2007;149(5):487-493. [doi: 10.1007/s00701-007-1139-8] [Medline: 17387427]
10. Zumofen D, Regli L, Levivier M, Krayenbühl N. Chronic subdural hematomas treated by burr hole trepanation and a subperiostal drainage system. Neurosurgery 2009 Jun;64(6):1116-1121. [doi: 10.1227/01.NEU.0000345633.45961.BB] [Medline: 19487891]
11. Kaliaperumal C, Khalil A, Fenton E, Okafo U, Kaar G, O'Sullivan M, et al. A prospective randomised study to compare the utility and outcomes of subdural and subperiosteal drains for the treatment of chronic subdural haematoma. Acta Neurochir (Wien) 2012 Nov;154(11):2083-2088. [doi: 10.1007/s00701-012-1483-1] [Medline: 22932864]
12. Almenawer S, Farrokhyar F, Hong C, Alhazzani W, Manoranjan B, Yarascavitch B, et al. Chronic subdural hematoma management: a systematic review and meta-analysis of 34,829 patients. Ann Surg 2014 Mar;259(3):449-457. [doi: 10.1097/SLA.0000000000000255] [Medline: 24096761]

Abbreviations

CI: confidence interval
CT: computed tomography
cSDH: chronic subdural hematoma
MRI: magnetic resonance imaging
mRS: modified Rankin Scale
RCT: randomized clinical trial
SAE: serious adverse events
SDD: subdural drain
SPD: subperiosteal drain

Edited by G Eysenbach; submitted 12.11.15; peer-reviewed by E Brand, C Kaliaperumal; comments to author 30.12.15; revised version received 03.01.16; accepted 03.01.16; published 08.04.16.

Please cite as:
Soleman J, Lutz K, Schaedelin S, Mariani L, Fandino J
Use of Subperiosteal Drain Versus Subdural Drain in Chronic Subdural Hematomas Treated With Burr-Hole Trepanation: Study Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2016;5(2):e38
URL: http://www.researchprotocols.org/2016/2/e38/
doi:10.2196/resprot.5339
PMID:27059872

Protocol

The Effectiveness of Parent Training as a Treatment for Preschool Attention-Deficit/Hyperactivity Disorder: Study Protocol for a Randomized Controlled, Multicenter Trial of the New Forest Parenting Program in Everyday Clinical Practice

Anne-Mette Lange[1], MApsych, MSc (Clinical Psychology); David Daley[2], PhD; Morten Frydenberg[3], PhD; Charlotte U Rask[1,4], MD, PhD; Edmund Sonuga-Barke[5,6,7], PhD; Per H Thomsen[1,8], MD, DMSc

[1]Centre for Child & Adolescent Psychiatry, Research Department, Aarhus University Hospital, Risskov, Denmark

[2]Division of Psychiatry and Applied Psychology, School of Medicine & Centre for ADHD and Neurodevelopmental Disorders Across the Lifespan & NIHR MindTech Health Care Technology Cooperative, Institute of Mental Health, University of Nottingham, Nottingham, United Kingdom

[3]Section for Biostatistics, Department of Public Health, Aarhus University, Aarhus, Denmark

[4]Research Clinic for Functional Disorders and Psychosomatics, Aarhus University Hospital, Aarhus, Denmark

[5]Developmental Brain-Behaviour Laboratory, Academic Unit of Psychology, University of Southampton, Southampton, United Kingdom

[6]Research Department, Centre for Child & Adolescent Psychiatry, Aarhus University Hospital, Risskov, Denmark

[7]Department of Experimental Clinical & Health Psychology,, Ghent University, Ghent, Belgium

[8]Faculty of Medicine, Trondheim University, Trondheim, Norway

Corresponding Author:
Anne-Mette Lange, MApsych, MSc (Clinical Psychology)
Centre for Child & Adolescent Psychiatry
Research Department
Aarhus University Hospital
Skovagervej 2
Risskov, 8240
Denmark
Phone: 45 28771566
Fax: 45 7847 3299
Email: annelang@rm.dk

Abstract

Background: Parent training is recommended as the first-line treatment for attention-deficit/hyperactivity disorder (ADHD) in preschool children. The New Forest Parenting Programme (NFPP) is an evidence-based parenting program developed specifically to target preschool ADHD.

Objective: The objective of this trial is to investigate whether the NFPP can be effectively delivered for children referred through official community pathways in everyday clinical practice.

Methods: A multicenter randomized controlled parallel arm trial design is employed. There are two treatment arms, NFPP and treatment as usual. NFPP consists of eight individually delivered parenting sessions, where the child attends during three of the sessions. Outcomes are examined at three time points (T1, T2, T3): T1 (baseline), T2 (week 12, post intervention), and T3 (6 month follow/up). 140 children between the ages of 3-7, with a clinical diagnosis of ADHD, informed by the Development and Well Being Assessment, and recruited from three child and adolescent psychiatry departments in Denmark will take part. Randomization is on a 1:1 basis, stratified for age and gender.

Results: The primary endpoint is change in ADHD symptoms as measured by the Preschool ADHD-Rating Scale (ADHD-RS) by T2. Secondary outcome measures include: effects on this measure at T3 and T2 and T3 measures of teacher reported Preschool ADHD-RS scores, parent and teacher rated scores on the Strength & Difficulties Questionnaire, direct observation of ADHD behaviors during Child's Solo Play, observation of parent-child interaction, parent sense of competence, and family stress. Results will be reported using the standards set out in the Consolidated Standards of Reporting Trials Statement for Randomized Controlled Trials of nonpharmacological treatments.

Conclusions: The trial will provide evidence as to whether NFPP is a more effective treatment for preschool ADHD than the treatment usually offered in everyday clinical practice.

Trial Registration: ClinicalTrials.gov NCT01684644; https://clinicaltrials.gov/ct2/show/NCT01684644?term=NCT01684644&rank=1 (Archived by WebCite at http://www.webcitation/6eOOAe8Qe)

(JMIR Res Protoc 2016;5(2):e51) doi:10.2196/resprot.5319

KEYWORDS

ADHD; preschool; child; treatment; parents; parent training; psycho-social; RCT, clinical; psychological; multi-centre; TAU; non-pharmacological

Introduction

Attention Deficit/Hyperactivity-Disorder Costs for Children

Attention deficit/hyperactivity-disorder (ADHD) is a neuro-developmental disorder with symptoms frequently occurring in early childhood, however, there is a parenting program that was developed specifically for the management of ADHD in preschool children, noted below [1,2]. ADHD is one of the most common psychiatric disorders in childhood [3] and the most common reason for referral to child mental health services (CAMHS) [4]. Studies indicate that ADHD is as common in preschoolers as it is in school-age children, with population based prevalence rates ranging between 2 and 5% [5,6]. Impairment is equally common [7], including marked impairments in relationships with parents, siblings, and peers [8-11]; social and preacademic skills [12]; and neuropsychological functioning [13]. Preschool children with ADHD are at greater risk of placement in special educational classes and use more special needs services [14]. Young children with ADHD are more likely to suffer physical injury and accidental poisoning related to impulsive behaviors [7]. ADHD symptoms in preschoolers show persistence over time [15,16]. Lahey et al [17] found that 4-6 year old children who met full criteria for ADHD were highly likely to continue to meet criteria 3 years later. Preschool hyperactivity is associated with long-term economic burden. Evidence from a longitudinal health economic analysis of costs incurred across childhood, adolescence, and young adulthood found significantly higher costs for this group of individuals in areas of mental health, education, social service, and the criminal justice system [18]. In a large register-based study, it was found that childhood ADHD, by the time the child is 10, reduces parental socioeconomic status by lowering labor supply and earnings, and reduces parental relationship stability [19]. Left untreated, preschool ADHD is associated with long-term poor outcomes for the patient [20]. Hence, it is of central public priority generally, and for CAMHS specifically, to offer evidence-based and cost-effective treatments at an early stage of development in an attempt to reduce the long-term risks and change the negative trajectories that ADHD presents to the individual and to society [2].

Behavior-Based Treatment

Although medication is recommended as the front-line treatment for older children and adolescents with ADHD, international treatment guidelines do not recommend pharmacological therapies for preschool ADHD [21,22]. Indeed, available data suggest that stimulant medication such as methylphenidate is less efficacious in the preschool years and side effects are more common [23]. Long-term effects on growth and brain development are currently not definitively established. Because of these factors, psychosocial behavioral treatments for ADHD, including behavioral parent training and behaviorally based day-care interventions, are recommended as first-line treatments for ADHD in the preschool years [21]. A number of psychosocial interventions have been applied and evaluated for the treatment of preschool ADHD. A recent systematic review found that behavioral parent training is valuable as a treatment for preschool ADHD [24]. Furthermore, Sonuga-Barke et al [25] found that trials evaluating behaviorally based parent interventions had the largest effects for preschool children with ADHD.

Whereas many behaviorally based interventions are generic in nature, in that they were originally developed to help parents manage preschoolers' oppositional and challenging behavior, the New Forest Parenting Programme (NFPP) [1] is a parenting program that was developed specifically for the management of ADHD in preschool children. In addition to behavioral strategies, it includes ideas for games and activities aimed at targeting some of the self-regulatory and attention deficits that cause impairment in the condition. Supporting the child's development through parental scaffolding is a key component of the NFPP, and everyday play scenarios in the home constitute opportunities for parents to train and improve the child's ADHD symptoms. A single practitioner delivers NFPP to families in their home during eight weekly sessions.

Each session lasts approximately 90 minutes and is either for the parent only (five sessions) or the parent and child together. In an evaluation of the NFPP, Sonuga-Barke et al [1] found that the intervention reduced ADHD symptoms as reported by parents and improved behavior during a play observation task, as rated by blinded observers. Similarly, Thompson et al [26] reported that NFPP improved parent-reported ADHD symptoms in a sample of preschool children with ADHD.

At present, the evidence of the effect of NFPP is based on efficacy research carried out by the expert team of researchers and clinicians who developed the program originally, with therapists receiving support from lead investigators, and with children who have not been referred for treatment through regular community pathways. Yet, it is unexplored if the findings from the original research can be replicated in different clinical and cultural contexts, including in a different language.

This leaves open the question of whether effects shown in specialist research led services can be translated in the everyday practice of established clinical CAMHS [27]. In a review of implementation studies [28], it was shown that there is a risk that interventions will lose impact and potency when implemented in everyday clinical settings. Hence, it is emphasised that the transition of efficacious treatments has to be carefully planned and adapted to the clinical setting in which the treatment is being implemented [27,29].

Evidence-based parent training interventions specifically designed for preschool ADHD, such as the NFPP, are not currently provided by Danish CAMHS. The development and implementation of effective psychosocial treatments for young children with ADHD represent an important health policy objective. The trial described in this protocol is designed to evaluate the effectiveness of the NFPP in the treatment of young children diagnosed with ADHD referred through established clinical pathways to child psychiatry departments in Denmark. It is the first time that the NFPP has been tested in a European country outside the United Kingdom, and the first time the NFPP has been tested on children referred through established clinical pathways to tertiary child psychiatry services, to our knowledge. For these purposes, the NFPP program has been adjusted to fit the clinical and cultural context of Danish child and adolescent psychiatry services.

Aim of the Study

The objective of the trial is to examine whether the NFPP can be implemented effectively as a treatment for preschool ADHD in everyday clinical settings of existing services. To do this, we will examine ADHD and other outcomes at the end of treatment and also at a 6-month follow-up.

Methods

Trial Design

A randomized controlled trial will be carried out to investigate the effectiveness of the NFPP against a treatment as usual condition (TAU) in the treatment of ADHD in a clinical sample of young children referred to, assessed, and diagnosed at tertiary, preschool child psychiatry services in Denmark. The effectiveness of the NFPP intervention will be examined at three time points: T1 (baseline), T2 (week 12, post intervention), and T3 (6 month follow/up).

Ethics

The study is approved by the Ethics Committee for Central Danish Region (No: 1-10-72-140-12), and is approved by the Danish Data Protection Agency. The trial is registered at ClinicalTrial.gov identity no: NCT01684644, September 4, 2012.

Setting

Participants will be enlisted from the regional, hospital-based child psychiatry departments for preschool children at the three participating centers in the trial: Centre for Child and Adolescent Psychiatry-Risskov; Centre for Child and Adolescent Psychiatry-Herning; and Centre for Child and Adolescent Psychiatry-Glostrup. The departments are highly specialized, tertiary CAMH services, and lie at the end of the referral pathway for young children with mental health problems in Denmark. Prior to their referral to specialist child psychiatry services, children will usually have received an initial assessment and intervention by primary care professionals, such as an early years educational psychologist, a community pediatrician, and social services.

Eligibility Criteria

Inclusion Criteria

Inclusion criteria are: (1) child age between 3-7 years old; (2) child must have received a clinical diagnosis of ADHD, as informed by the Development and Well-Being Assessment (DAWBA) [4]; and (3) Danish must be first language spoken in the home.

Exclusion Criteria

Child exclusion criteria are: (1) intellectual disabilities (IQ < 70); (2) diagnosis of autism spectrum disorders; and (3) child currently receiving pharmacological or other psychosocial treatment for ADHD.

Parent exclusion criteria are: (1) severe psychiatric disorder (eg, untreated psychosis or untreated bipolar or severe depressive disorder) and (2) severe social adversity in the home, as defined by active child protection issues.

Recruitment Procedures

A total of 140 children (age 3-7) referred through official referral routes to a general child psychiatry service for preschool children and their parents will be recruited into the trial. A clinical psychologist or a specialist in child and adolescent psychiatry initially screens all referrals for eligibility. Referrals indicating noneligibility, due to direct descriptions of exclusion criteria in the referral letter, receive standard clinical assessment from the preschool child psychiatry team. At this point, all other referrals are regarded as eligible and parents are sent a letter including a personal access code asking them to complete the Internet DAWBA [4] or the Preschool DAWBA (DAWBA-preschool for 2-4 year olds) [30]. The DAWBA generates computerized diagnostic profiles, which are scored by child and adolescent psychiatrists and clinical psychologists trained in DAWBA rating. The DAWBA is employed at all three participating sites in an attempt to homogenize diagnostic practices and is used to compliment and inform the clinical, diagnostic assessment process.

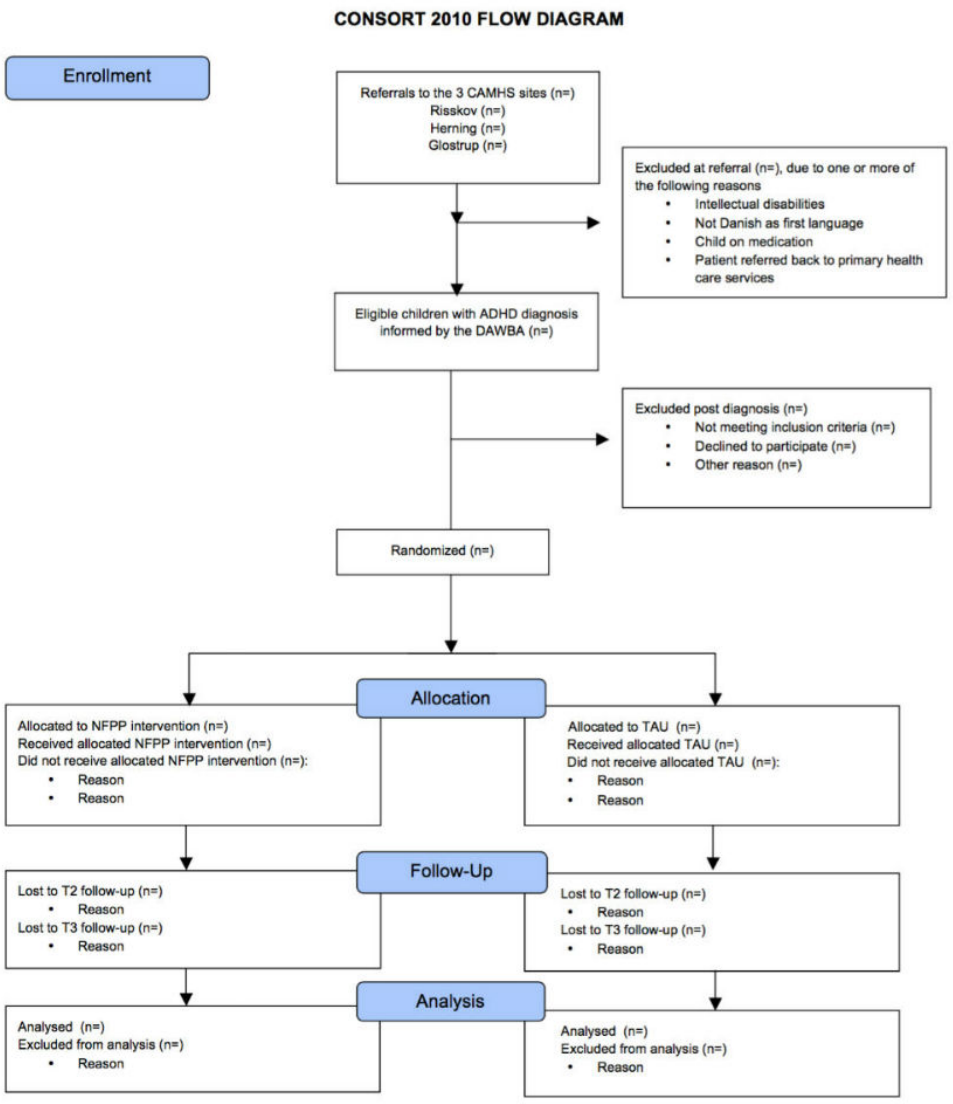
In conjunction with the DAWBA, eligible children will undergo standard clinical assessment at the referral site. For referrals to preschool child psychiatry services in Denmark, this standard clinical assessment usually consists of: interview with parents regarding the child's developmental history and current difficulties; child cognitive assessment and neuropsychological tests or neuropsychological tests; child medical examination; and, at Risskov and Herning, a semistructured observation of the child at the child's day-care facility. Results from clinical assessments and results from the Internet DAWBA are presented and discussed at weekly multidisciplinary clinical team meetings where a specialist doctor in child and adolescent psychiatry issues final clinical diagnoses.

Parents of children meeting the research criteria are invited to join the study, and are included in the trial, once written consent is obtained. Figure 1 shows the recruitment flow according to Consolidated Standards of Reporting Trials (CONSORT) guidelines [31].

Randomization Procedures

Since outcome may be dependent on treatment center and regional variations in referral pathways, as well as gender and age of the child, the study uses stratified allocation to treatment condition to ensure a balanced number of participants over conditions. Randomization is based on the defined strata as well as on the assigned treatment condition of earlier randomized participants within the strata. Parents will be randomized to one of the two arms using an allocation ratio of 1:1 for NFPP and TAU. Randomization to NFPP and TAU (1:1) will be generated by a Web-based randomization computer program within the Internet data management service Trialpartner [32], which allows for on-the-spot randomization of participants into an arm of the study. Randomization is done in blocks of size four or six and in 12 strata defined by center, gender, and age of the child (3-5 and 6-7 years). Once the parent has provided written informed consent to participate in the study, the administrator completes participant registration on the Internet in Trialpartner and enters a randomization request, at which point the randomization program randomly assigns the treatment condition, for example, NFPP or TAU, to the respective participant ID number. Trialpartner simultaneously generates an automated email message for the administrator and the main investigator of the study, in which participant ID, site, and treatment allocation is outlined. Parents are informed of their respective treatment condition following completion of the T1 visit, so that the first assessment is not influenced by participant's knowledge of treatment condition. Information about treatment allocation is delivered to parents in a telephone call by the researcher who initially informed the parent of the study.

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram of recruitment. Child mental health services (CAMHS); attention deficit/hyperactivity-disorder (ADHD); Development and Well-Being Assessment (DAWBA); New Forest Parenting Programme (NFPP); treatment as usual (TAU); T2 (week 12, post intervention); and T3 (6 month follow/up).



Data Management

All T1, T2, and T3 assessment schedules administered to parents and to day-care staff are set up electronically in Trialpartner [32] by the The Data Management Unit in The Central Denmark Region and are administered for completion on the Internet to parents and day-care staff by a research assistant. All data are stored and managed by The Data Management Unit in The Central Denmark Region. Data will remain locked until all participants have completed T3.

Blinding

Research assistants carrying out research assessments and observations at the three time-points will be blinded. Parents are instructed not to reveal treatment allocation to research assistants. All raters of videotaped observations will be blinded. Research assistants and raters are postgraduate psychology students and newly qualified psychologists. Parents, NFPP therapists, NFPP supervisor, and TAU mental health professionals will not be blinded. Efforts will be made to keep teachers blind to treatment allocation. Yet full blinding cannot be guaranteed, as participants may spontaneously talk about treatment to teachers.

Sample Size Estimation

The primary endpoint is parent ADHD ratings at T2. Sample size has been estimated at 126 children to obtain power at 0.80, ES=.50 (Cohen's d). The usual convention that is generally proposed and accepted for randomized trials is that power in a study ought to be 0.80 when ES is estimated at 0.50 [33]. An estimated effect size of 0.5 is deemed reasonable for a trial evaluating the effect of parenting interventions in the treatment of ADHD. By comparison, a recent meta-analysis of parent training interventions for ADHD obtained an ES of 0.4 [34].

For a design comparing two groups, for example, NFPP versus TAU, and allowing for a participant drop out of 10%, a total of 140 children, for example, a sample of 70 children per group is needed to attain a power of 0.80 [35]. A drop out rate of 7% was reported in a Dutch parent training trial implemented in routine clinical CAMHS with a similar age group [36]. In this light, the present trial has chosen to operate with a potential drop out rate of 10%. The preschool child psychiatry sites at Risskov and Herning are expected to enroll 2/3 of participants and the Glostrup site is expected to enroll 1/3 of participants for the trial.

Treatment Conditions

Adapted New Forest Parenting Programme

The original NFPP [1] was developed to be delivered in the child's home over the course of 8 sessions. However, the catchment areas of the three Danish hospital-based sites participating in this study cover large geographical areas. The distance between the furthermost points in the catchment area of Risskov, for example, is in excess of 150 km, which makes home-visits very time consuming and difficult to carry out to the degree outlined in the original NFPP protocol. Second, child psychiatric services in Denmark do not have a tradition of offering home-based assessment or treatment. As a rule, these are offered on an outpatient basis. To optimize the acceptability and deliverability of the NFPP in Danish CAMHS, the current study has made changes to the delivery of the original program and offers the majority of the 8 treatment sessions in the clinic. The third and the fifth treatment sessions, where the child is present, will be offered in the home. The other six sessions will be offered in the clinic in designated child and family friendly treatment rooms. The content of the NFPP manual remains otherwise unchanged.

The NFPP is centered around five broad themes [37].

1. The importance of psychoeducation about the nature and manifestation of preschool ADHD in order for parents to understand reasons for the child's behavior.
2. Emphasis on scaffolding to help parents work from the child's level of development and skills.
3. The importance of parent-child interaction, and how it might be enhanced to support child development and reduce parental stress.
4. Guiding parents in the use of behavioral strategies to improve behavior and ADHD symptoms.
5. Training to improve child's ADHD related, neuropsychological deficits, where parents are instructed to play with the child using attention training games, and helping the child manage delay, waiting, and self-regulation.

The NFPP manual, course materials, hand-outs, and a treatment DVD have been translated from English into Danish by a professional translation agency and A-ML with permission from the original developers [26]. The original developers have approved all corrections or changes to original wording.

In this trial, families are also given basic play materials that are recommended in the manual for use in specific training tasks with the child, for example, two card games and a special relaxation mat for the child.

Treatment as Usual

TAU is likely to be different at the three sites, reflecting the different clinical practice and traditions in everyday outpatient child psychiatry in Denmark. In Risskov, TAU traditionally consists of three sessions of psychoeducation delivered in groups of parents to referred children diagnosed with ADHD. In Herning, TAU typically consists of one individual session with parents, following diagnosis, and one psychoeducation session in a group of parents. In Glostrup, it consists of four psychoeducation sessions in groups for parents. Children do not participate in the psychoeducation groups at any of these services. Clinical decisions may be taken in individual cases that give rise to intrasite variations in TAU. Based on the individual clinical need of the child and the parents, treatment may occasionally be offered by a mental health professional through 2-3 individual sessions to parents. TAU at all sites is carried out by existing clinic staff with many years of clinical experience in relation to preschool ADHD. The nature of treatment provided to parents in the TAU groups will be carefully recorded.

Fidelity to Treatment Manual

The NFPP intervention is manual based. All treatment sessions will be videotaped. To verify treatment fidelity based on the

NFPP intervention manual, independent raters will code a number of treatment sessions per therapist.

New Forest Parenting Programme Training of Danish Therapists and Supervisor

During 2010 and 2011, the lead investigator A-ML participated during two NFPP training events held by the developers of the NFPP, for example, Dr Margaret Thompson (MT) and Ms Cathy Laver-Bradbury's (CLB), University of Southampton in the United Kingdom. A-ML subsequently saw two young children diagnosed with ADHD and their parents from the preschool child psychiatry clinic in Risskov for 8 sessions NFPP under close supervision from MT and CLB. All treatment sessions were videotaped and translated in order for MT and CLB to supervise A-ML to achieve NFPP therapist certification. Following therapist certification, A-ML embarked upon NFPP supervisor certification and received biweekly supervision from MT and CLB in preparation to supervise Danish therapists employed in this trial.

A total of four therapists: a clinical psychologist and a pedagog from the preschool team at the Glostrup site and a clinical psychologist and a nurse specialist from the Risskov site are employed to train as NFPP therapists for the trial. They have all undergone a 4-day NFPP training course conducted by MT and CLB. Following training, all four therapists provided NFPP treatment to two families each, and received weekly supervision in relation to these families by A-ML. MT and CLB conducted a one-day top up training session after six months, in order to clarify specific questions in relation to the NFPP intervention. Therapists will receive 2-hour clinical supervision sessions in groups of two by A-ML throughout the trial. In turn, A-ML will receive biweekly supervisor supervision via Skype calls by MT and CLB to ensure adherence to the NFPP.

Assessment and Outcome Measures

Measures administered in this trial are listed in Table 1.

Table 1. Trial outcome measures.

Measures		Collected
Primary outcome measure		
	ADHD symptoms	
	Preschool ADHD-RS (parent rated) [38]	T1, T2, T3
Secondary outcome measures		
	ADHD symptoms	
	Preschool ADHD-RS (teacher rated) [38]	T1, T2, T3
	Child Solo Play - observation measure	T1, T2, T3
	Behavioral symptoms and impact	
	SDQ[a]P2-4 & P4-16 - SDQ[a]and impact supplement (parent rated) [30,39]	T1, T2, T3
	SDQ[a]T2-4 & T4-16 - SDQ[a]and impact supplement (teacher rated) [30,39]	T1, T2, T3
	Parent ADHD	
	The Adult ADHD Self-Report Scale (ASRS-V1.1) [40]	T1
	Perceived parenting	
	PSOC[b][41]	T1, T2, T3
	FSI[c][42]	T1, T2, T3
	Positive and constructive parenting	
	GIPCI[e](jigsaw/tidy up/freeplay) observation measure [43]	T1, T2, T3
	Parent mental health	
	GHQ[d]:12 [44]	T1, T2, T3

[a] SDQ: Strength and Difficulties Questionnaire

[b]PSOC: Parenting Sense of Competence Scale

[c]FSI: Family Strain Index

[d] GHQ: General Health Questionnaire

[e] GIPCI: Global Impressions of Parent-Child Interactions

Primary Outcome Measure

Child Attention Deficit / Hyperactivity-Disorder: Attention Deficit / Hyperactivity-Disorder Rating Scale-IV–Preschool Version

The ADHD Rating Scale (ADHD RS)-IV-Preschool Version [38] is a questionnaire adapted for the use in preschoolers from the 18-item ADHD-RS-IV [45]. In this preschool version, symptom statements have been modified to be more appropriate to the developmental level of preschoolers. The scale includes 18 behavioral descriptors of ADHD as determined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [46]. Raters can consist of parents and teachers who respond to each question on a 4-point scale from 0 (not at all) to 3 (very often) to reflect the child's behavior. Scores can be obtained of Inattention, Hyperactive/Impulsive, and Total Scales. Internal consistency for the three scales has been established in the range from .92 to .95 on the Teacher Version and from .85 to .92 on the Parent Version. Test-retest reliability correlations for the three scales ranged from .93 to .96 for the Teacher Version and between .8 and .87 for the Parent Version [38].

Attention Deficit / Hyperactivity-Disorder Rating Scale-IV-Preschool Version Translated

The ADHD RS-IV-Preschool Version has been translated into Danish for the purpose of the present study with permission from and formal approval by Kara McGoey (see Multimedia Appendix 1) according to international guidelines for the translation of questionnaires [47].

Secondary Outcome Measures

Child Solo Play

The Child Solo Play [1] instrument is an independent, direct observation measure administered by a research assistant during 5 minutes of solo play with a standard activity, multipurpose toy. Patterns of attending to and switching from one activity to another during play with the toy are measured and indexed in terms of attention and engagement. High index scores represent more attention and less switching. Good test-retest reliability (Pearson r=.81), interrater reliability (Pearson r=.76), and validity—discriminating children with ADHD from non-ADHD children—have been established. Research assistants, for example, postgraduate psychology students and newly qualified psychologists, employed in the trial are trained in the administration and scoring of Child's Solo Play by the original developer of the measure and coauthor on this paper, DD.

Parenting Sense of Competence Scale The Parenting Sense of Competence Scale (PSOC) [41] is the most frequently used questionnaire applied to measure parental self-efficacy and satisfaction [48]. It measures parental competence on two dimensions: Satisfaction and Efficacy. Separate scales are developed for mothers and fathers, who respond to 16 questions on a 6-point Likert-scale (ranging from strongly agree to strongly disagree) [1,6]. There are 9 questions that are related to Satisfaction and seven are related to Efficacy. The Satisfaction section examines parents' anxiety, motivation, and frustration, while the Efficacy section looks at parents' competence, capability levels, and problem-solving abilities in their parental role. A number of studies have demonstrated the scale's good psychometric properties reporting internal consistency of .75 [41], and internal consistencies of .72 (mothers) and .76 (fathers) [48]. Charlotte Johnston gave permission and approval for the PSOC to be translated for the purpose of the present study (see Multimedia Appendix 4) according to international guidelines for the translation of questionnaires [47].

Strength and Difficulties Questionnaire Parent and Teacher Version

The Strength and Difficulties Questionnaire (SDQ) [39] is a brief behavioral five factor instrument developed to assess emotional and behavioral problems in children. The SDQ consists of 25 questions scored on a 3 point Likert scale ("not true", "somewhat true", "certainly true"). The questions cover five domains of child psychopathology by five subscales: hyperactivity/inattention, conduct problems, emotional symptoms, peer relationship problems, and prosocial behavior. Each area is covered by five questions. In addition, the SDQ contains an impact supplement inquiring about distress, burden, and impairment of the child. The questionnaire is widely used for clinical as well as research [49]. The standard SDQ is developed for use in the age-range of 4-17 years. The early years SDQ is developed for use in the age range of 2-4 years. A teacher version is developed for each scale, and a scale for completion by the young person is developed for use in the age range 11-17.

The SDQ has been used extensively in European as well as non-European contexts, and has been translated into more than 60 languages [50]. A recent review of the psychometric properties of the parent and teacher versions of the SDQ included 48 studies from 17 different cultural settings and a total of 131,223 raters [50]. The internal reliability and factor structure of the Danish versions of the SDQ were established in a sample of 71,840 parent and teacher raters of 5-, 7-, and 10- to 12-year-old children included in four large-scale Danish cohorts [51]. The predictive validity of the SDQ has been demonstrated in another large Danish study where the SDQ was shown to identify a group of children with highly increased risk of later being diagnosed and treated for ADHD or treated for ADHD in school age [52].

The early years SDQ—parent and teacher version Goodman [30]—has been translated into Danish for the purpose of the present study with personal permission and approval by Robert Goodman (see Multimedia Appendix 2) following standard guidelines for the translation of questionnaires [47]. The early years SDQ has shown good psychometric properties in a recent study [53].

Family Strain Index The Family Strain Index (FSI) [42] is a 6-item parent-report questionnaire developed to assess the effects of ADHD on families to better understand and address the level of stress, strain, and burden that families experience. The FSI is designed to measure two major aspects of stress and demand, for example, the "emotional" and the "restrictiveness" experiences in the context of living with a child with ADHD. The FSI has demonstrated good internal consistency across the six items (Cronbach alpha= .83 to .87) and for the full scale (Cronbach alpha=.87) [42].

The FSI has been translated into Danish for the purpose of the present study (see Multimedia Appendix 3) following standard guidelines for the translation of questionnaires [47] with permission from and approval by the original developer Anne Riley.

Global Impressions of Parent-Child Interactions

The Global Impressions of Parent-Child Interactions (GIPCI-R) [43] is a direct, semistructured observation schedule developed to evaluate parent and child interaction. Parent-Child dyads are videotaped in 15 minutes sessions during three tasks, each of 5 minutes duration: “jigsaw”, “free play”, and “tidy-up”. Videotapes are rated using the GIPCI coding manual at a later stage by a rater who is blinded to the randomization of the child. Child behavior items include: respect, disruptive, social skills, and destruction. Parents items rated include: responsiveness, warmth, praise, enjoyment, scaffolding, criticism, and punishment. Ratings produce global summary scores for child and parent with a higher score reflecting a more positive outcome. Thompson et al [26] found adequate interrater reliability for child scores (.62: range .48-.77) and for parent scores (.64: range .48 to .79). Good internal consistency was established for parent and child scales (.84; .87). Training in the administration and scoring is carried out by one of the authors of this paper, DD.

The Adult Attention Deficit/Hyperactivity-Disorder Self-Report Scale

The Adult ADHD Self-Report Scale (ADRS-v1.1) is an 18-item Symptom Checklist covering the 18 DSM-IV-TR criteria for ADHD. The scale has been developed in conjunction with the World Health Organization (WHO), and the Workgroup on Adult ADHD [40]. The first 6 questions have been found most sensitive in the screening for ADHD in adults [54]. The 18-item scale has been translated into Danish and has been approved by the original investigators of the WHO Work Group. The scale provides a method of identifying ADHD symptoms in adults and is a powerful tool to discriminate DSM-IV cases from noncases [54]. The scale has good psychometric properties and is widely used in scientific research [55]. The validity and clinical feasibility of the Danish version of the ADHD-RS has been demonstrated in a multicenter study [56]. The measure will be used to evaluate the extent to which parental ADHD symptoms are associated to outcome [57].

The General Health Questionnaire

The General Health Questionnaire (GHQ) [44] is the most common assessment measure for assessing of mental well-being in adults. Developed as a screening tool to detect those likely to have or be at risk of developing psychiatric disorders, it is a measure of the common mental health problems/domains of depression, anxiety, somatic symptoms, and social withdrawal. It is available in a variety of versions using 12, 28, 30, or 60 items, which have all been translated into Danish. The present study will use the 12-item version GHQ:12. The measure will be used to evaluate the extent to which parental mental health is associated to outcome [58].

Results

Statistical Analysis

The data will be analyzed on an intention to treat basis. All outcomes will be analyzed with a repeated measure model with a randomization arm, gender, age (above or below 5 year), center, year, and a random level for each child as covariates. We will estimate the effect of the intervention at T2 (intervention, TAU) in terms of the difference between the change from T1-T2 and its effect at T3 in terms of change between the T3-T1. Missing data will be imputed assuming Missingness At Random in relevant analysis models including additional control variables if relevant. Outcomes with more than fifty percent missing will not be analyzed. To examine the effect of outliers, a sensitivity analysis will be performed excluding observation with residuals exceeding 2.5*SD. In addition, four other sensitivity analyses will be performed for each analysis exploring how sensitive the results are for reasonable deviations from the Missing At Random assumption. The missing data will be predicted based on the analysis of the observed data. In the first sensitivity analysis, we will reanalyze the data including the predicted value for the missing values, but add .2*SD to the missing data in the intervention group only. In the second sensitivity analysis, we will subtract .2*SD from the missing data in the intervention group only. In the third, we add .2*SD to the missing data in the TAU group only, and, in the last, subtract .2*SD from the missing data in the TAU group only.

The results for the primary outcome as a supplement will be split according to gender, single parenting (yes/no), oppositional defiant disorder/conduct disorder-comorbidity, and maternal ADHD symptoms. A number of scientific articles will be generated on the basis of collected data from this trial, including publications outlining moderator and mediator analyses. Results will be reported according to the CONSORT statement for nonpharmacological interventions [31].

Time-Line Funding for this trial was granted in 2011 and in 2014. Enrollment of participants started in August, 2012, and the data collection is expected to be finalized at the end of December, 2015. The primary outcome paper will be submitted for publication mid-year 2016.

Discussion

Attention Deficit/Hyperactivity-Disorder in Children

This trial addresses the need to investigate the effect of nonpharmacological treatments for young children with ADHD in everyday clinical practice. It is the first trial of the NFPP to be based on the recruitment of children referred directly to a child psychiatry department through official community pathways, to our knowledge. In this sense, this randomized trial tests the effectiveness of the NFPP with the children, families, and clinicians in the clinical setting for which the intervention is ultimately intended, and compares directly to the usual clinical care on offer for young children diagnosed with ADHD. The trial is also the first evaluation of the NFPP outside an English speaking context, to our knowledge.

Given the controversies surrounding the ADHD diagnoses in young children, and the challenge that confronts assessment of preschool children with ADHD symptoms, diagnostic procedures require particular attention [59]. This trial is the first to include young children with a formal clinical diagnosis of ADHD following standard clinical and DAWBA assessment, to our knowledge. The clinical assessment ensures thorough medical, psychological, and psychosocial evaluation of the child and the child's environment, and the adjunct systematic DAWBA evaluation ensures standardization in the assessment procedure for children entering the trial.

Reducing Chance of Bias

To reduce the chance of bias, the trial includes measures involving direct observation of children and of parenting by blinded raters as well as ratings by naïve informants (ie, day-care staff) along with parent ratings. This will allow for the investigation of rater effect on child outcome, and facilitate the exploration of whether child outcome is stable across settings.

Identifying efficacious treatments for young children with ADHD is important, but finding evidence from trials in settings created for research (eg, university labs, specialist clinics) or with participants recruited through advertisements does not guarantee that a treatment will work well in everyday clinical practice, across different populations, clinical contexts, cultures, and countries [27]. The current trial has carefully adapted the NFPP to fit clinical and cultural needs and commenced an evaluation of its effectiveness compared to the usual treatment interventions offered to young children with ADHD and their families referred through official community pathways. To these ends, the trial will provide important information about the effectiveness and replicability of the NFPP in the treatment of young children with ADHD in an everyday CAMHS setting. This level of investigation is needed to shrink the gap between intervention research and clinical practice [60].

ADHD is a disorder that presents with major personal and social costs. The immediate and long-term impact and adverse outcomes of ADHD for individuals and their families are considerable [61]. The benefits of early intervention for ADHD is an area of current scientific and public health focus, but is not fully documented [62]. It is therefore important that carefully implemented effectiveness trials of evidence-based treatments for young children are translated and implemented into different cultures with a view to enhance outcome for a broader population of children with ADHD and their families.

Acknowledgments

This trial is based upon work supported by the Danish foundation TrygFonden. Acknowledgments are extended to the Danish foundation Helsefonden and the Central Denmark Region Foundation for Psychiatric Research for financial support in the preparation and implementation of this trial. We thank the Central Management at the Centre of Child & Adolescent Psychiatry in the Central Denmark Region and the Capital Denmark Region, respectively, for persistently supporting the implementation of the trial in everyday clinical practice. We gratefully acknowledge the clinical advice and commitment of MT and CLB, Southampton University, and their assistance in early discussions regarding the trial. We also acknowledge the hard work and dedication by Rikke Lambek, Aarhus University, and Kirsten Krabek Frantzen, Aarhus University Hospital, in the translation of measures for the trial. We thank original authors Robert Goodman, Kings College London; Kara McGoey, Duquesne University; George DuPaul, Lehigh University; Charlotte Johnston, University of British Columbia, and Anne Riley, Johns Hopkins University, for their permission to translate outcome measures and for their efforts in approving translations and back translations of their respective measures.

Conflicts of Interest

ES-B and DD are the original codevelopers of the NFPP and benefit from royalties from the self-help version of the program.

Multimedia Appendix 1

Adfærd.

[PDF File (Adobe PDF File), 93KB - resprot_v5i2e51_app1.pdf]

Multimedia Appendix 2

Spørgeskema om barnets styrker og vanskeligheder (SDQ skema SMÅBØRN, til forælder).

[PDF File (Adobe PDF File), 116KB - resprot_v5i2e51_app2.pdf]

Multimedia Appendix 3

Family strain.

[PDF File (Adobe PDF File), 51KB - resprot_v5i2e51_app3.pdf]

Multimedia Appendix 4

Parenting Sense of Competence Scale, PSOC, Charlotte Johnston, University of British Columbia.

[PDF File (Adobe PDF File), 100KB - resprot_v5i2e51_app4.pdf]

References

1. Sonuga-Barke EJ, Daley D, Thompson M, Laver-Bradbury C, Weeks A. Parent-based therapies for preschool attention-deficit/hyperactivity disorder: A randomized, controlled trial with a community sample. J Am Acad Child Adolesc Psychiatry 2001 Apr;40(4):402-408. [doi: 10.1097/00004583-200104000-00008] [Medline: 11314565]
2. Sonuga-Barke Edmund J S, Halperin JM. Developmental phenotypes and causal pathways in attention deficit/hyperactivity disorder: Potential targets for early intervention? J Child Psychol Psychiatry 2010 Apr;51(4):368-389. [doi: 10.1111/j.1469-7610.2009.02195.x] [Medline: 20015192]
3. Wichstrøm L, Berg-Nielsen TS, Angold A, Egger HL, Solheim E, Sveen TH. Prevalence of psychiatric disorders in preschoolers. J Child Psychol Psychiatry 2012 Jun;53(6):695-705. [doi: 10.1111/j.1469-7610.2011.02514.x] [Medline: 22211517]
4. Goodman R, Ford T, Richards H, Gatward R, Meltzer H. The development and well-being assessment: Description and initial validation of an integrated assessment of child and adolescent psychopathology. J Child Psychol Psychiatry 2000 Jul;41(5):645-655. [Medline: 10946756]
5. Lavigne JV, Gibbons RD, Christoffel KK, Arend R, Rosenbaum D, Binns H, et al. Prevalence rates and correlates of psychiatric disorders among preschool children. J Am Acad Child Adolesc Psychiatry 1996 Feb;35(2):204-214. [doi: 10.1097/00004583-199602000-00014] [Medline: 8720630]
6. Lavigne JV, Lebailly SA, Hopkins J, Gouze KR, Binns HJ. The prevalence of ADHD, ODD, depression, and anxiety in a community sample of 4-year-olds. J Clin Child Adolesc Psychol 2009 May;38(3):315-328. [doi: 10.1080/15374410902851382] [Medline: 19437293]
7. Greenhill LL, Posner K, Vaughan BS, Kratochvil CJ. Attention deficit hyperactivity disorder in preschool children. Child Adolesc Psychiatr Clin N Am 2008 Apr;17(2):347-366, ix. [doi: 10.1016/j.chc.2007.11.004] [Medline: 18295150]
8. Pelham WE, Milich R. Peer relations in children with hyperactivity/attention deficit disorder. J Learn Disabil 1984 Nov;17(9):560-567. [Medline: 6389737]
9. Wehmeier PM, Schacht A, Barkley RA. Social and emotional impairment in children and adolescents with ADHD and the impact on quality of life. J Adolesc Health 2010 Mar;46(3):209-217. [doi: 10.1016/j.jadohealth.2009.09.009] [Medline: 20159496]
10. DuPaul GJ, McGoey KE, Eckert TL, VanBrakle J. Preschool children with attention-deficit/hyperactivity disorder: Impairments in behavioral, social, and school functioning. J Am Acad Child Adolesc Psychiatry 2001 May;40(5):508-515. [doi: 10.1097/00004583-200105000-00009] [Medline: 11349694]
11. Gardner DM, Gerdes AC. A review of peer relationships and friendships in youth with ADHD. J Atten Disord 2015 Oct;19(10):844-855. [doi: 10.1177/1087054713501552] [Medline: 24062277]
12. Daley D, Birchwood J. ADHD and academic performance: Why does ADHD impact on academic performance and what can be done to support ADHD children in the classroom? Child Care Health Dev 2010 Jul;36(4):455-464. [doi: 10.1111/j.1365-2214.2009.01046.x] [Medline: 20074251]
13. Sonuga-Barke Edmund J S, Dalen L, Daley D, Remington B. Are planning, working memory, and inhibition associated with individual differences in preschool ADHD symptoms? Dev Neuropsychol 2002;21(3):255-272. [doi: 10.1207/S15326942DN2103_3] [Medline: 12233938]
14. DuPaul GJ, Gormley MJ, Laracy SD. School-based interventions for elementary school students with ADHD. Child Adolesc Psychiatr Clin N Am 2014 Oct;23(4):687-697. [doi: 10.1016/j.chc.2014.05.003] [Medline: 25220080]
15. Lee SS, Lahey BB, Owens EB, Hinshaw SP. Few preschool boys and girls with ADHD are well-adjusted during adolescence. J Abnorm Child Psychol 2008 Apr;36(3):373-383. [doi: 10.1007/s10802-007-9184-6] [Medline: 17914666]
16. Biederman J, Petty CR, Evans M, Small J, Faraone SV. How persistent is ADHD? A controlled 10-year follow-up study of boys with ADHD. Psychiatry Res 2010 May 30;177(3):299-304 [FREE Full text] [doi: 10.1016/j.psychres.2009.12.010] [Medline: 20452063]
17. Lahey BB, Pelham WE, Loney J, Kipp H, Ehrhardt A, Lee SS, et al. Three-year predictive validity of DSM-IV attention deficit hyperactivity disorder in children diagnosed at 4-6 years of age. Am J Psychiatry 2004 Nov;161(11):2014-2020. [doi: 10.1176/appi.ajp.161.11.2014] [Medline: 15514401]
18. Chorozoglou M, Smith E, Koerting J, Thompson MJ, Sayal K, Sonuga-Barke Edmund J S. Preschool hyperactivity is associated with long-term economic burden: Evidence from a longitudinal health economic analysis of costs incurred across childhood, adolescence and young adulthood. J Child Psychol Psychiatry 2015 Sep;56(9):966-975 [FREE Full text] [doi: 10.1111/jcpp.12437] [Medline: 26072954]
19. Kvist AP, Nielsen HS, Simonsen M. The importance of children's ADHD for parents' relationship stability and labor supply. Soc Sci Med 2013 Jul;88:30-38. [doi: 10.1016/j.socscimed.2013.04.001] [Medline: 23702207]

20. Uchida M, Spencer TJ, Faraone SV, Biederman J. Adult outcome of ADHD: An overview of results from the MGH longitudinal family studies of pediatrically and psychiatrically referred youth with and without ADHD of both sexes. J Atten Disord 2015 Sep 22. [doi: 10.1177/1087054715604360] [Medline: 26396145]
21. Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management, Wolraich M, Brown L, Brown RT, DuPaul G, et al. ADHD: Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics 2011 Nov;128(5):1007-1022 [FREE Full text] [doi: 10.1542/peds.2011-2654] [Medline: 22003063]
22. Kendall T, Taylor E, Perez A, Taylor C, Guideline DG. Diagnosis and management of attention-deficit/hyperactivity disorder in children, young people, and adults: Summary of NICE guidance. BMJ 2008;337:a1239. [Medline: 18815170]
23. Greenhill L, Kollins S, Abikoff H, McCracken J, Riddle M, Swanson J, et al. Efficacy and safety of immediate-release methylphenidate treatment for preschoolers with ADHD. J Am Acad Child Adolesc Psychiatry 2006 Nov;45(11):1284-1293. [doi: 10.1097/01.chi.0000235077.32661.61] [Medline: 17023867]
24. Charach A, Carson P, Fox S, Ali MU, Beckett J, Lim CG. Interventions for preschool children at high risk for ADHD: A comparative effectiveness review. Pediatrics 2013 May;131(5):e1584-e1604 [FREE Full text] [doi: 10.1542/peds.2012-0974] [Medline: 23545375]
25. Sonuga-Barke Edmund J S, Brandeis D, Cortese S, Daley D, Ferrin M, Holtmann M, van der Oord Saskia, Wong Ian C K, European ADHD Guidelines Group. Nonpharmacological interventions for ADHD: Systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. Am J Psychiatry 2013 Mar;170(3):275-289. [doi: 10.1176/appi.ajp.2012.12070991] [Medline: 23360949]
26. Thompson Margaret J J, Laver-Bradbury C, Ayres M, Le PE, Mead S, Dodds C, Sonuga-Barke Edmund J S. A small-scale randomized controlled trial of the revised new forest parenting programme for preschoolers with attention deficit hyperactivity disorder. Eur Child Adolesc Psychiatry 2009 Oct;18(10):605-616. [doi: 10.1007/s00787-009-0020-0] [Medline: 19404717]
27. Santucci LC, Thomassin K, Petrovic L, Weisz JR. Building evidence-based interventions for the youth, providers, and contexts of real-world mental-health care. Child Dev Perspect 2015 Apr 11;9(2):67-73 [FREE Full text] [doi: 10.1111/cdep.12118]
28. Barwick M, Boydell K, Stasiulis E, Ferguson H, Blase K, Fixsen D. Ontario Canada: Children's Mental Health Ontario. Knowledge transfer and implementation of evidence-based practices in childrens mental health URL: http://nirn.fpg.unc.edu/sites/nirn.fpg.unc.edu/files/resources/CMHO-KTAndImplementationOfEBPInChildrensMentalHealth-2005.pdf [accessed 2016-01-09] [WebCite Cache ID 6eSDzJ2Cy]
29. Weisz JR, Gray JS. Evidence-based psychotherapy for children and adolescents: Data from the present and a model for the future. Child Adolesc Ment Health 2008 May;13(2):54-65. [doi: 10.1111/j.1475-3588.2007.00475.x]
30. Goodman R. Report. London Assessing preschool childrens emotional and behavioural adjustment URL: http://www.dawba.info/EarlyYears/EarlyYearsDAWBAReport9jan11.pdf [accessed 2016-01-09] [WebCite Cache ID 6ePzDoaY3]
31. Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: Explanation and elaboration. Ann Intern Med 2008 Feb 19;148(4):295-309. [Medline: 18283207]
32. Datamanagement U. https://trialpartner.dk. Central Denmark Region, Oluf Palmes Allé 15, 8200 Aarhus N, Denmark: Datamanagement Unit; 2012. Trialpartner URL: http://www.webcitation.org/6eUITZ1GZ [accessed 2016-01-12] [WebCite Cache ID 6eUITZ1GZ]
33. Kazdin A. Research design in clinical psychology: Pearson New International Edition. Harlow, Essex: Pearson Education, Limited; 2013:9781292042787.
34. Coates J, Taylor JA, Sayal K. Parenting interventions for ADHD: A systematic literature review and meta-analysis. J Atten Disord 2015 Oct;19(10):831-843. [doi: 10.1177/1087054714535952] [Medline: 24915737]
35. Cohen J. A power primer. Psychol Bull 1992 Jul;112(1):155-159. [Medline: 19565683]
36. van den Hoofdakker Barbara J, van der Veen-Mulders Lianne, Sytema S, Emmelkamp Paul M G, Minderaa RB, Nauta MH. Effectiveness of behavioral parent training for children with ADHD in routine clinical practice: A randomized controlled study. J Am Acad Child Adolesc Psychiatry 2007 Oct;46(10):1263-1271. [doi: 10.1097/chi.0b013e3181354bc2] [Medline: 17885567]
37. McCann DC, Thompson M, Daley D, Barton J, Laver-Bradbury C, Hutchings J, et al. Study protocol for a randomized controlled trial comparing the efficacy of a specialist and a generic parenting programme for the treatment of preschool ADHD. Trials 2014;15:142 [FREE Full text] [doi: 10.1186/1745-6215-15-142] [Medline: 24767423]
38. McGoey KE, DuPaul GJ, Haley E, Shelton TL. Parent and teacher ratings of attention-deficit/hyperactivity disorder in preschool: The ADHD rating scale-IV preschool version. J Psychopathol Behav Assess 2007 Jun 28;29(4):269-276. [doi: 10.1007/s10862-007-9048-y]
39. Goodman R. The extended version of the strengths and difficulties questionnaire as a guide to child psychiatric caseness and consequent burden. J Child Psychol Psychiatry 1999 Jul;40(5):791-799. [Medline: 10433412]
40. Kessler RC, Adler L, Ames M, Demler O, Faraone S, Hiripi E, et al. The World Health Organization adult ADHD self-report scale (ASRS): A short screening scale for use in the general population. Psychol Med 2005 Feb;35(2):245-256. [Medline: 15841682]

41. Johnston C, Mash E. A measure of parenting satisfaction and efficacy. Journal of Clinical Child Psychology 1989 Jun;18(2):167-175. [doi: 10.1207/s15374424jccp1802_8]
42. Riley AW, Lyman LM, Spiel G, Döpfner M, Lorenzo MJ, Ralston SJ. The family strain index (FSI). Reliability, validity, and factor structure of a brief questionnaire for families of children with ADHD. Eur Child Adolesc Psychiatry 2006 Dec;15 Suppl 1:I72-I78. [doi: 10.1007/s00787-006-1010-0] [Medline: 17177019]
43. Rush A. Symptom-specific measures for disorders usually first diagnosed in infancy, childhood, or adolescence. In: Handbook of psychiatric measures. Washington, DC: American Psychiatric Association; 2000.
44. Goldberg D. Manual of the general health questionnaire. UK: NFER; 1978.
45. DuPaul G, Reid R, Anastopoulos AD, Lambert MC, Watkins MW, Power TJ. Parent and teacher ratings of attention-deficit/hyperactivity disorder symptoms: Factor structure and normative data. Psychol Assess 2016 Feb;28(2):214-225. [doi: 10.1037/pas0000166] [Medline: 26011476]
46. Diagnostic and statistical manual of mental disorders: DSM-IV. Washington, DC: American Psychiatric Association; 2000.
47. Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. Spine (Phila Pa 1976) 2000 Dec 15;25(24):3186-3191. [Medline: 11124735]
48. Gilmore L, Cuskelly M. Factor structure of the parenting sense of competence scale using a normative sample. Child Care Health Dev 2009 Jan;35(1):48-55. [doi: 10.1111/j.1365-2214.2008.00867.x] [Medline: 18991983]
49. Vostanis P. Strengths and difficulties questionnaire: Research and clinical applications. Curr Opin Psychiatry 2006 Jul;19(4):367-372. [doi: 10.1097/01.yco.0000228755.72366.05] [Medline: 16721165]
50. Stone LL, Otten R, Engels Rutger C M E, Vermulst AA, Janssens Jan M A M. Psychometric properties of the parent and teacher versions of the strengths and difficulties questionnaire for 4- to 12-year-olds: A review. Clin Child Fam Psychol Rev 2010 Sep;13(3):254-274 [FREE Full text] [doi: 10.1007/s10567-010-0071-2] [Medline: 20589428]
51. Niclasen J, Teasdale TW, Andersen AN, Skovgaard AM, Elberling H, Obel C. Psychometric properties of the Danish strength and difficulties questionnaire: The SDQ assessed for more than 70,000 raters in four different cohorts. PLoS One 2012;7(2):e32025 [FREE Full text] [doi: 10.1371/journal.pone.0032025] [Medline: 22384129]
52. Rimvall MK, Elberling H, Rask CU, Helenius D, Skovgaard AM, Jeppesen P. Predicting ADHD in school age when using the strengths and difficulties questionnaire in preschool age: A longitudinal general population study, CCC2000. Eur Child Adolesc Psychiatry 2014 Nov;23(11):1051-1060. [doi: 10.1007/s00787-014-0546-7] [Medline: 24737124]
53. Croft S, Stride C, Maughan B, Rowe R. Validity of the strengths and difficulties questionnaire in preschool-aged children. Pediatrics 2015 May;135(5):e1210-e1219. [doi: 10.1542/peds.2014-2920] [Medline: 25847804]
54. Kessler RC, Adler LA, Gruber MJ, Sarawate CA, Spencer T, Van Brunt David L. Validity of the World Health Organization adult ADHD self-report scale (ASRS) screener in a representative sample of health plan members. Int J Methods Psychiatr Res 2007;16(2):52-65 [FREE Full text] [doi: 10.1002/mpr.208] [Medline: 17623385]
55. Kessler RC, Adler L, Barkley R, Biederman J, Conners CK, Demler O, et al. The prevalence and correlates of adult ADHD in the United States: Results from the National Comorbidity Survey Replication. Am J Psychiatry 2006 Apr;163(4):716-723 [FREE Full text] [doi: 10.1176/ajp.2006.163.4.716] [Medline: 16585449]
56. Szomlaiski N, Dyrborg J, Rasmussen H, Schumann T, Koch SV, Bilenberg N. Validity and clinical feasibility of the ADHD rating scale (ADHD-RS) A Danish nationwide multicenter study. Acta Paediatr 2009 Feb;98(2):397-402. [doi: 10.1111/j.1651-2227.2008.01025.x] [Medline: 18775056]
57. Sonuga-Barke Edmund J S, Daley D, Thompson M. Does maternal ADHD reduce the effectiveness of parent training for preschool children's ADHD? J Am Acad Child Adolesc Psychiatry 2002 Jun;41(6):696-702. [doi: 10.1097/00004583-200206000-00009] [Medline: 12049444]
58. Reyno SM, McGrath PJ. Predictors of parent training efficacy for child externalizing behavior problems--a meta-analytic review. J Child Psychol Psychiatry 2006 Jan;47(1):99-111. [doi: 10.1111/j.1469-7610.2005.01544.x] [Medline: 16405646]
59. Ghuman J, Ghuman H. ADHD in preschool children. New York: Oxford University Press; 2014:9780199948925.
60. Weisz JR, Krumholz LS, Santucci L, Thomassin K, Ng MY. Shrinking the gap between research and practice: Tailoring and testing youth psychotherapies in clinical care contexts. Annu Rev Clin Psychol 2015;11:139-163. [doi: 10.1146/annurev-clinpsy-032814-112820] [Medline: 25822345]
61. Daley D, Jacobsen R, Lange A-M, Sorensen A, Walldorf J. Costing adult attention deficit hyperactivity disorder: Impact on the individual and society. New York: Oxford University Press; 2015:0198745559.
62. Halperin JM, Bédard ACV, Curchack-Lichtin JT. Preventive interventions for ADHD: A neurodevelopmental perspective. Neurotherapeutics 2012 Jul;9(3):531-541 [FREE Full text] [doi: 10.1007/s13311-012-0123-z] [Medline: 22692794]

Abbreviations

ADHD: attention deficit/hyperactivity-disorder
ADHD RS: ADHD Rating Scale-IV
ADRS-v1.1: Adult ADHD Self-Report Scale
CAMHS: child mental health services
CLB: Ms Cathy Laver-Bradbury

CONSORT: Consolidated Standards of Reporting Trials
DAWBA: Development and Well-Being Assessment
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders
FSI: Family Strain Index
GHQ: General Health Questionnaire
GIPCI-R: Global Impressions of Parent-Child Interactions
MT: Dr Margaret Thompson
NFPP: New Forest Parenting Programme
PSOC: Parenting Sense of Competence Scale
SDQ: Strength and Difficulties Questionnaire
TAU: treatment as usual condition
WHO: World Health Organization

Edited by G Eysenbach; submitted 04.11.15; peer-reviewed by S Van der Oord; comments to author 20.11.15; revised version received 23.11.15; accepted 25.11.15; published 13.04.16.

Please cite as:
Lange AM, Daley D, Frydenberg M, Rask CU, Sonuga-Barke E, Thomsen PH
The Effectiveness of Parent Training as a Treatment for Preschool Attention-Deficit/Hyperactivity Disorder: Study Protocol for a Randomized Controlled, Multicenter Trial of the New Forest Parenting Program in Everyday Clinical Practice
JMIR Res Protoc 2016;5(2):e51
URL: http://www.researchprotocols.org/2016/2/e51/
doi:10.2196/resprot.5319
PMID:27076496

Protocol

Patient-Centered Pain Care Using Artificial Intelligence and Mobile Health Tools: Protocol for a Randomized Study Funded by the US Department of Veterans Affairs Health Services Research and Development Program

John D Piette[1,2,3], MSc, PhD; Sarah L Krein[2,3], PhD; Dana Striplin[1,2], MHSA; Nicolle Marinec[1,2], MPH; Robert D Kerns[4,5], PhD; Karen B Farris[6], PhD; Satinder Singh[7], PhD; Lawrence An[3], MD; Alicia A Heapy[4,5], PhD

[1]Center for Managing Chronic Disease, Department of Health Behavior and Health Education, University of Michigan School of Public Health, Ann Arbor, MI, United States

[2]Center for Clinical Management Research, VA Ann Arbor Healthcare System, Ann Arbor, MI, United States

[3]Department of Internal Medicine, University of Michigan, Ann Arbor, MI, United States

[4]Pain Research, Informatics, Multimorbidities and Education (PRIME) Center, VA Connecticut Healthcare System, West Haven, CT, United States

[5]Department of Psychiatry, Yale School of Medicine, West Haven, CT, United States

[6]Department of Clinical, Social, and Administrative Sciences, College of Pharmacy, University of Michigan, Ann Arbor, MI, United States

[7]Department of Electrical Engineering and Computer Science, College of Engineering, University of Michigan, Ann Arbor, MI, United States

Corresponding Author:
John D Piette, MSc, PhD
Center for Managing Chronic Disease
Department of Health Behavior and Health Education
University of Michigan School of Public Health
1415 Washington Heights
Ann Arbor, MI, 48109
United States
Phone: 1 734 763 1457
Fax: 1 734 763 9115
Email: jpiette@umich.edu

Abstract

Background: Cognitive behavioral therapy (CBT) is one of the most effective treatments for chronic low back pain. However, only half of Department of Veterans Affairs (VA) patients have access to trained CBT therapists, and program expansion is costly. CBT typically consists of 10 weekly hour-long sessions. However, some patients improve after the first few sessions while others need more extensive contact.

Objective: We are applying principles from "reinforcement learning" (a field of artificial intelligence or AI) to develop an evidence-based, personalized CBT pain management service that automatically adapts to each patient's unique and changing needs (AI-CBT). AI-CBT uses feedback from patients about their progress in pain-related functioning measured daily via pedometer step counts to automatically personalize the intensity and type of patient support. The specific aims of the study are to (1) demonstrate that AI-CBT has pain-related outcomes equivalent to standard telephone CBT, (2) document that AI-CBT achieves these outcomes with more efficient use of clinician resources, and (3) demonstrate the intervention's impact on proximal outcomes associated with treatment response, including program engagement, pain management skill acquisition, and patients' likelihood of dropout.

Methods: In total, 320 patients with chronic low back pain will be recruited from 2 VA healthcare systems and randomized to a standard 10 sessions of telephone CBT versus AI-CBT. All patients will begin with weekly hour-long telephone counseling, but for patients in the AI-CBT group, those who demonstrate a significant treatment response will be stepped down through less resource-intensive alternatives including: (1) 15-minute contacts with a therapist, and (2) CBT clinician feedback provided via interactive voice response calls (IVR). The AI engine will learn what works best in terms of patients' personally tailored treatment plans based on daily feedback via IVR about their pedometer-measured step counts, CBT skill practice, and physical functioning. Outcomes will be measured at 3 and 6 months post recruitment and will include pain-related interference, treatment satisfaction,

and treatment dropout. Our primary hypothesis is that AI-CBT will result in pain-related functional outcomes that are at least as good as the standard approach, and that by scaling back the intensity of contact that is not associated with additional gains in pain control, the AI-CBT approach will be significantly less costly in terms of therapy time.

Results: The trial is currently in the start-up phase. Patient enrollment will begin in the fall of 2016 and results of the trial will be available in the winter of 2019.

Conclusions: This study will evaluate an intervention that increases patients' access to effective CBT pain management services while allowing health systems to maximize program expansion given constrained resources.

(JMIR Res Protoc 2016;5(2):e53) doi:10.2196/resprot.4995

KEYWORDS

Medical Informatics; mhealth; artificial intelligence; comparative effectiveness

Introduction

Prevalence and Consequences of Chronic Pain among Veterans

Musculoskeletal disorders are highly prevalent among Department of Veterans Affairs (VA) patients, with chronic back pain the most frequently reported type [1-3]. VA data suggest an annualized increase in the prevalence of low back pain of 4.8% per year due to factors such as an aging population and increasing prevalence of obesity [1,4]. The cost of treating back pain in VA is $2.2 billion annually [2]. Chronic low back pain is associated with work interruption, emotional distress, and risky heath behaviors such as substance use [5]. Emerging evidence suggests that chronic pain compromises successful treatment and management of other chronic conditions [6]. For all of these reasons, increasing access to effective and convenient treatments for chronic low back pain is a national VA priority [7]. Historically, treatment for chronic low back pain has emphasized pharmacotherapy and surgery, while underutilizing evidence-based behavioral approaches that have comparable or superior benefit [8]. Opioid medications are commonly used to manage severe chronic pain, but their use can lead to serious adverse effects [9,10]. Despite its frequent use, there is no evidence of the long-term efficacy of opioid therapy for chronic pain [8].

Cognitive and Behavioral Interventions to Improve Pain Management

Cognitive behavioral therapy (CBT) is the most widely accepted evidence-based psychological treatment for chronic pain [11,12]. CBT is an attractive alternative to pharmacotherapy because impacts on functioning can last long after treatment is discontinued, and CBT does not entail the negative side effects of opioids. The goal of pain CBT is to assist patients in developing an adaptive problem-solving approach to pain management, and CBT targets both reductions in pain symptoms as well was their associated disability and emotional distress. VA recommendations regarding pain CBT recommend 10 hour-long sessions delivered weekly and focusing on pain education, practice of pain self-management skills, and productive and pleasurable activity and exercise. Skills address both cognitive processes (eg, catastrophizing) and behaviors (eg, relaxation). Meta-analyses have found that CBT has moderate to large effects on pain-related outcomes [13,14].

Because pain CBT is labor intensive and therapists are scarce, many veterans do not have access to these services. A review of data for veterans receiving outpatient opioid prescriptions showed that less than half received any mental health treatment [15], and a survey by VA's National Program for Pain Management found that half of VA facilities did not have any pain-focused psychological services such as CBT. This suggests that VA needs to identify creative strategies to ensure that patients receive the treatment they need, which could be achieved through a stepped-care model: assigning some patients to interventions with more clinician contact and others to more self-directed interventions.

Ideally, patient feedback could be used to assign patients to the appropriate level of stepped care; however, to date, the use of patient feedback in pain CBT has been suboptimal. For patients receiving pain CBT, retrospective symptom reports are often collected using paper-and-pencil surveys and are vulnerable to recall and social desirability biases; for example, reports may be disproportionately influenced by recent experiences and patients' emotional states at the time of assessment [16]. Patient feedback is least likely to be available among veterans with the greatest risk for missing in-person sessions, that is, the very patients who may have the greatest need for adjustments in their treatment plan. For all of these reasons, scarce CBT services can be slow to adapt to variation in patients' treatment response.

Standardization of mental health services such as CBT has improved care relative to unsystematic differences in delivery across patients and therapists; however, new models of CBT need to incorporate a systematic stepped approach to ensure that care is patient-centered, efficient, and targeted to veterans' unique needs. VA CBT pain treatment is based on evidence that typically reflects average effects in controlled trials, rather than taking into account the substantial variation across patients in treatment response. As such, guidelines are at odds with evidence regarding variability in the characteristics of CBT delivery models with demonstrated efficacy. Recommendations for 10 hour-long CBT pain treatment sessions likely represent the upper bound of what is feasible, given VA budgets and some patients' limited tolerance for frequent contacts. As many as 25% of patients receiving psychotherapy improve after 1-2 sessions [17], and patients often drop out of treatment that is providing only marginal benefit. Some evidence-based CBT programs have as few as 6 sessions while others have twice that many [18]. Studies from other areas of chronic disease management show wide variation in providers'

recommendations regarding visit frequencies [19,20]. Providers typically make these decisions based on the patient's perceived stability or expected likelihood of treatment response. However, one study found no correlation between visit frequency and hypertension control [21], and visit intervals can sometimes be substantially lengthened without decreasing quality [22]. No single "dose" of CBT is likely to be appropriate for all veterans, and neither clinicians nor patients may be able to judge *a priori* who needs more resource-intensive forms of care.

Prior Research on Adapting Treatment to Patients' Individual Needs

Lambert and colleagues demonstrated the benefits of adapting psychotherapy based on feedback about patients' progress [23-26]. Other recent work by DeRubeis and colleagues has demonstrated that pretreatment characteristics of patients can be identified that suggest an advantage with respect to the likely response of a given therapy (eg, antidepressant medications versus CBT) and could be used to recommend one course over an alternative [27,28]. While these studies represent an important step toward the goal of tailored treatments, prior efforts to personalize therapy have used patient surveys at the time of intake or (at most) in-person encounters with patients to obtain information about predicted treatment response. As a result, opportunities to adjust therapy have been limited, and the impact of patient tailoring has been modest. Other investigators have suggested that monitoring and feedback could best be accomplished using health IT [29] to allow treatment decisions to be based on real-time information about patients' functioning. Another key weakness of prior work is that feedback on treatment response is typically provided to clinicians along with nonevidence-based algorithms for modifying patients' treatment plans [17]. As such, steps toward a more systematic and evidence-based approach to adaptive treatment have been left with a format that cannot respond effectively to real-time information about what works best for each patient.

Another foundational area of research for this study is the theory of tailored health communication, which suggests that patients are more likely to internalize health messages when those messages are relevant to them personally [30]. The state-of-the-science in tailoring uses surveys to identify patients' needs, health beliefs, learning styles, cultural context, and other factors prior to crafting messages targeting behavioral changes. The data needed to tailor these messages is substantial, and many patients may not be willing or able to accurately report that information at program outset [31,32]. For example, CBT skills training was found to be no more effective when skill presentation was tailored according to what patients thought they wanted before initiating treatment [33]. Also, previous systems typically tailor based on static patient traits, rather than on updated information about patients' status or treatment response. In this study, we will tailor the intensity and mode of delivering pain CBT services using IVR-reported feedback about patients' pain-related physical functioning measured objectively via pedometer step counts, perceived functioning scores, and progress with CBT skill practice. Based on this real-time feedback, AI-CBT will personalize each patient's course of treatment automatically to achieve the greatest benefits for the population, while using clinical resources as efficiently as possible.

Mobile Health (mHealth) Approaches to Self-Management Support

Because mHealth services have low marginal costs, they can cost-effectively reach large numbers of patients between face-to-face encounters to provide self-management support [34-37]. More than 50 studies have demonstrated that patients can provide reliable and valid information about psychiatric symptoms and substance abuse disorders via IVR and other mobile health technologies [38-41]. The benefits of standard CBT diminish after patients discontinue therapy, and maintenance interventions delivered via IVR sustain those improvements in symptom and self-management skills [37,42]**.** Despite their potential, mHealth interventions typically deliver a simplistic series of messages based on pre-determined "if-then" rules and deterministic protocols. As a result, interactions can feel "robotic" to users and many disengage [43]. In this study, we will test a model to take advantage of the cost and accessibility benefits of mHealth services, while ensuring that these powerful tools are integrated systematically with personal and professional care by trained CBT therapists.

Conceptual Framework

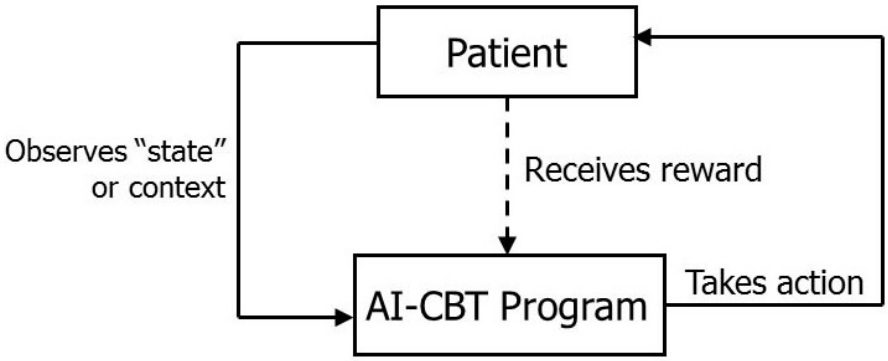
The intervention we will evaluate is based clinically on widely adopted and evidence-based models of CBT for pain management (described above) [44], and links those concepts with a strategy for personalized stepped care using *reinforcement learning (RL)*. RL is a field of artificial intelligence that allows an "intelligent agent" to learn what treatment choices work best to optimize a measurable outcome (termed the system's "reward"; see Figure 1). For readers new to this approach, it is important to emphasize that here we use "learning" to describe the RL system's progressive statistical adaptation based on patient data, rather than to describe a process through which the patient learns self-care skills by exposure to the intervention. The process used to optimize treatment choices in RL mimics the way that humans learn skills such as riding a bicycle, that is, through systematic adaptation and generalization accompanied by targeted trials of new behaviors with measurable outcomes. RL algorithms similar to those we will apply in this study are the basis of online consumer targeting programs such as Netflix, Google, and Amazon [45], where a service learns automatically how to deliver information that is most relevant to each user. In the current trial, the RL agent will be a computer system that makes weekly recommendations for each patient with respect to the mode and intensity of CBT that the patient should receive (ie, the "actions" that the system can take). Those recommendations will be based on the patient's progress, progress of similar patients, and other contextual information for that action choice.

Potential actions the AI-CBT program will take include a standard one-hour telephone CBT therapy session, a 15-minute telephone CBT therapy session, and an IVR automated therapy session designed to teach and reinforce skill-based learning. Fifteen minutes was chosen to be consistent with the time increments of the health and behavior CPT codes (15, 30, 45, and 60) used to bill for behavioral interventions for chronic

pain. Content for each session type will be based on standard CBT programs for pain management, modified by a panel of experts to be most effective given the length and mode of each contact. The AI-CBT agent's recommendation regarding which action to take will be based on each patient's IVR-reported pedometer step counts (ie, the "reward") as well as other "state" information (Figure 1) also collected via IVR. Importantly, the RL algorithm will learn not only based on each patient's own treatment response, but will incorporate experience from the response of other patients who have similar characteristics and response trajectories as indicated by the "state space."

Based on this feedback loop, the RL engine will modify the probability distribution across treatment choices and make recommendations for each patient each week. Because actions will be probabilistic rather than "hard-wired," the AI-CBT program will avoid potentially overreactive treatment changes that can result when therapists attempt to tailor care nonsystematically or using deterministic flow diagrams. All patients will begin with a standard one-hour CBT session. Based on their progress as measured by feedback on the "reward" and "state" space, patients who progress toward functional goals will be moved through less resource intensive options, and patients who need more intensive follow-up will be moved automatically to more time-intensive, therapist-delivered CBT.

Figure 1. The Reinforcement Learning feedback loop. The AI-CBT actions are the 3 CBT session types; the Ã¢â‚¬Å"rewardÃ¢â‚¬Â is IVR-reported pedometer step counts, and Ã¢â‚¬Å"stateÃ¢â‚¬Â data is IVR-collected information on patientsÃ¢â‚¬â„¢ CBT skill practice and pain-related functioning.



Prior Work by the Investigators

Patient Engagement in IVR Self-Care Support Calls

Dr Piette and his team have more than 15 years of experience developing IVR systems to enhance care for chronically-ill veterans, and over the past 5 years, more than 2000 patients have participated in their IVR programs. In an analysis of data from more than 1200 program participants with 29,000 patient-weeks of follow-up, patients completed 83% of weekly IVR assessment and self-management support calls, and completion rates were similar across groups defined by sociodemographic risk factors [46]. Other recent studies [47,48] found that completion rates of IVR assessments are high among patients with depression, and patients' IVR reports are at least as reliable as mental health information collected via other methods. Dr Heapy and colleagues also have found high levels of adherence to IVR call schedules in 2 studies among Veterans with chronic pain. In one study, participants with endpoint data completed 85% of expected IVR calls, and participants who withdrew or were disqualified completed 74% of potential calls [49]. In a pilot study designed to obtain feedback from veterans with chronic pain about self-management, 65% indicated a willingness to receive self-management support via IVR, and 11% indicated they might be willing.

Impact of IVR Self-Management Support on Outcomes of Chronic Illness Care

In 3 randomized trials directed by Dr Piette, results indicated that IVR call-supported chronic-illness care can improve patients' self-care and health outcomes [50-52]. In one trial conducted among diabetes patients [51], intervention patients receiving weekly IVR monitoring and self-care support with follow-up by a telephone nurse therapist reported significantly better home glucose monitoring, foot care, medication adherence, and weight monitoring than control patients at their 12-month follow-up. More than twice as many intervention patients had acceptable glycemic control at 12 months (P=.01), as well as fewer diabetic symptoms, greater satisfaction with care, fewer symptoms of depression, greater perceived access to care, and greater self-efficacy in managing their self-care (all P<.05). In another trial [50], veterans receiving IVR-supported telephone care management reported better self-management behaviors, were more likely to be seen in diabetes-related specialty clinics, had better glycemic control, and reported better patient-centered outcomes.

Pedometers for Monitoring Patients' Physical Activity

Dr Piette was the principal investigator for an NIH-funded randomized trial of telephone CBT plus physical activity promotion among patients with diabetes and depression [53]. Investigators used standard pedometers to objectively measure patients' physical activity at baseline and 12-month follow-up, and intervention patients also used pedometers as part of their CBT self-management program. We observed high rates of adherence to the collection of pedometer data, and the opportunity to use a pedometer to pursue physical activity goals was an important motivator for trial participation. In another recently completed trial [54], veterans with chronic back pain were randomized to a pedometer-based, Internet-mediated

walking intervention or usual care. Intervention participants reported a greater decrease in back pain-related disability in the 6 months following study enrollment. Intervention participants uploaded pedometer data at least once per week for a median of 32 weeks (62% of the recommended time) and more than 25% of participants uploaded data for at least 42 weeks. In summary, we have found consistently that pedometers represent an important alternative to self-reported activity levels, which often have high rates of random reporting error as well as social desirability biases [54-56].

Preparatory Collaborative Work

We performed simulations to estimate the impact of AI-CBT compared to 10 standard, one-hour CBT sessions delivered by a therapist. We focused on AI-CBT's impacts on patients' physical functioning (in this case pedometer-measured step counts) and on therapist time. We assumed that (as in the proposed study) the AI-CBT program would start each patient with a one-hour therapist session and then would automatically develop a personalized step-care program that included additional one-hour "live" telephone therapy sessions, 15-minute live sessions, or IVR sessions. We assumed that patients responding to IVR therapy would also respond to a 15-minute live call or an hour-long call, and patients who responded to a 15-minute therapist call (but not IVR) would also respond to an hour-long session. Simulations evaluated variations in the expected benefit of CBT delivered via different modes, the speed in which patients were recruited into the AI-CBT program (which would affect the system's ability to learn from prior experience), and whether the AI engine could move a patient directly from a one-hour session to IVR, or whether choices were constrained so that the system would "step down" from one hour to 15 minutes, and from 15 minutes to IVR. We also explored the effect of random error in the expected effect of each CBT session, and the effect of patients' nonadherence to IVR requests for daily step count data (patients with more missing step count data would be progressed more slowly to less resource-intensive options). See Multimedia Appendix 1 for a summary of those simulations. In brief, using conservative assumptions, we estimate that AI-CBT will be able to achieve an improvement in physical activity that is 93% as great as that seen in standard CBT, but using only 44% of the clinician time required for 10 one-hour sessions for all patients.

Methods

Overview

This will be a randomized noninferiority study comparing standard pain CBT to an innovative strategy that uses mobile health technology and artificial intelligence in conjunction with trained CBT therapists to deliver evidence-based, stepped pain therapy so that pain management is as efficient as possible while maintaining the effectiveness of current approaches. Patients in both groups will receive CBT delivered via telephone by the site's trained pain CBT therapist. For patients in the standard CBT group, the therapist will deliver 10 hour-long CBT sessions based on content used throughout VA. Patients randomized to the AI-CBT treatment group will begin with one standard, hour-long telephone CBT session and will be asked to report their pedometer-measured step counts, pain-related functioning, and CBT skill practice via 5-minute daily IVR calls. Some of those IVR calls also will include reminders regarding the dates and modalities for upcoming CBT sessions. Based on patients' IVR feedback, the AI-CBT engine will make recommendations to carefully step-down the intensity of each patient's CBT follow-up using more brief telephone therapy sessions (15 minutes), or IVR therapy. Based on experience gained from each patient's history and the overall population of patients, the AI-CBT engine will seek to optimize the population's total improvement in functioning while maintaining each patient at the least resource-intensive mode of CBT delivery. Outcomes will be measured via telephone survey at 3 and 6 months post recruitment, and additional data will be collected via clinical records. We will use data from therapists' activity logs and administrative files to conduct a budget impact analysis. Additional data to aid translation of study findings from research into practice will be collected via qualitative interviews with CBT therapists, other clinical team members, and patients with various levels of program response.

Patient Identification and Recruitment

The study will be conducted among patients with chronic low back pain in facilities affiliated with the VA Ann Arbor Healthcare System and the VA Connecticut Healthcare System. Participants who have a diagnosis of low back pain and a pain score of ≥ 4 (indicating moderate pain) on the 0-10 Numerical Rating Scale during at least two separate outpatient encounters in the past year will be identified via electronic medical records. Eligible patients must: (1) report at least moderate pain-related disability as determined by a score of 5+ on the Roland Morris Disability Questionnaire at baseline, (2) report at least moderate musculoskeletal pain for at least 3 of the prior 6 months [57], (3) not be actively psychotic, suicidal, or severely depressed (ie, a score of 20+ on the 9-item Patient Health Questionnaire or PHQ-9 [58]), (4) not report behavior flags related to emotional dysregulation, bipolar disorder, or active substance abuse that could impede participation in the study, (5) be free of life-threatening conditions that could impede participation, such as chronic lung disease requiring oxygen or cancer requiring chemotherapy, (6) be free of dementia defined by a score of 20 or greater on the St. Louis University Mental Status screener [59], (7) have a mobile phone or touch-tone land line phone, (8) be free of sensory deficits that would impair participation in telephone calls, and (9) report that they are not currently receiving CBT and have no plans for surgical treatment related to their back pain. After obtaining agreement from patients' primary care providers, a letter will be sent to veterans informing them about the study and inviting participation. Veterans who do not opt-out by postage-paid response card will be called by research staff to explain the study, conduct screening, and solicit their involvement. If the veteran is willing, s/he will be sent the consent form by mail along with a postage-paid return envelope. We have used this same process in numerous prior studies and found that it is an efficient and effective way to recruit large samples of veterans without requiring an in-person recruitment visit. The study coordinator will track the percentage of eligible veterans who enroll in the trial and will actively solicit reasons for declining. This

information will be used to assess the intervention's reach, as described in the implementation portion of the application (Aim 3).

In preparation for this study, we used VA Corporate Data Warehouse records for 2012 to identify patients treated in Ann Arbor and West Haven with low back pain (International Classification of Diseases [ICD-9] codes 742.01, 724.02, 724.03, 724.09, 724.1, 724.2, 724.3, 724.4, and 724.5) and a pain score of ≥ 4 on the 0-10 Numerical Rating Scale during at least two separate outpatient encounters. We identified 105,344 patients and estimate that we would have to recruit 3-4% at a rate of 4.4 patients per site per month to reach accrual goals. Our prior studies based on similar populations have recruited 5 to 10 veterans with chronic pain per month per recruiter; therefore, we expect no difficulty recruiting the target sample within the proposed timeframe and staffing.

Randomization

After completing baseline assessments, patients will be randomized to AI-CBT or standard telephone CBT. Randomization will be done by research staff using sealed opaque envelopes and the computer-generated randomization series. To ensure balance across treatment arms in potential modifiers of the intervention effect, randomization will be done within strata defined by site and age.

Common Elements of Standard and AI-CBT

Overview

Both CBT conditions will involve 10 treatment modules delivered over 10 weeks. The same therapist at each site will provide treatment to patients in both groups. In each arm, the 10-week course of therapy will include an introductory module, followed by 8 pain coping skills training modules and concluding with a final session emphasizing skill consolidation and relapse prevention. The introductory module will present the biopsychosocial model, which explains how chronic pain can lead to dysfunction across numerous domains and provides a rationale for the efficacy of pain coping skills to manage chronic pain. The 8 skills that will be presented were selected based on their efficacy in improving pain outcomes and their appeal to patients in prior trials. These include sessions focused on physical activity, behavioral activation, pacing, and relaxation. We have included modules that address common maladaptive cognitions such as pain catastrophizing and fear of movement or kinesiophobia; a module on sleep hygiene techniques was also included to address sleep complaints that are common among persons with chronic pain and whose treatment has positive effects on pain intensity. Using procedures developed in two previous VA-funded studies, during sessions 2-9, participants will be assigned a goal related to newly presented adaptive pain coping skills (eg, "practice relaxation exercise for 20 minutes daily") and a daily walking goal (average daily steps over the prior week plus 10%). As participants progress through treatment, they will continue to practice prior goals. In order to maintain equivalence across treatments, participants in both groups will be assigned the same skill practice goals and the same formula will be used for assigning steps goals.

Patient and Therapist Materials

Patients in both treatment conditions will use a handbook based on those used in prior trials. The handbook will be identical for both conditions, except that the AI-CBT handbook will contain additional information that describes the three AI modes (one-hour, 15-minute, and IVR sessions) and how to prepare for each type of session. The therapist manuals will be adapted from materials developed for our IVR-based CBT for Chronic Low Back Pain trial. The AI-CBT section will detail specific guidelines for each treatment mode (ie, one-hour, 15-minute, and IVR).

Therapist Training and CBT Fidelity

Therapists will be Master's or doctoral-level clinicians (clinical psychologists or social workers). Therapists will receive 20 hours of training in delivering CBT. Training will include review of the treatment manual, education regarding the nature of chronic pain, the treatment and its rationale, and role-playing the intervention. Therapists will demonstrate mastery of the treatment manual and its procedures by passing a series of quizzes on the module content with at least 85% correct. Therapists will then provide treatment to mock patients and the Co-PI will review the audio-taped sessions, rate fidelity to the treatment manual, and provide feedback to the therapists until they are able to demonstrate proficiency in treatment delivery and adherence to the treatment protocol.

During the intervention trial, all treatment sessions will be digitally audio-recorded. Thirty percent of treatment sessions will be randomly selected and rated for treatment fidelity using the Yale Adherence and Competence Scale (YACS) [60], a validated scale that assesses therapist adherence and competence in delivering manualized behavioral therapy. Because treatment sessions vary in length in the AI treatment condition, we will assess 100% of treatment sessions to ensure that actual session time is within 15% of the AI system-assigned treatment session length (one hour or 15 minutes). Corrective feedback will be given throughout the study to prevent therapist drift.

Pedometers for Monitoring Patients' Physical Activity

All patients will be given a pedometer and a log for monitoring their step counts. We expect to use a Yamax DigiWalker pedometer because it is accurate and used frequently in research [61]. Patients will be mailed a pedometer after completing their baseline assessment and returning their consent form.

Standard Telephone CBT (Control)

Control patients will receive telephone CBT consisting of 10 weekly modules delivered via one-hour telephone contacts with a therapist. The format of each session will include (1) review of patients' pedometer logs and coping skill practice, (2) review of previous material and correction of misunderstandings of the information, (3) assignment of new step count goals and discussion of new skills-based material, and (4) discussion of specific step and skill practice goals. Positive feedback and praise will be offered for any skill practice and step goal efforts and accomplishments. Barriers to practice or goal completion will be identified and problem-solving techniques will be used to address them.

Cognitive Behavioral Therapy Supported by Artificial Intelligence (AI-CBT)

Daily IVR Reports

Patients will report their pedometer-measured step counts, CBT skill practice, and pain-related functioning via daily 5-minute IVR calls. Patients will receive calls at times they indicate as convenient and will respond to recorded inquiries using their touch-tone phone. If the initial call is missed, the system will automatically try again 15 minutes later and again 1 hour later. We have successfully used these methods in studies achieving high patient response rates. Pedometer step counts will measure activity over the prior 24 hours, and patients will report their skill practice using a 0-10 scale. Pain-related functioning will be assessed using a single item from the West Haven-Yale Multidimensional Pain Inventory (WHYMPI) [62].

Step counts will be used in the "reward function" that the RL algorithm will seek to optimize, and skill practice and physical functioning reports will be used as "state" information that the system will take into account when making decisions that optimize patients' treatment course. The definition of the reward function is of course a crucial decision in AI, since all action choices will be evaluated in terms of whether or not they optimize that goal. We chose step counts because they represent an objective measure of patients' physical function, a direct behavioral target of CBT, and an outcome of pain CBT programs as defined by national guidelines. Perceived pain-related interference, sleep quality, and other subjective experiences of chronic pain syndromes also will be collected via IVR and periodic surveys. In post-hoc analyses, we will be able to evaluate whether a weighted composite reward (eg, taking both steps and symptoms into account) might lead to more efficient optimization and more effective action choices. The AI system will be able to accommodate missing IVR reports, and patients who fail to complete more than 50% of the daily IVR calls in a 2-week period will be called by a research associate to troubleshoot problems and encourage compliance with feedback. In addition to being the source of data with which AI-CBT will personalize each patient's course of treatment, data from IVR calls will be used to inform therapists of participants' treatment adherence and progress. These data will be particularly important for informing abbreviated 15-minute therapist sessions when priority is placed on the efficient use of treatment time and during IVR sessions when the entire session is pre-recorded. Once a week, the IVR call will include a brief weekly message alerting patients of the date, time, and modality for their subsequent week's session.

AI-CBT Action Recommendations

After Week 1, session options will include (a) one-hour telephone treatment sessions, (b) 15-minute live telephone therapist sessions, and (c) IVR treatment sessions. To avoid scheduling conflicts, AI-CBT patients will be assigned a one-hour block of time each week in which both they and the CBT therapist are available for treatment. This same time slot will be used for either the hour-long therapist sessions, the 15-minute therapist sessions, or the IVR CBT sessions. Each Monday morning, the CBT therapists will receive a list of AI-CBT personalized treatment recommendations for that week for each patient. By noon on Monday, the therapist will have a finalized schedule of which patients require what types of contact that week, and which patients need to have a summary of the therapist's comments and recommendations recorded for the week's IVR CBT therapy call.

During *Week 1*, all patients in AI-CBT will have an hour-long telephone session with the CBT therapist. During that session, the therapist will review the goals and process of the program and will present the standard introductory material contained in Session 1 of the standard CBT program. The *one-hour AI-CBT sessions* will be identical to those of the control condition (see above for details) and will follow the same progression of content used for control patients. The *15-minute telephone CBT sessions* will mirror the content of the one-hour sessions, though in a compressed form. Protocols in the therapist manual and patient handbook will emphasize the importance of using session time efficiently and using a consistent format that includes reviewing the patient's daily IVR reports, clarifying patient handbook information regarding the current week's adaptive pain coping skill, and setting goals for skill practice and step counts for the coming week. Prior to the session, therapists will review patient-reported information collected via daily IVR calls. If participants have not been successful in meeting step or skill practice goals, the therapist will help the participant identify barriers to goal attainment and use problem-solving strategies to address barriers. The therapist then will ask the patient to describe the current week's adaptive pain coping skill as a brief check of their understanding and will clarify any misunderstood information. Finally, the therapist will review goals for the coming week and discuss any anticipated barriers to meeting goals. Any remaining time will be used to review the skill and to encourage the patient to read their patient handbook. Much of the content for the *IVR CBT sessions* has been developed and implemented as part of our ongoing IVR-based CBT for Chronic Low Back Pain trial. Our experience in that trial suggests that patients complete the IVR sessions more than 90% of the time and that satisfaction rates are high. During these sessions, patient will receive 2-5 minutes of pre-recorded feedback from their therapist, during which the therapist will review the patient's recent IVR-reported changes in step counts, pain-related functioning, and skill practice. Reinforcement will be provided for effort, and improvements will be noted. IVR messages will include a review of the pain coping skill practice and step goals for the coming week, and participants will have the option of leaving a message for their therapist via the IVR system, should they have a question. Therapists can leave a response message, also on the IVR system. These IVR CBT sessions typically take 15 minutes to complete.

The AI Engine

Patients' IVR-reported step counts, skill practice, and pain-related functioning will be accessed by the AI engine daily to update the probabilities that the system uses to determine which treatment step to recommend for each patient the next week. We will use a state-of-the-art AI algorithm (LinUCB) designed to make careful choices while learning quickly from a patient's treatment response as well as the experience of other patients with similar characteristics [45]. With increased

interactions, the system will learn to tailor these decisions more effectively to maximize population-level improvements in functioning while minimizing clinician time. In this way, AI-CBT will function similar to the best clinicians, who learn from experience within and across patients to improve their care. In the context of the trial, this means that patients enrolled early will likely receive less personalized CBT courses that are relatively similar to the standard CBT approach (ie, with a greater number of hour-long sessions), while patients enrolled later will receive services that are more personalized and include a greater frequency of 15-minute therapist sessions and IVR sessions. To maximize the efficiency of this "learning curve," (1) patients will be recruited over a longer period than would potentially be necessary, so that the AI-CBT program can gain as much experience as possible from patients recruited first and apply that knowledge to patients entering the program later, and (2) patients will be randomized with a greater "N" in the AI-CBT group so as to maximize the system's experience (see power calculation, below). As part of our evaluation, we have planned an a priori subgroup analysis in which we will compare randomization groups on each specific aim separately for early versus later enrollees, to test the hypothesis that AI-CBT will result in greater benefits over time. These analyses also will allow us to estimate program benefits if AI-CBT were implemented with thousands of patients and multiple years of experience.

CBT Treatment Fidelity

CBT treatment fidelity will be assessed using a modified version of the Yale Adherence and Competence Scale [60], a validated scale that assesses therapist adherence and competence in delivering manualized behavioral therapy. Dr Heapy will rate audiotapes of 30% of all CBT therapist sessions to assure that treatment is consistent with the manual and will provide corrective feedback to therapists whenever drift occurs.

Role of the Expert Panel

The AI-CBT program will be supervised with ongoing input from an expert panel comprised of experts in pain management, CBT for chronic pain, clinical trials using behavioral interventions, adaptation of therapy materials for telephone delivery, and IVR. The panel will meet several times by teleconference during the study start-up period to review and revise the proposed treatment materials and refine the AI algorithm to reflect any constraints that should be put into place to limit the choices that the RL algorithm can make, for example, "if the patient's physical activity level decreases more than 20% during 2 weeks in a row, recommend 2 hour-long CBT sessions regardless of what their prior week's contact was." Experts will meet by teleconference quarterly and in ad hoc sessions if important concerns or questions arise during the intervention.

Measurement

Overview

We have selected outcome measures based on recommendations from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) [57,63]. Endpoint measures are consistent with CONSORT guidelines recommending that equivalence trials use outcomes that are similar to those used in efficacy studies. We also will examine treatment satisfaction, treatment credibility, patient engagement and dropout, and goal accomplishment. Process and outcome data will be collected via the following sources: (1) *Patient surveys* will be conducted at baseline, 3 months, and 6 months via telephone by trained research assistants. Participants will receive a $20 incentive for each interview completed; (2) *Qualitative interviews* will be conducted with purposive samples of patients in the AI-CBT group at follow-up. We will target patients who demonstrate significant improvement, patients who were very satisfied with AI-CBT, patients without significant improvement, patients who were dissatisfied, and patients who dropped out of the intervention. Additional qualitative interviews will be conducted at follow-up with CBT therapists and clinician team members; (3) *CBT therapist logs* will be used to track therapist time spent in patient treatment and in attempting to reach patients, as well as key information about the content of those interactions; (4) The *AI-CBT IVR system* will automatically capture information about intervention patients' pedometer-measured step counts, pain-related functioning, CBT skill practice, and missed data reporting events; and (5) *Administrative and clinical data systems* will be used to track patients' use of other VA inpatient and outpatient services for pain management, mental health, and medical care.

Primary Outcome

The 24-item Roland Morris Disability Questionnaire (RMDQ) is an IMMPACT endorsed measure [63] of pain-related disability for persons with chronic low back pain. Strong evidence supports the RMDQ's reliability, validity, and responsiveness to change during trials [64].

Secondary Outcomes

Global pain intensity will be assessed using the Numeric Rating Scale (NRS-I) an IMMPACT-recommended 11-point numeric rating scale of pain severity [57]. *Pain-related interference* will be measured using the 9-item Interference subscale of the West Haven-Yale Multidimensional Pain Inventory (WHYMPI). This IMMPACT-recommended measure assesses pain-related interference in daily activities and has demonstrated good internal consistency [57,62]. *Emotional functioning* will be assessed using the 65-item Profile of Mood States (POMS) [65], which is designed to assess six dimensions of mood. Internal consistency and test-retest reliability for the POMS are good, and it requires only 3-5 minutes to complete. *Depression symptom severity* will be assessed using the 21-item Beck Depression Inventory (BDI), a widely used measure with excellent internal consistency and stability [66]. The BDI takes 5-10 minutes to complete. The Patient Global Perception of Change scale is a single-item measure that quantifies a participant's overall *perception of improvement* since beginning treatment and the clinical importance of that improvement. Participants indicate improvement on a 7-point "much worse" to "much better" scale. This is a well-validated measure recommended by IMMPACT [63]. Finally, we will use the Veterans SF-12 to assess *health-related quality of life.* This measure has demonstrated good internal consistency and is

strongly correlated with socioeconomic status and morbidities [67].

Resource Use (Aim 2)

To assess *intervention costs*, therapists will use a log to record time spent in intervention-related activities, including patient treatment and consulting with other care providers, for a random 20% of all days for which they are treating patients. These time records will be combined with wage data from the VA Financial Management System to estimate intervention-specific personnel costs. Technology costs of the AI-CBT program include fixed costs (eg, software development and computer maintenance) plus variable costs (eg, minute costs for IVR calls). One-time fixed start-up costs will be reported separately. *VA inpatient and outpatient service use* data will be obtained from the Musculoskeletal Diagnoses Cohort (MSD). The MSD is developing validated algorithms for using VA electronic health record data to identify utilization events, comorbid conditions, receipt of opioid medications, and pain screening results, for patients with pain-related diagnoses. The primary data source is the National VA Corporate Data Warehouse (CDW), which contains electronic pharmacy data, and inpatient and outpatient encounters. The MSD soon will include data from sources currently transitioning to the CDW, such as Decision Support System National Data Extracts (which include the Outpatient and Inpatient Encounter files). Information on non-VA admissions will be collected by the patient survey. To mitigate recall bias, we will use a 2-timeframe method that asks about utilization over the past 6 months and past 2 months, with more weight given to the shorter timeframe [68].

Treatment Satisfaction and Engagement (Aim 3)

For patients in the AI-CBT group, we will calculate *IVR adherence* as we have in the past [46], that is, as the proportion of days during which an assessment was attempted in which one was successfully completed and the number of weeks during which the patient completed at least 4 out of 7 requested IVR reports. Participants' judgments of *treatment credibility* will be assessed using a reliable questionnaire adapted from Borkovec and Nau [69]. Treatment credibility has been shown to be significantly associated with treatment satisfaction, engagement in treatment, and number of sessions attended. The Pain Treatment Satisfaction Scale of the Patient Outcomes Questionnaire will be used to assess *patient satisfaction* with various domains of pain care [70]. This 5-item measure shows good internal consistency and significant associations with staff and patient ratings of patient improvement. To understand *attendance in "live" telephone CBT sessions and program dropout*, we will attempt to reach samples of patients with low levels of engagement for qualitative interviews. Participants will rate their *continued skill use* at follow-up for each of the target behaviors emphasized in the CBT program on a 0 (not at all accomplished) to 10 (completely accomplished) scale. These survey items will be based on those we have used successfully to collect similar data from veterans during IVR assessment calls. As described above, *daily IVR calls* will be used to collect data in the AI-CBT condition regarding pedometer measured step counts, CBT skill practice, and pain-related functioning using pre-recorded questions we have used successfully in our prior studies.

Demographics and Covariates Measured at Baseline

Demographics and other covariates have been selected to be consistent with data collected in prior trials of chronic pain and pain-related CBT, including factors that can influence important mediation and moderation processes such as access to care, barriers to enacting behavior changes, and substance abuse and mental health comorbidity. Variables will reflect characteristics predicting psychological treatment response in the Personalized Advantage Index, that is, marital status, employment status, life events, comorbid personality disorder, and prior experience with medications [28]. We will measure patients' baseline *sociodemographic and pain characteristics* that have been shown to be associated with treatment outcomes such as age, sex, education level, racial/ethnic background, marital status, occupational status, pain duration, and number and location of pain sites. We also will gather data on participants' level of health literacy [71]. *Psychiatric and substance abuse comorbidities* will be measured using medical record diagnoses and mental health encounters. Additional self-report information will be collected using subscales of the Mini International Neuropsychiatric Interview (MINI) [72] related to mood and substance abuse disorders. *Pain medication use* will be assessed through patient surveys and a review of computerized pharmacy records. Pain medication will be coded as non-steroidal anti-inflammatory, non-narcotic analgesics, narcotic analgesics, and benzodiazepines and other sedative/hypnotics. For each category, ratings also will be made post-treatment, to determine whether patients have experienced an increase, no change, or decrease in their medication use. *Distance from VA* will be calculated using Google maps and used as a measure of geographic access. The *Pain Catastrophizing Scale* is a 13-item self-report scale that examines thoughts and feelings people may experience when they are in pain including rumination, magnification, and helplessness [73]. Finally, *pain-related fear* will be measured using the Tampa Scale of Kinesiophobia-revised (TSK-R), which has two subscales (Fear of Harm/Activity Avoidance and Pathophysiological Beliefs) and has been shown to be sensitive to treatment-related change.

Sample Size and Power Calculation

To ensure that the AI-CBT program retains a clinically relevant effect relative to standard CBT, the noninferiority margin was set at a 2-point reduction in pain-related disability as measured by the Roland Morris Disability Questionnaire (RMDQ) [64]. A 2-point reduction in the RMDQ is considered to be a minimally clinically significant effect [74]. To detect noninferiority within a margin of 2 points (SD 4.5) with 90% power and Type I error (1-sided) of .025, we will need 108 participants in each group after attrition. If we assume 20% attrition, we would need to randomize 135 patients to each study arm, for a total of 270 patients enrolled. However, given that we expect no difficulty recruiting sufficient numbers of patients, our target sample size will be 320. The additional 40 patients, that is, (320 - 270) - 10 dropouts, will allow us to ensure that we are well powered to detect inferiority in the event of a higher dropout rate, and also will allow us to randomize patients to the

AI-CBT versus standard CBT groups using a ratio of 1.37:1. The additional patients in the AI-CBT group will have the added benefit of allowing the AI engine to improve its ability to personalize patients' stepped care program as quickly as possible.

Analysis

Baseline Comparability

We will examine baseline differences across groups in measures of study endpoints as well as other potential prognostic indicators, such as patients' age, comorbid diagnoses, and history of pain treatment. Any differences across groups in baseline characteristics will be controlled statistically in analyses comparing outcomes.

Intervention Reach and Sample Representativeness

The RE-AIM framework (ie, Reach, Efficacy, Adoption, Implementation, and Maintenance) is a methodology for systematically considering all strengths and weaknesses of an intervention to better guide program planning [75]. To evaluate reach, we will ask patients who decline study participation whether they would be willing to provide informed consent to participate in a brief survey that identifies their reasons for declining participation and the characteristics that differentiate them from enrollees.

Analysis of Endpoints (Addressing Specific Aim 1)

We will compare standard telephone CBT to AI-CBT on the RMDQ pain intensity scores at the 12-week follow-up using a one-sided, 2-sample t-test. Because intent-to-treat analysis can raise the risk of Type I error in a noninferiority trial [76], we will conduct both a per protocol and intent-to-treat analysis. Analyses of all other outcomes will be conducted on an intent-to-treat basis. Because the more efficient AI-CBT program will be less burdensome to patients, engagement and outcomes could actually be superior to standard CBT. Our primary outcome analyses will be able to detect superiority in the AI-CBT group, although the study has been designed to detect noninferiority. We expect that RMDQ scores will be normally distributed. If not, we will use transformations to achieve normality. We also will develop a 2-level mixed linear model that uses both RMDQ follow-up scores as the dependent variables; treatment group, time, and the treatment by time interaction as categorical explanatory variables; and baseline RMDQ score as a continuous covariate. This model will also allow for adjustment for design-related factors (eg, site and age). Age will be examined as a blocking variable within 5-year age groups, because randomization will be done within site x age block strata. An unstructured variance-covariance matrix will be used to model the error variance. Secondary outcomes including pain intensity, emotional functioning, global perception of change, and quality of life will be analyzed in a manner similar to that used for the primary outcome.

Intensity of Service Use (Specific Aim 2)

We will compare service utilization by category (eg, CBT therapist time, PCP visits, and pharmacy use) between groups. We will conduct a budget impact analysis [77] from the perspective of the VA medical center and will include the cost of the intervention (personnel, supplies, CBT therapist training, and IVR fixed/variable costs) as well as costs for specific medical care services likely to be affected by the intervention. Data from CBT therapists time records will be combined with wage data from the VA Financial Management System to produce estimates of intervention-specific personnel costs. Costs associated with the use of specific medical care services, such as medications, will be obtained from the Decision Support System (DSS) files. Cost analysis will be conducted in accordance with the guidance provided by Mauskopf et al [77], including the use of sensitivity analysis and scenarios that allow for varying assumptions about intervention uptake, compliance, or component costs. All resource use and cost comparisons will be adjusted for any observed baseline differences in patient characteristics. Because costs of resource utilization are usually skewed, alternative modeling techniques (eg, log-transformed costs, negative binomial regression) will be used.

Intervention Engagement and Satisfaction with Care (Specific Aim 3)

As in our prior research [46], we will conduct extensive analyses of the process of intervention delivery in both arms. We will monitor the proportion of telephone CBT sessions that are completed, and determine the patient and session characteristics associated with patients' reports of skill practice. Patients in the AI-CBT group will report their satisfaction with aspects of the intervention (eg, whether it provided information useful for achieving behavioral targets), and satisfaction ratings will be correlated with measures of intervention engagement, patients' baseline characteristics, and changes in pain-related functioning. Differential dropout across experimental conditions will be examined using Kaplan-Meier curves and survival models.

Preplanned Subgroup Analysis

Because AI-CBT will continue to learn patterns in patients' experience throughout the intervention period, we hypothesize that the second 50% of patients randomized will show an even larger difference in clinician time than the first 50%, while still maintaining near equivalence in pain-related outcomes. Differences in pain-related functioning and in clinician treatment time across treatment groups will be tested in this subgroup analysis after stratifying the sample into early versus later recruits.

Approach to Missing Data

If more than 15% of a covariate is missing, we will use multiple imputation methods based on the SAS MI Procedure [78]. Specifically, we will model patients' likelihood of having data and define strata within which values are missing at random. We will then stratify patients according to these propensities, randomly sample from the observed outcome distributions, and impute these values for missing data within each stratum. When data are missing for items within scale scores, we will use recommended imputation procedures rather than deleting patients list-wise from the analysis.

Mediators and Moderators of Intervention Effects

We will use multivariate modeling to identify the mechanisms through which the intervention achieves effects on outcomes and whether there are differential effects across subgroups [79].

Initial models will include only treatment group as the predictor. Subsequent nested models will introduce potential mediators (such as the amount of time spent via telephone with CBT therapists), and we will evaluate changes in the relationship between experimental condition and outcomes before and after covariates are introduced. Analyses of effect moderation will focus on baseline pain severity and comorbid diagnoses using standard approaches to evaluate interactions between these covariates and patients' experimental condition [80]. Significant interactions will be interpreted by plotting regression lines for predicted outcomes of patients with high and low values of the moderator.

Evaluating the Reliability of Patients' IVR Reports

We will evaluate the integrity of IVR-reported step counts and functioning by examining associations between IVR reports and patients' baseline characteristics that the literature suggests would be associated with patients' functioning (eg, baseline SF-12 scores, comorbid medical diagnoses, and age). We also will examine serial correlations across IVR reports under the assumption that all correlations between scores and proximal scores should be positive and roughly of equal magnitude, controlling for the time difference between reports.

Evaluating Intervention Adoption, Implementation, and Maintenance

These dimensions of an RE-AIM evaluation [75] will be assessed as follows. Adoption will be evaluated by examining variation in study participation and intervention engagement across sociodemographic and clinical subgroups of eligible patients. For example, we will determine whether older patients or those with less education have more difficulty responding to queries about their step counts or other aspects of pain-related functioning via IVR. Adoption at the provider level will be monitored by recording the proportion of primary care providers who are willing to have their patients participate in the trial and providers' reasons for not participating. Implementation and maintenance will be evaluated through semi-structured questions at follow-up designed to identify program characteristics that might be a barrier to patients' use of the intervention in other settings and intervention characteristics that patients feel would make it more valuable to others with chronic pain. We also will meet with clinicians at each site to gauge their willingness to adopt and maintain a similar intervention, and the ways such a system can be designed to best complement existing services.

Qualitative Interviews and Mixed-Methods Analysis

We will use audio-taped interviews with 20 patients (15 from the AI-CBT arm), CBT therapists (N=2), and clinician team members (5 from each of the two recruitment sites) to provide a context for interpreting intervention effects and suggest additional subgroup analyses. The focus of patient interviews will be on satisfaction with pain care, barriers and facilitators of pain management, and motivation for making behavior changes using automated systems. AI-CBT patient interviews will focus on patients' satisfaction with the adaptive intervention and the extent to which patients felt that it was able to provide them with the care they needed while using their time effectively. Staff and clinician interviews will focus on barriers to recruitment and maintenance in a larger-scale roll-out of the intervention and the extent to which staff feel that services like this are feasible and useful given their workflow. Staff will be interviewed by the two study PI's, and patients will be surveyed by a research associate with training by an expert in qualitative analysis. Interviews will be transcribed verbatim, and 20% of the transcripts will be verified by comparing the transcript to the audiotape. We will enter the transcripts into NVivo, for file storage and selective retrieval. Using accepted techniques [81], two reviewers will independently read transcripts, approaching the data with analytic categories in mind, but also identifying other categories in the data. An iterative process will be used until agreement is reached on categories and their definitions, after which we will develop a coding template and enter it into NVivo as a tree diagram. Dr Heapy has experience in gathering and analyzing qualitative data on CBT goal setting and outcomes, and the University of Michigan Center for Managing Chronic Disease has extensive expertise in this important focus of implementation science.

Results

The trial is currently in the start-up phase. Patient enrollment will begin in the fall of 2016 and results of the trial will be available in the winter of 2019. If successful, the study will establish a new approach for using artificial intelligence to improve pain care. Similar methods could be used to improve the efficiency of chronic disease management services for patients with depression, hypertension, diabetes, and other priority conditions.

Discussion

Expected Findings

The AI engine will only make productive decisions about patients' subsequent therapy sessions to the extent that it has valid, reliable, and current information about patients' progress. In this respect, the AI-CBT program is identical to clinicians who must rely on patients' feedback about behaviors such as adherence, to judge treatment response after a change in management. We will examine patients' IVR reports carefully as described above to identify aberrant patterns that need to be taken into account when evaluating the intervention's effectiveness and potential of this system for broader dissemination. The AI engine will also be programmed to disregard reports of dramatic changes in patients' step counts that are likely to be inaccurate. These reports will be treated as missing data, thereby making conservative decisions that leave patients in the relatively intensive treatment modes. Missing data on step counts and CBT skill practice will result in conservative choices in the AI-CBT group, which in the extreme will leave patients with weekly one-hour telephone CBT identical to that received by patients in the control arm. In contrast to other applications of reinforcement learning, for which AI systems can receive millions of "reward" indicators across users in short intervals of time (eg, purchase decisions among Amazon users), the AI engine in this intervention will only be receiving data on a relatively small number of patients and time points. As such, the system will learn relatively slowly

for a given patient, especially for patients enrolled in the initial phases of recruitment. We expect that this will lessen the system's ability to maximize cost-savings by offering less resource-intensive but equally effective alternatives to extended telephone CBT sessions. As such, the differences in per-patient treatment cost across groups will be a lower bound of what could be expected if the service were implemented with larger samples of patients over longer periods of time.

Dissemination and Implementation Plan

We will engage clinicians at both sites during regularly scheduled primary care meetings to discuss how to make the service most impactful and consistent with their workflow. We also will disseminate short newsletter-style emails with information about the study, and will make PowerPoint presentations and videos of educational presentations available via the National Pain Program Office website. Of particular relevance to engaging other pain researchers is the Pain Research, Informatics, Medical comorbidities, and Education (PRIME) Center, directed by Dr Robert Kerns. PRIME Center resources will be made available to assist with this dissemination plan. An additional avenue for dissemination is the National Pain Research Working Group, which includes pain investigators that teleconference regularly to identify priorities for pain research and develop collaborative projects. The PRIME Center has a well-established collaboration with the Health Services Research and Development (HSR&D) Center for Information Dissemination and Education Resources (CIDER) and the Employee Education System. These will be leveraged to further target policy makers through cyber seminars and other dissemination strategies. We believe that AI-CBT will be an exciting alternative for consumers because it will be less burdensome than standard care and will automatically personalize each patient's treatment course.

Acknowledgments

This study has been funded by VA HSR&D IIR #13-350. John Piette is a Senior VA Research Career Scientist.

Conflicts of Interest

None declared

Multimedia Appendix 1

Reinforcement Learning: description of the adaptive algorithm with simulations.

[PDF File (Adobe PDF File), 1MB - resprot_v5i2e53_app1.pdf]

Multimedia Appendix 2

Funding confirmation from the VA Health Services Research and Development Program.

[PDF File (Adobe PDF File), 89KB - resprot_v5i2e53_app2.pdf]

References

1. Sinnott P, Wagner TH. Low back pain in VA users. Arch Intern Med 2009 Jul 27;169(14):1338-1339; author reply 1339. [doi: 10.1001/archinternmed.2009.201] [Medline: 19636039]
2. Yu W, Ravelo A, Wagner TH, Phibbs CS, Bhandari A, Chen S, et al. Prevalence and costs of chronic conditions in the VA health care system. Med Care Res Rev 2003 Sep;60(3 Suppl):146S-167S. [Medline: 15095551]
3. Kerns RD, Dobscha SK. Pain among veterans returning from deployment in Iraq and Afghanistan: Update on the Veterans Health Administration Pain Research Program. Pain Med 2009 Oct;10(7):1161-1164. [doi: 10.1111/j.1526-4637.2009.00722.x] [Medline: 19818026]
4. Institute of Medicine Committee on Advancing Pain Research, Care, and Education. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington, DC: National Academies Press; 2011.
5. Kerns RD, Otis J, Rosenberg R, Reid MC. Veterans' reports of pain and associations with ratings of health, health-risk behaviors, affective distress, and use of the healthcare system. J Rehabil Res Dev 2003;40(5):371-379 [FREE Full text] [Medline: 15080222]
6. Krein SL, Heisler M, Piette JD, Butchart A, Kerr EA. Overcoming the influence of chronic pain on older patients' difficulty with recommended self-management activities. Gerontologist 2007 Feb;47(1):61-68. [Medline: 17327541]
7. Kerns RD, Booss J, Bryan M, Clark ME, Drake A, Gallagher RM, et al. Veterans health administration national pain management strategy: Update and future directions. American Pain Society Bulletin 2006;16:1-15.
8. Martell BA, O'Connor PG, Kerns RD, Becker WC, Morales KH, Kosten TR, et al. Systematic review: Opioid treatment for chronic back pain: Prevalence, efficacy, and association with addiction. Ann Intern Med 2007 Jan 16;146(2):116-127. [Medline: 17227935]
9. Centers for Control and Prevention. Vital Signs. Prescription Painkiller Overdoses in the US URL: http://www.Cdc.Gov/vitalsigns/painkilleroverdoses/index.Html [accessed 2016-03-09] [WebCite Cache ID 6ft0wPIdN]

10. Macey TA, Morasco BJ, Duckart JP, Dobscha SK. Patterns and correlates of prescription opioid use in OEF/OIF veterans with chronic noncancer pain. Pain Med 2011 Oct;12(10):1502-1509 [FREE Full text] [doi: 10.1111/j.1526-4637.2011.01226.x] [Medline: 21899715]
11. Chou R, Huffman LH, American PS, American College of Physicians. Nonpharmacologic therapies for acute and chronic low back pain: A review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. Ann Intern Med 2007 Oct 2;147(7):492-504. [Medline: 17909210]
12. Turk D, Meichenbaum D, Genest M. Pain and Behavioral Medicine: A Cognitive-Behavioral Perspective. New York: Guilford Press; 1983.
13. Hoffman BM, Papas RK, Chatkoff DK, Kerns RD. Meta-analysis of psychological interventions for chronic low back pain. Health Psychol 2007 Jan;26(1):1-9. [doi: 10.1037/0278-6133.26.1.1] [Medline: 17209691]
14. Williams AC, Eccleston C, Morley S. Psychological therapies for the management of chronic pain (excluding headache) in adults. Cochrane Database Syst Rev 2012;11:CD007407. [doi: 10.1002/14651858.CD007407.pub3] [Medline: 23152245]
15. Trafton JA, Martins SB, Michel MC, Wang D, Tu SW, Clark DJ, et al. Designing an automated clinical decision support system to match clinical practice guidelines for opioid therapy for chronic pain. Implement Sci 2010;5:26 [FREE Full text] [doi: 10.1186/1748-5908-5-26] [Medline: 20385018]
16. Gorin AA, Stone AA. Recall biases and cognitive errors in retrospective self-reports: A call for momentary assessments. In: Baum A, Revenson TA, Singer JE, editors. Handbook of Health Psychology. Mahwah, NJ: Lawrence Erlbaum Associates; 2001.
17. Lambert MJ. Early response in psychotherapy: Further evidence for the importance of common factors rather than "placebo effects". J Clin Psychol 2005 Jul;61(7):855-869. [doi: 10.1002/jclp.20130] [Medline: 15827996]
18. Ostelo RWJG, van Tulder MW, Vlaeyen JWS, Linton SJ, Morley SJ, Assendelft WJJ. Behavioural treatment for chronic low-back pain. Cochrane Database Syst Rev 2005(1):CD002014. [doi: 10.1002/14651858.CD002014.pub2] [Medline: 15674889]
19. Tobacman JK, Zeitler RR, Cilursu AM, Mori M. Variation in physician opinion about scheduling of return visits for common ambulatory care conditions. J Gen Intern Med 1992;7(3):312-316. [Medline: 1613613]
20. DeSalvo KB, Bowdish BE, Alper AS, Grossman DM, Merrill WW. Physician practice variation in assignment of return interval. Arch Intern Med 2000 Jan 24;160(2):205-208. [Medline: 10647759]
21. Parchman ML, Bisonni RS, Lawler FH. Hypertension management: Relationship between visit interval and control. Fam Pract Res J 1993 Sep;13(3):225-231. [Medline: 8296586]
22. Schectman G, Barnas G, Laud P, Cantwell L, Horton M, Zarling EJ. Prolonging the return visit interval in primary care. Am J Med 2005 Apr;118(4):393-399. [doi: 10.1016/j.amjmed.2005.01.003] [Medline: 15808137]
23. Hansen NB, Lambert MJ. An evaluation of the dose-response relationship in naturalistic treatment settings using survival analysis. Ment Health Serv Res 2003 Mar;5(1):1-12. [Medline: 12602642]
24. Lutz W, Lambert MJ, Harmon SC, Tschitsaz A, Schürch E, Stulz N. The probability of treatment success, failure and duration—what can be learned from empirical data to support decision making in clinical practice? Clin Psychol Psychother 2006 Jul;13(4):223-232. [doi: 10.1002/cpp.496]
25. Slade K, Lambert MJ, Harmon SC, Smart DW, Bailey R. Improving psychotherapy outcome: The use of immediate electronic feedback and revised clinical support tools. Clin Psychol Psychother 2008;15(5):287-303. [doi: 10.1002/cpp.594] [Medline: 19115449]
26. Crits-Christoph P, Ring-Kurtz S, Hamilton JL, Lambert MJ, Gallop R, McClure B, et al. A preliminary study of the effects of individual patient-level feedback in outpatient substance abuse treatment programs. J Subst Abuse Treat 2012 Apr;42(3):301-309 [FREE Full text] [doi: 10.1016/j.jsat.2011.09.003] [Medline: 22036697]
27. Lorenzo-Luaces L, DeRubeis RJ, Webb CA. Client characteristics as moderators of the relation between the therapeutic alliance and outcome in cognitive therapy for depression. J Consult Clin Psychol 2014 Apr;82(2):368-373 [FREE Full text] [doi: 10.1037/a0035994] [Medline: 24547921]
28. DeRubeis RJ, Cohen ZD, Forand NR, Fournier JC, Gelfand LA, Lorenzo-Luaces L. The Personalized Advantage Index: Translating research on prediction into individualized treatment recommendations. A demonstration. PLoS One 2014;9(1):e83875 [FREE Full text] [doi: 10.1371/journal.pone.0083875] [Medline: 24416178]
29. Percevic R, Lambert MJ, Kordy H. Computer-supported monitoring of patient treatment response. J Clin Psychol 2004 Mar;60(3):285-299. [doi: 10.1002/jclp.10264] [Medline: 14981792]
30. Hawkins RP, Kreuter M, Resnicow K, Fishbein M, Dijkstra A. Understanding tailoring in communicating about health. Health Educ Res 2008 Jun;23(3):454-466 [FREE Full text] [doi: 10.1093/her/cyn004] [Medline: 18349033]
31. Piette JD, Heisler M. Problems due to medication costs among VA and non-VA patients with chronic illnesses. Am J Manag Care 2004 Nov;10(11 Pt 2):861-868 [FREE Full text] [Medline: 15609740]
32. Piette JD, Heisler M, Krein S, Kerr EA. The role of patient-physician trust in moderating medication nonadherence due to cost pressures. Arch Intern Med 2005;165(15):1749-1755. [doi: 10.1001/archinte.165.15.1749] [Medline: 16087823]
33. Kerns RD, Burns JW, Shulman M, Jensen MP, Nielson WR, Czlapinski R, et al. Can we improve cognitive-behavioral therapy for chronic back pain treatment engagement and adherence? A controlled trial of tailored versus standard therapy. Health Psychol 2014 Sep;33(9):938-947. [doi: 10.1037/a0034406] [Medline: 24295024]

34. Waegemann CP. mHealth: The next generation of telemedicine? Telemed J E Health 2010;16(1):23-25. [doi: 10.1089/tmj.2010.9990] [Medline: 20070168]
35. Free C, Phillips G, Galli L, Watson L, Felix L, Edwards P, et al. The effectiveness of mobile-health technology-based health behaviour change or disease management interventions for health care consumers: A systematic review. PLoS Med 2013;10(1):e1001362 [FREE Full text] [doi: 10.1371/journal.pmed.1001362] [Medline: 23349621]
36. Bender BG, Apter A, Bogen DK, Dickinson P, Fisher L, Wamboldt FS, et al. Test of an interactive voice response intervention to improve adherence to controller medications in adults with asthma. J Am Board Fam Med 2010;23(2):159-165 [FREE Full text] [doi: 10.3122/jabfm.2010.02.090112] [Medline: 20207925]
37. Free C, Phillips G, Watson L, Galli L, Felix L, Edwards P, et al. The effectiveness of mobile-health technologies to improve health care service delivery processes: A systematic review and meta-analysis. PLoS Med 2013 Jan;10(1):e1001363 [FREE Full text] [doi: 10.1371/journal.pmed.1001363] [Medline: 23458994]
38. Moore HK, Mundt JC, Modell JG, Rodrigues HE, DeBrota DJ, Jefferson JJ, et al. An examination of 26,168 Hamilton Depression Rating Scale scores administered via interactive voice response across 17 randomized clinical trials. J Clin Psychopharmacol 2006 Jun;26(3):321-324. [doi: 10.1097/01.jcp.0000219918.96434.4d] [Medline: 16702899]
39. Perrine MW, Mundt JC, Searles JS, Lester LS. Validation of daily self-reported alcohol consumption using interactive voice response (IVR) technology. J Stud Alcohol 1995 Sep;56(5):487-490. [Medline: 7475027]
40. Kobak KA, Taylor LH, Dottl SL, Greist JH, Jefferson JW, Burroughs D, et al. Computerized screening for psychiatric disorders in an outpatient community mental health clinic. Psychiatr Serv 1997 Aug;48(8):1048-1057. [Medline: 9255838]
41. Piette JD. Interactive voice response systems in the diagnosis and management of chronic disease. Am J Manag Care 2000 Jul;6(7):817-827 [FREE Full text] [Medline: 11067378]
42. Bachofen M, Nakagawa A, Marks IM, Park JM, Greist JH, Baer L, et al. Home self-assessment and self-treatment of obsessive-compulsive disorder using a manual and a computer-conducted telephone interview: Replication of a UK-US study. J Clin Psychiatry 1999 Aug;60(8):545-549. [Medline: 10485637]
43. Piette JD. Interactive behavior change technology to support diabetes self-management: Where do we stand? Diabetes Care 2007 Oct;30(10):2425-2432. [doi: 10.2337/dc07-1046] [Medline: 17586735]
44. Keefe FJ. Cognitive behavioral therapy for managing pain. The Clinical Psychologist 1996;49:4-5.
45. Lihong L, Chu W, Langford J, Schapire RE. A contextual bandit approach to personalized news article recommendation. WWW 2010:661-670. [doi: 10.1145/1772690.1772758]
46. Piette JD, Rosland A, Marinec NS, Striplin D, Bernstein SJ, Silveira MJ. Response to letter with regard to our paper "Engagement with automated patient monitoring and self-management support calls": Experience with a thousand chronically ill patients. Med Care 2013 Nov;51(11):1027-1028. [doi: 10.1097/MLR.0b013e3182a9632b] [Medline: 24113814]
47. Piette JD, Sussman JB, Pfeiffer PN, Silveira MJ, Singh S, Lavieri MS. Maximizing the value of mobile health monitoring by avoiding redundant patient reports: Prediction of depression-related symptoms and adherence problems in automated health assessment services. J Med Internet Res 2013;15(7):e118 [FREE Full text] [doi: 10.2196/jmir.2582] [Medline: 23832021]
48. Piette JD, Aikens JE, Trivedi R, Parrish D, Standiford C, Marinec NS, et al. Depression self-management assistance using automated telephonic assessments and social support. Am J Manag Care 2013 Nov;19(11):892-900 [FREE Full text] [Medline: 24511987]
49. Heapy A, Sellinger J, Higgins D, Chatkoff D, Bennett TC, Kerns RD. Using interactive voice response to measure pain and quality of life. Pain Medicine 2007 Oct;8(s3 Computer and):S145-S154. [doi: 10.1111/j.1526-4637.2007.00378.x]
50. Piette JD, Weinberger M, Kraemer FB, McPhee SJ. Impact of automated calls with nurse follow-up on diabetes treatment outcomes in a Department of Veterans Affairs Health Care System: A randomized controlled trial. Diabetes Care 2001 Feb;24(2):202-208. [Medline: 11213866]
51. Piette JD, Weinberger M, McPhee SJ, Mah CA, Kraemer FB, Crapo LM. Do automated calls with nurse follow-up improve self-care and glycemic control among vulnerable patients with diabetes? Am J Med 2000 Jan;108(1):20-27. [Medline: 11059437]
52. Piette JD, Datwani H, Gaudioso S, Foster SM, Westphal J, Perry W, et al. Hypertension management using mobile technology and home blood pressure monitoring: Results of a randomized trial in two low/middle-income countries. Telemed J E Health 2012 Oct;18(8):613-620 [FREE Full text] [doi: 10.1089/tmj.2011.0271] [Medline: 23061642]
53. Piette JD, Richardson C, Himle J, Duffy S, Torres T, Vogel M, et al. A randomized trial of telephonic counseling plus walking for depressed diabetes patients. Med Care 2011 Jul;49(7):641-648 [FREE Full text] [doi: 10.1097/MLR.0b013e318215d0c9] [Medline: 21478777]
54. Krein SL, Metreger T, Kadri R, Hughes M, Kerr EA, Piette JD, et al. Veterans walk to beat back pain: Study rationale, design and protocol of a randomized trial of a pedometer-based internet mediated intervention for patients with chronic low back pain. BMC Musculoskelet Disord 2010;11:205 [FREE Full text] [doi: 10.1186/1471-2474-11-205] [Medline: 20836856]
55. Bravata DM, Smith-Spangler C, Sundaram V, Gienger AL, Lin N, Lewis R, et al. Using pedometers to increase physical activity and improve health: A systematic review. JAMA 2007 Nov 21;298(19):2296-2304. [doi: 10.1001/jama.298.19.2296] [Medline: 18029834]

56. Moy ML, Janney AW, Nguyen HQ, Matthess KR, Cohen M, Garshick E, et al. Use of pedometer and Internet-mediated walking program in patients with chronic obstructive pulmonary disease. J Rehabil Res Dev 2010;47(5):485-496 [FREE Full text] [Medline: 20803392]
57. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008 Feb;9(2):105-121. [doi: 10.1016/j.jpain.2007.09.005] [Medline: 18055266]
58. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: Validity of a brief depression severity measure. J Gen Intern Med 2001 Sep;16(9):606-613 [FREE Full text] [Medline: 11556941]
59. Tariq SH, Tumosa N, Chibnall JT, Perry MH, Morley JE. Comparison of the Saint Louis University mental status examination and the mini-mental state examination for detecting dementia and mild neurocognitive disorder--a pilot study. Am J Geriatr Psychiatry 2006 Nov;14(11):900-910. [doi: 10.1097/01.JGP.0000221510.33817.86] [Medline: 17068312]
60. Carroll KM, Nich C, Sifry RL, Nuro KF, Frankforter TL, Ball SA, et al. A general system for evaluating therapist adherence and competence in psychotherapy research in the addictions. Drug Alcohol Depend 2000 Jan 1;57(3):225-238. [Medline: 10661673]
61. Bassett DR, Ainsworth BE, Leggett SR, Mathien CA, Main JA, Hunter DC, et al. Accuracy of five electronic pedometers for measuring distance walked. Med Sci Sports Exerc 1996 Aug;28(8):1071-1077. [Medline: 8871919]
62. Kerns RD, Turk DC, Rudy TE. The West Haven-Yale Multidimensional Pain Inventory (WHYMPI). Pain 1985 Dec;23(4):345-356. [Medline: 4088697]
63. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, IMMPACT. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005 Jan;113(1-2):9-19. [doi: 10.1016/j.pain.2004.09.012] [Medline: 15621359]
64. Roland M, Fairbank J. The Roland-Morris Disability Questionnaire and the Oswestry Disability Questionnaire. Spine 2000 Dec 15;25(24):3115-3124. [Medline: 11124727]
65. McNair D, Lorr M, Doppleman L. Profile of Mood States. San Diego, CA: Educational and Industrial Testing Service; 1971.
66. Beck A, Steer R, Carbin MG. Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. Clin Psychol Rev 1988 Jan;8(1):77-100. [doi: 10.1016/0272-7358(88)90050-5]
67. Kazis LE, Lee A, Spiro A, Rogers W, Ren XS, Miller DR, et al. Measurement comparisons of the medical outcomes study and veterans SF-36 health survey. Health Care Financ Rev 2004;25(4):43-58 [FREE Full text] [Medline: 15493443]
68. Bhandari A, Wagner T. Self-reported utilization of health care services: Improving measurement and accuracy. Med Care Res Rev 2006 Apr;63(2):217-235. [doi: 10.1177/1077558705285298] [Medline: 16595412]
69. Borkovec TD, Nau SD. Credibility of analogue therapy rationales. J Behav Ther Exp Psychiatry 1972 Dec;3(4):257-260. [doi: 10.1016/0005-7916(72)90045-6]
70. Clark ME, Gironda RJ, Young RW. Development and validation of the Pain Outcomes Questionnaire-VA. J Rehabil Res Dev 2003;40(5):381-395 [FREE Full text] [Medline: 15080223]
71. Chew LD, Bradley KA, Boyko EJ. Brief questions to identify patients with inadequate health literacy. Fam Med 2004 Sep;36(8):588-594 [FREE Full text] [Medline: 15343421]
72. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59 Suppl 20:22-33; quiz 34. [Medline: 9881538]
73. Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and validation. Psychol Assess 1995;7(4):524-532. [doi: 10.1037/1040-3590.7.4.524]
74. Bombardier C, Hayden J, Beaton DE. Minimal clinically important difference. Low back pain: Outcome measures. J Rheumatol 2001 Feb;28(2):431-438. [Medline: 11246692]
75. Glasgow RE, McKay HG, Piette JD, Reynolds KD. The RE-AIM framework for evaluating interventions: What can it tell us about approaches to chronic illness management? Patient Educ Couns 2001 Aug;44(2):119-127. [Medline: 11479052]
76. Piaggio G, Elbourne DR, Pocock SJ, Evans SJW, Altman DG. Reporting of noninferiority and equivalence randomized trials: Extension of the CONSORT 2010 statement. JAMA 2012 Dec 26;308(24):2594-2604. [doi: 10.1001/jama.2012.87802] [Medline: 23268518]
77. Mauskopf JA, Sullivan SD, Annemans L, Caro J, Mullins CD, Nuijten M, et al. Principles of good practice for budget impact analysis: Report of the ISPOR Task Force on good research practices--budget impact analysis. Value Health 2007;10(5):336-347. [doi: 10.1111/j.1524-4733.2007.00187.x] [Medline: 17888098]
78. Lavori PW, Dawson R, Shera D. A multiple imputation strategy for clinical trials with truncation of patient data. Stat Med 1995 Sep 15;14(17):1913-1925. [Medline: 8532984]
79. MacKinnon DP, Lockwood CM, Hoffman JM, West SG, Sheets V. A comparison of methods to test mediation and other intervening variable effects. Psychol Methods 2002 Mar;7(1):83-104 [FREE Full text] [Medline: 11928892]
80. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. J Pers Soc Psychol 1986 Dec;51(6):1173-1182. [Medline: 3806354]

81. Crabtree BF, Miller W. Negotiating the coresearcher mandate - service users' experiences of doing collaborative research on mental health. In: Doing Qualitative Research. Thousand Oaks, CA: Sage Publications; 1999.

Abbreviations

AI: artificial intelligence
BDI: Beck Depression Inventory
CBT: cognitive behavioral therapy
IVR: interactive voice response
mHealth: mobile health
PCP: primary care provider
POMS: Profile of Mood States
RL: reinforcement learning
VA: Department of Veterans Affairs
WHYMPI: West Haven Multidimensional Pain Inventory

Edited by G Eysenbach; submitted 31.07.15; peer-reviewed by S Dobscha, S Bernecker; comments to author 09.09.15; revised version received 04.10.15; accepted 07.10.15; published 07.04.16.

Please cite as:
Piette JD, Krein SL, Striplin D, Marinec N, Kerns RD, Farris KB, Singh S, An L, Heapy AA
Patient-Centered Pain Care Using Artificial Intelligence and Mobile Health Tools: Protocol for a Randomized Study Funded by the US Department of Veterans Affairs Health Services Research and Development Program
JMIR Res Protoc 2016;5(2):e53
URL: http://www.researchprotocols.org/2016/2/e53/
doi:10.2196/resprot.4995
PMID:27056770

Protocol

Testing Activity Monitors' Effect on Health: Study Protocol for a Randomized Controlled Trial Among Older Primary Care Patients

Zakkoyya H Lewis[1,2], BS; Kenneth J Ottenbacher[1,2], PhD, OTR; Steve R Fisher[1,3], PhD, PT; Kristofer Jennings[2], PhD; Arleen F Brown[4], MD, PhD; Maria C Swartz[1], PhD, MPH; Elizabeth J Lyons[1,5], PhD, MPH

[1]University of Texas Medical Branch, Division of Rehabilitation Sciences, Galveston, TX, United States

[2]University of Texas Medical Branch, Department of Preventive Medicine and Community Health, Galveston, TX, United States

[3]University of Texas Medical Branch, Department of Physical Therapy, Galveston, TX, United States

[4]University of California Los Angeles, Department of Medicine, Division of General Internal Medicine/Health Services Research, Los Angeles, CA, United States

[5]University of Texas Medical Branch, Department of Nutrition and Metabolism, Galveston, TX, United States

Corresponding Author:
Zakkoyya H Lewis, BS
University of Texas Medical Branch
Division of Rehabilitation Sciences
301 University Blvd
School of Health Professions Bldg room 2.252B
Galveston, TX, 77555
United States
Phone: 1 409 772 2576
Fax: 1 409 747 1638
Email: zalewisp@utmb.edu

Abstract

Background: Cardiovascular disease is the leading cause of mortality in the United States. Maintaining healthy levels of physical activity is critical to cardiovascular health, but many older adults are inactive. There is a growing body of evidence linking low motivation and inactivity. Standard behavioral counseling techniques used within the primary care setting strive to increase motivation, but often do not emphasize the key component of self-control. The addition of electronic activity monitors (EAMs) to counseling protocols may provide more effective behavior change and increase overall motivation for exercise through interactive self-monitoring, feedback, and social support from other users.

Objective: The objective of the study is to conduct a three month intervention trial that will test the feasibility of adding an EAM system to brief counseling within a primary care setting. Participants (n=40) will be randomized to receive evidence-based brief counseling plus either an EAM or a pedometer.

Methods: Throughout the intervention, we will test its feasibility and acceptability, the change in primary outcomes (cardiovascular risk and physical activity), and the change in secondary outcomes (adherence, weight and body composition, health status, motivation, physical function, psychological feelings, and self-regulation). Upon completion of the intervention, we will also conduct focus groups with the participants and with primary care stakeholders.

Results: The study started recruitment in October 2015 and is scheduled to be completed by October 2016.

Conclusions: This project will lay the groundwork and establish the infrastructure for intervention refinement and ultimately translation within the primary care setting in order to prevent cardiovascular disease on a population level.

Trial Registration: ClinicalTrails.gov NCT02554435; https://clinicaltrials.gov/ct2/show/NCT02554435 (Archived by WebCite at http://www.webcitation/6fUlW5tdT)

(JMIR Res Protoc 2016;5(2):e59) doi:10.2196/resprot.5454

KEYWORDS

physical activity; cardiovascular disease; prevention; activity monitors; technology; primary care; 5 A counseling; intervention

Introduction

Cardiovascular Disease and Physical Activity

In the United States, more than 85 million adults have at least one type of cardiovascular disease (CVD) [1]. It is the most deadly disease in the United States (accounting for 1 in 3 deaths) and the world [1,2]. By 2020, the American Heart Association (AHA) strives to reduce this number by 20% [3]. It is well established that lifestyle behaviors, such as physical activity (PA), are related to CVD [4-9]. Therefore, intervening on PA is an important step toward meeting this goal [10]. The Centers for Disease Control recommendation for primary and secondary prevention of CVD is 30 minutes of PA a day, 6-7 days per week [7]. However, analysis of the Behavioral Risk Factor Surveillance System reports the prevalence of older adults meeting this recommendation only reaches 39.3% [11]. Lack of motivation to exercise appears to be a barrier that impedes meeting the recommendation for many older adults [12].

A promising strategy for increasing motivation for exercise is promotion by primary care providers [13-16]. The United States Preventive Services Task Force (USPSTF) developed the 5 A's counseling intervention to be used in the primary care setting [17]. The components of 5 A's stand for assess, advise, agree, assist, and arrange. Five A's is a comprehensive and validated counseling technique to elicit behavioral change during a typical medical visit [10,17]. This counseling is based on the Self-Determination Theory, which targets perceptions of autonomy, competence, and relatedness to increase autonomous motivation, that is, motivation that is volitional and internal rather than external [18,19].

Most primary care physicians use at least one 5 A's measure with their patients [20]; however, comprehensive behavioral counseling or complete 5 A's counseling is not routinely conducted [15,20]. Even if proper 5 A's counseling was done routinely, providing knowledge and professional support alone is insufficient for changing behavior [21]. Emphasizing self-control through self-monitoring of behavior is an effective behavioral change technique (BCT) when combined with other techniques, such as shaping knowledge and social support [21,22]. Use of technology is a promising method for delivering these techniques [16]. The AHA recommends both 5 A's counseling and technology-based interventions to improve cardiovascular health for individuals at moderate risk for disease [10].

PA interventions that utilize self-monitoring technologies have been shown to be efficacious [23-25]. Moreover, self-monitoring technologies are feasible to implement with 5 A's counseling [23] and, thus, may help prevent the onset and progression/or progression of chronic diseases [26]. A self-monitoring technology commonly used is a pedometer [23,27-32]. Pedometers are cost-effective activity monitors that provide a simple method of promoting self-control via self-monitoring of steps [33]. Pedometer use is associated with improvements in PA, weight, and blood pressure [27-29]. These improvements may be sustained to prevent chronic disease risk factors (measured by the Framingham risk calculator) [31]. In a previous primary care intervention, individuals wearing a pedometer had significant increases in PA compared to usual care [34]. Ideally, technologies for preventing CVD should provide self-monitoring, education, personalized feedback, and should also be customizable [35]. Since standard pedometers cannot provide all of these features, they may not be optimal for CVD prevention.

More advanced pedometers, or electronic activity monitors (EAMs), are readily available on the market (estimated 3.3 million units sold in 2014) [36] and offer many features that standard pedometers do not. Like pedometers, EAMs count total steps, but they can also measure duration and intensity of PA. EAMs can sync wirelessly to an application (app) on a smart device (phone or tablet). The data it collects are displayed clearly and concisely through the app. EAMs are programmable in that the individual can set his or her personal activity goals [37]. Lyons et al [38] found that EAMs include numerous behavioral techniques commonly associated with PA change including: self-monitoring, feedback, goal-setting, planning, social support, social comparisons, commitment, instructions on how to perform a behavior, and information on consequences [39,40]. EAMs have the potential to change behavior alone, but they will likely be more successful if combined with structured engagement [41], such as a research intervention. Providing an EAM in addition to 5 A's counseling shows promise in preventing CVD because: (1) an EAM can deliver counseling components that may not have been targeted by the physician [42]; (2) it provides adaptive PA goals based on progress, which is more effective than a static exercise prescription [43]; and (3) it can improve perceptions of relatedness by providing social support from other users.

Specific Aims

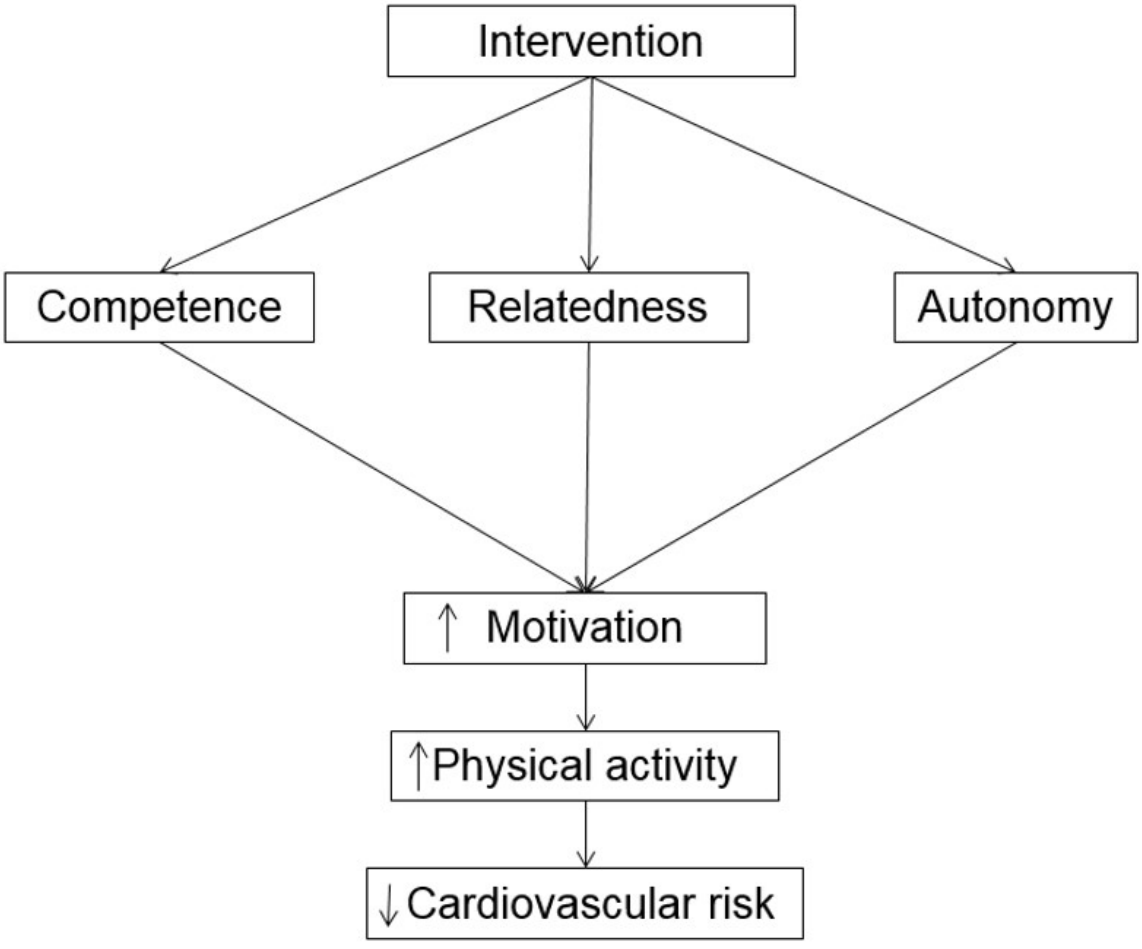
Testing Activity Monitors' Effect (TAME) on health (NCT02554435) will implement and evaluate a 12 week intervention that incorporates 5 A's counseling and self-monitoring with an activity monitor among older primary care patients. Participants (n=40) will be randomized to receive 5 A's counseling and an EAM system or 5 A's counseling and a standard pedometer. Figure 1 shows the conceptual framework of TAME health (also outlined in Table 1). As a follow-up to the intervention, separate focus groups with research participants and primary care stakeholders will be conducted to further gauge the intervention's feasibility and acceptability.

Table 1. Conceptual constructs underpinning the research design.

Theoretical construct	BCT[a]	Intervention components		
		5 A's counseling (both groups)	Pedometer	EAM
Self-Determination Theory				
Autonomy	Goal-setting/intention formation	X		X
	Provide information on consequences of behavior in general	X		X
	Barrier identification/problem solving			X
	Action planning	X		X
Competence	Provide feedback on performance	X	X	X
	Provide instruction	X		X
	Teach to use prompts/cues			X
	Self-control: Prompt self-monitoring of behavior		X	X
Relatedness	Facilitate social comparison			X
	Social support	X		X

[a] BCTs described are associated with Self-Determination Theory constructs based on previous research [22,44-46].

Figure 1. Conceptual framework of the intervention.



Methods

Preliminary Studies

Several preliminary studies have shaped the proposed intervention. In a preexperimental pilot study, we recruited 10 sedentary older adults (55-79 years of age) into a six week intervention in which they received an EAM (UP by Jawbone), a mini tablet, and weekly counseling. Adding an EAM to the PA intervention was both feasible and acceptable within this older adult population that already used smart devices. There were nine out of the 10 participants that agreed or strongly agreed with the following statements: "I would continue to wear the monitor"; "I felt very confident using the tablet"; "The UP app encouraged me to view my steps"; and "It was convenient for me to use the UP app". As a follow-up, we are completing a pilot intervention to determine changes in PA outcomes within this same population using an UP24 by Jawbone. We will compare PA outcomes between those who received the intervention to wait-list controls. Among the 38 participants to complete the intervention at this time, we found that nearly all used social support features of some kind. Several participants (8/38) even commented over 50 times across the 12 week period.

In addition to conducting PA interventions, we analyzed the content of EAMs. We evaluated 13 different EAMs and coded them for present BCTs [38] and validated their measurements of steps over the span of a week compared to research-grade activity monitors. We found that EAMs commonly incorporate important BCTs [38] and they reasonably estimate the number of steps per day.

The research team, led by ZHL, also conducted a systematic review of PA interventions that utilized EAMs [37]. This review evaluated different intervention methodologies and EAMs used by researchers. Findings suggested that EAM interventions produced equivocal results when compared to behavioral counseling alone. However, the devices investigated did not provide social support and used apps with fewer behavior change techniques than provided in Jawbone's app. Compliance outcomes indicated that devices were regularly worn and utilized by participants [37]. Overall, our work to date suggests that EAMs are motivational devices that are acceptable for use by older adults and can change PA behavior in conjunction with behavioral counseling.

Protocol

This protocol has been approved by the University of Texas Medical Branch (UTMB) Institutional Review Board (Protocol 15-0014, Version 5, 12/02/15) and is registered on a website (NCT02554435). This protocol also follows SPIRIT reporting guidelines (see Multimedia Appendix 1). The TAME health study design is displayed in Table 2.

We intend to recruit older primary care patients (n=40) to participate in the 12 week TAME health study. Primary eligibility criteria include: age (55-74 years), physically inactive (less than 60 min/week of PA), body mass index between 25-35, in good health as measured by the PA Readiness Questionnaire Plus (Par-Q+) [47], and access to a smart device. Eligibility criteria were determined based on our previous work using EAMs in this population. A smart device is operationally defined as a mobile phone or tablet using the iOS operating system or Android 4.3 or later. Reports suggest that 45% of adults over the age of 65 own a smart device [48]. Individuals will be excluded from the study if participation in PA is inadvisable by their doctor, they are involved in another PA intervention currently or within the past 6 months, utilized an EAM in the past 6 months, are unwilling to travel for scheduled visits, currently taking medications that affect body composition, a current smoker, report of alcohol or drug problem, institutionalizations for psychiatric illness within the last year, or do not consent. As advised in the Par-Q+ [47], prospective participants with comorbid conditions are eligible if they provide a letter from their physician stating that it is safe for them to participate in PA.

Table 2. TAME health time frame.

	Study period				
	Enrollment	Allocation	Post allocation		Close-out
Study week	-12	0	1	12	12
Enrollment:					
Eligibility screen	X	X			
Informed consent	X				
Allocation		X			
Interventions:					
5 A's counseling		X	X		
Pedometer			X	X	
EAM			X	X	
Assessments:					
Age (date of birth)	X	X			
Gender	X	X			
Education		X			X
Cardiovascular risk		X			X
PA	X	X	X		X
Weight	X	X			X
Body mass index	X	X			X
Body composition		X			X
Blood pressure		X			X
Exercise motivation		X			X
Health status and quality of life		X			X
Physical function		X			X
Psychological feelings		X			X
Resting pulse		X			X

Recruitment and Screening Procedures

Participants will be recruited from two clinics affiliated with a large university-based health care system. Recruitment started in October 2015 and will continue until all participants are enrolled. Prospective participants will be recruited from flier postings in waiting rooms and in patient rooms, direct solicitation from a recruitment table in the lobby, and through recruitment letters mailed to their home.

Patient eligibility will be determined by using a screening script. Screenings will be completed in person at the recruitment table or over the phone. Once patients are deemed eligible, the researchers will obtain informed consent. This will be done promptly after screening for eligibility at the recruitment table for patients screened in person. For patients screened over the phone, a researcher will arrange a meeting with the patient at their primary care clinic to obtain informed consent.

After obtaining informed consent, an assessment visit will be scheduled. Reminders about the orientation meeting will be sent via email monthly (for those recruited prior to the data collection start date of January 1, 2016) and one week prior to the scheduled meeting. In addition, participants will receive a phone call reminder the day before the meeting. Enrollment into the intervention is postponed until after January 1, 2016 to minimize seasonal variations in PA [49].

Intervention Procedures

5 A's Counseling

All participants will receive brief PA counseling following the USPSTF 5 A's model [17,18]. The counseling provided in this intervention is referred to the "5A-S model" for it emphasizes the importance of self-control. The counseling components included: assess, advise, agree, assist, arrange, and self-monitor. The brief PA counseling will occur during the private assessment visit at the participant's primary care clinic, before randomization. An experienced PA counselor with a background in exercise physiology and training in motivational interviewing will conduct the counseling. To facilitate transition into clinical practice, participants will go through counseling at baseline and will be instructed to self-monitor with their assigned device for the subsequent 12 weeks. After counseling, the researcher will

provide the participant with an exercise prescription to follow. A phone call will be arranged with the participant a week after the counseling to assess progress and resolve technical issues.

Table 3 provides a description and an example of how each 5 A's component will be operationalized in the current study.

Table 3. Counseling components.

	Description[a]	Example
Assess	Ask about/assess behavioral risk	Review steps per day and minutes of PA per day from research-grade monitor
Advise	Advise participant to increase their PA to meet healthy levels	Compare current PA level to CDC guideline Define moderate and vigorous PA Suggest new PA goal
Agree	Reach agreement with the participant about appropriate weekly PA goal and a long term goal	Set weekly step goal Active planning of step goal Set long term PA goal
Assist	Teach behavioral change strategies	Identify social support Identify barriers Provide PA prescription
Arrange	Arrange a follow-up appointment to assess progress and any issues that arise	Schedule phone call in 1 week Review health changes Go through the "Agree" step on new weekly goal

[a] The descriptions are modified from Whitlock et al [17].

Grouping the Participants

All participants will be given an activity monitor to encourage self-regulation of PA. After counseling, participants will be randomized to one of the two groups: pedometer or EAM group. A random number generator available on the Internet will be used to randomly allocate group assignment [50]. Assignment into the EAM group will be selected randomly by the generator using the following settings: 1 set, 5 unique numbers, numbers range from 1 to 10, and sorted lowest to highest. This process will be repeated for 3 more sets of numbers ranging from 11-20, 21-30, and 31-40. Each number represents a participant identification number selected to be in the EAM group. Group assignment will be written on a piece of paper wrapped in foil and carbon paper and concealed inside an envelope prior to group allocation. A blinded researcher will prepare all of the envelopes. After group allocation, participants will be given all intervention materials and detailed instructions on all intervention components. For participants in the EAM group, the researcher will also test the monitor and the participant's smart device to ensure they are working properly. Due to the nature of the intervention, the participants and the accessor will not be blinded to group assignment after randomization.

Pedometer Group

Participants will be provided with a digital pedometer (Digi-walker CW-700/701, YAMAX, San Antonio, TX). The pedometer records total number of steps (steps), activity time (hour/minute), distance walked (mile), and calories burned (kcal). The device stores this information every day and up to the previous 7 days. Weekly totals for steps, activity time, distance walked, and calories burned are stored for the current and previous week. The pedometer also displays a clock and an informative graph that estimates the number of calories burned based on the number of steps [51]. Participants will be instructed to log their daily steps, activity time, and distance walked measured by the pedometer in an activity diary.

Electronic Activity Monitors Group

All participants will be given an EAM (UP24 by Jawbone, San Francisco, CA) and the corresponding UP app on their smart device. UP24 by Jawbone is widely used and is one of the top selling EAMs [52]. Furthermore, UP24 implements the most BCTs compared to other available EAMs and provides vital techniques that are missing in the counseling. In total, Jawbone UP24 provided 27 BCTs in 2014, but with continual software updates, this number is likely higher [38]. Some examples include goal setting on behavior and on a health outcome, self-monitoring of behavior, emotional social support, providing instructions, providing information on consequences, social comparison, prompts, and focus on past success [38]. For these reasons, UP24 was selected for the intervention.

The UP app provides information related to PA, diet, weight, sleep, and socialization. Participants will not be counseled on improving sleep or diet, but they are additive features of the app. The home screen of the app provides immediate feedback to the user on their activity for the day. On the home screen, the wearer also has access to their activity feed, which displays all their activities and their teammates' activities. All activities in the app are stored forever so the user can review all past activity. In addition, the app allows the user to set goals, record activity, and review activity trends. The user can also set reminders for activity and learn more information about their health from the Smart Coach tailoring messaging feature [53]. The specific features throughout the app are described in Multimedia Appendix 2 (see Multimedia Appendix 2).

All participants will be given a deidentified account with an anonymous name and icon to use in the app. We have chosen to use board game pieces names and icon pictures (eg,

Battleship, Cat, Hotel) based upon suggestions from previous participants and enjoyment of this system in our pilot studies. Participants will be required to add other participants as their "teammate" in order to utilize the socializing features within the app. Only PA information will be required to be visible by their teammates. Participants will be able to customize their account if they wish to share any other behaviors with their teammates. Participants that do not consent to have their deidentified information shared with other participants will be ineligible and dropped from the intervention. In order to view the participant's activity, the participants will also add the research account as a teammate. The researchers will not socialize or interact with the participants through the app; it will be for surveillance purposes only. Participants will be given a trouble-shooting guide to help with any issues with the app. The researcher will also review and resolve any technical issues reported during the "Arrange" phone call.

Assessment Procedures

The primary purpose of this study is to investigate the feasibility and acceptability of a low-intensity intervention that combines 5 A's counseling and an EAM system. We will also compare the effects of these high-tech activity monitors to low-tech ones (pedometers) on PA and other cardiovascular risk indicators (Framingham risk calculator, fitness). The study includes two assessments conducted at baseline and 12 weeks. Upon initial recruitment at the clinic, participants will provide informed consent and schedule their first assessment visit. Approximately 7 days before their initial assessment, participants will be given a baseline questionnaire and a research-grade activity monitor (discussed below) to wear for a 7 day baseline period. Participants will return to their primary care facility to complete the assessment. At 11 weeks, participants will be given a follow-up questionnaire and the research-grade monitor to wear for 7 days. At 12 weeks, participants will return to their clinic to complete assessments identical to baseline. As reimbursement for taking part in this study, all participants will receive a US $25 gift card at the end of the 12 week assessment, and at that time participants also forfeit their EAM or pedometer device.

The primary outcomes of interest are feasibility and acceptability. Feasibility will be operationalized in several ways. Number of days logged for activity, interactions with other users in the mobile app, and additional use of the app will be abstracted using procedures we have previously pilot tested successfully. Acceptability will be measured using self-report (modeled on items previously developed) [54], responses, and focus groups conducted after completion of the intervention. The primary physiological variables of interest include cardiovascular risk indicators and PA. Secondary outcome variables are anthropometrics, body composition, blood pressure, exercise motivation, health status and quality of life, physical function, psychological feelings, resting pulse, and self-regulation. All physiological study variables are listed in Table 4.

Table 4. Study variables.

Variable	Measure	Subscales	Alpha statistics
Primary variables			
CVD risk	Framingham nonlaboratory risk score calculator	Age: yrs; body mass index: kg/m^2; systolic blood pressure: mmHg	
	Six minute walk test	Distance walked in 6 minutes: ft	
PA	Sensewear armband (BodyMedia, Pittsburgh, PA)	Minutes of METs ≥ 3 (7 days of measurement); steps per day	
Secondary variables			
Anthropometrics	Stadiometer (Seca Corp, Hamburg, Germany); scale (Tanita, Arlington Heights, IL)	Height (baseline only): cm; weight: kg; body mass index: kg/m^2	
Body composition	Tape measure (Singer, China)	Waist circumference: cm; hip circumference: cm; waist to hip ratio	
Blood pressure	Sphygmomanometer (Omron BP742N, Lake Forest, IL)	Systolic blood pressure: mmHg; diastolic blood pressure: mmHg	
Demographics	Self-report	Age: yrs; sex; race/ethnicity; education	
Exercise motivation	Behavioral Regulation in Exercise Questionnaire-2	Intrinsic, identified, introjected, extrinsic, amotivation	.73-.86
Health status and quality of life	36-Item Short Form Health Survey	Physical functioning, social functioning, physical role limitations, emotional role limitations, mental health, energy/vitality, pain	.76-.90
Physical function	Short physical performance battery	Repeated chair stands, balance, semitandem stand, side-by-side stand, tandem stand, 8 feet walk	
	PROMIS SF v1.2-Physical function 8b	Upper extremities, lower extremities, central regions	
Psychological feelings	Psychological Need Satisfaction in Exercise Scale	Perceived competence, perceived autonomy, perceived relatedness	>.90
Resting pulse	Sphygmomanometer (Omron BP791T, Lake Forest, IL)	Heart rate: bpm	
Self-regulation	Rovinak et al scale [55]	Exercise goals, exercise plans	.87-.89

Cardiovascular Risk

CVD risk is determined by measuring 10 year risk of cardiac event from the Framingham nonlaboratory equation [56] and from fitness measured by a six minute walk test [57]. The six minute walk test is an additive assessment of CVD risk because cardiorespiratory fitness is the result of chronic PA and is more strongly related to clinical outcomes [58]. The Framingham equation has been used to estimate CVD risk in previous studies [31,59]. It requires a combination of self-report and objective measures [56,60]. Self-report measures include sex, age, treatment of hypertension, smoking status, and diagnosis of diabetes. Objective measures included blood pressure and body mass index [56,60].

The six minute walk test requires participants to walk a 100 feet course continuously for 6 minutes. It has been validated in older adults to measure physical endurance ($0.71<r<0.82$) [57]. Percentile norms on the test have been established for active older adults [61].

Physical Activity

PA will be measured with a SenseWear Armband. The armband is worn on the upper arm for 7 days. SenseWear quantifies PA by measuring expended kcals/week, minutes of activity a day, and steps per day. There is a mean error < 5% in measuring total minutes of PA with the SenseWear armband [62]. To properly program the armband, age, gender, and body mass index (BMI) will be collected at enrollment. These variables will be formally measured at a study allocation, described below.

Secondary Outcomes

We will also assess anthropometrics, body composition, blood pressure, resting pulse, demographic information, health status and quality of life, physical function, exercise motivation, self-regulation, and psychological feelings toward exercise.

Anthropometrics include height (cm), weight (kg), and BMI (kg/m^2). To ensure accurate measurement of anthropometrics, height and weight will be measured to the nearest 0.1 unit. Participants will be instructed to remove their shoes and any bulky clothing before measurement. Height will be measured using a portable stadiometer [63] and weight will be measured using a calibrated electronic scale [64]. The same equipment

will be used at both clinics. The electronic scale will be transported in a cushioned carrying case to ensure it remains calibrated. BMI will be calculated by converting height into meters and squaring that value, then dividing weight by this value [65].

Body composition will be estimated based on the waist circumference (cm), hip circumference (cm), and waist-to-hip ratio. The waist will be measured at the smallest circumference of the torso, while the hip will be measured at the largest circumference at or below the anterior superior iliac spine [66]. The waist-to-hip ratio will be calculated by dividing the waist circumference by the hip circumference [66]. The average from three measurements of anthropometrics and body composition will be used.

Blood pressure and resting pulse will be measured by a sphygmomanometer (Omron BP742N, Lake Forest, IL) [67]. Blood pressure will be measured after the participant is seated for at least five minutes and before any other measurements are taken. The sphygmomanometer is validated for clinical and personal use according to the European Society of Hypertension International Protocol [67].

Demographic information will be collected at both assessments. This information includes date of birth (age), race/ethnicity, educational level, comorbid conditions, and medication use. The 36-Item Short Form Health Survey will be used to estimate health status and quality of life. Subscales of this instrument include physical functioning, social functioning, physical role limitations, emotional role limitations, mental health, energy/vitality, and pain [68].

Physical function will be measured objectively and subjectively. Physical function will be objectively assessed using the short physical performance battery. Total functional capacity is based on a composite score from the following subtests: repeated chair stands, balance (semitandem stand, side-by-side stand, tandem stand), and 8 feet up walk [69]. Physical function will be subjectively assessed using the PROMIS Short Form v1.2-Physical function 8b [70].

Several self-report measures will be used to estimate exercise motivation, self-regulation of exercise, and psychological feelings toward exercise [55,71,72]. Each measure includes subscales. Exercise motivation consists of intrinsic motivation, identified, introjected, external regulation, and amotivation [71]. Self-regulation consists of exercise goals and exercise plans [55]. Psychological feelings toward exercise consist of perceived competence, perceived autonomy, and perceived relatedness [72].

Focus Groups

We will conduct several focus groups with research participants at the end of the intervention to further evaluate feasibility and acceptability. These sessions will consist of 5-8 individuals and last for 1.5-2 hours. A trained professional will facilitate all of the focus groups. Groups will be separated based on the intervention modality and two groups will be completed for each study arm. The focus groups will explore the perceived effectiveness of the 5 A's counseling and the monitoring device. Participants will also be asked questions pertaining to their overall feelings toward the intervention and their thoughts of the intervention being implemented through their primary care physician.

Focus groups following the same structure, but with primary care stakeholders, will also be conducted at the conclusion of the intervention. Stakeholders (n=20) will consist of medical doctors, nurses, medical residents, physician assistants, and other staff personnel. Stakeholders will be recruited through coordination with the Department of Internal Medicine and Family Medicine at the clinics used in the study. All stakeholders will consent to be a part of the focus group and will be given the opportunity to wear the UP24 for one month. During the focus groups, stakeholders will be asked questions related to their perception of the intervention. Materials and equipment from the intervention will be provided and preliminary results of the intervention will be presented. The goal of the focus groups is to elicit reactions regarding the feasibility and acceptability of including this intervention into their primary care clinic. Stakeholders will also be asked about their familiarity with 5 A's counseling and the extent of its use in practice. Stakeholders will complete a brief questionnaire before and after the focus group. In addition, stakeholders that wear the UP24 for one month will complete a feasibility questionnaire upon returning the monitor.

Statistical Analyses

The Statistical Package for the Social Sciences (version 20) will be used to perform all quantitative statistical analyses. Analyses will be completed in two ways: first using the intent-to-treat principle (primary analysis) and then only with adherers to the intervention (secondary analysis for the purpose of informing further intervention refinement). The alpha-level to determine significance is set at .05. The specific statistical procedures, by research aim, are described below.

Aim 1

Feasibility findings will be primarily descriptive and used as a metric for improvement when compared to similar studies. For example, days worn will be compared to other EAM studies, whereas attrition will be compared to other primary care-based studies. Rather than determine dichotomous feasibility or not, we will use relative feasibility to determine areas of focus for intervention refinement; which is addressed in the follow-up questionnaire and in focus groups. Comparisons of adherence between EAM and pedometer groups is covered under Aim 2 below and the procedures for analyzing focus groups will be identical to procedures outlined in Aim 3 below.

We hypothesize that the intervention will be feasible among several improvement metrics including ≥ 70% days the monitor is worn [37], < 20% attrition [73], and < 8 moderate or higher adverse events (< 20% of participants reporting an adverse event) [74-76]. Hypotheses based on other feasibility metrics include a low frequency of technical difficulties and a high frequency of app usage. Additionally, the intervention will be accepted among participants based on self-report questionnaires and focus group responses. We also hypothesize that the EAM group will show higher feasibility and acceptability compared to the pedometer group.

Aim 2

Descriptive analyses will be conducted using means and frequencies for baseline characteristics. These characteristics include age, gender, race/ethnicity, educational level, CVD risk, PA, fitness, weight, BMI, blood pressure, pulse, wait and hip circumference, physical function, exercise motivation, health status, psychological feelings, and self-regulation. Mean group differences will be examined using independent samples *t* tests for normally distributed data and nonparametric tests (Kruskal-Wallis and Mann-Whitney U) for nonnormally distributed data. Differences in variable frequencies will be examined using chi-square tests. Little's Missing Completely at Random test will be performed to determine whether outcome data are missing at random.

Analysis of covariance will be used to test the postintervention difference at 12 weeks (PA, CVD risk, fitness) between the two groups. The covariates in the analysis will include baseline values of the dependent variable, clinic location, and any variables significantly different between groups at baseline. A blinded statistician will conduct analysis on the primary outcome variables (PA, CVD risk, fitness). This same procedure will be used to assess differences in weight, BMI, body composition, health status, motivation, physical function, psychological feelings, and self-regulation. Group mean values for adherence variables at 12 weeks (retention rate, days the monitor worn) will be analyzed by an independent *t* test.

The primary purpose of this study is to evaluate its feasibility and acceptability; therefore, the analyses described in this section are exploratory and no prespecified power calculation is needed. Although this is a pilot study and it is not powered to detect significant difference in small-to-moderate effects, we hypothesize that the EAM group will demonstrate greater improvement in all of the aforementioned variables compared to the pedometer group.

Aim 3

NVivo 11 Pro (QSR International) will be used to perform qualitative analyses. Thematic analysis will be conducted to analyze the focus groups [77]. Codes will be developed prior to the focus groups. Additional coding will be processed while the focus groups are conducted, adding codes based on new data. After including all study participants, the completed code list will be used to code transcripts of all groups. The PRECIS tool will also be used to estimate the intervention's potential success in real clinical app [78].

Power Calculation

Although the aim of the intervention is to improve behavioral and health outcomes related to cardiovascular risk, the primary purpose of this study is to investigate the feasibility of intervention components and study procedures and to inform a larger intervention. This is necessary in research related to CVD [79]. For these reasons, a sample size of 40 was deemed appropriate to test the intervention. The sample size of 40 is able to detect an increase of 1000 steps from baseline to follow-up, which is below the minimum expected increase in steps from pedometer-based interventions [80]. The findings from this pilot study will be used to establish initial effect sizes and inform the power and sample size estimates for future larger trials.

Limitations

The 5 A's counseling is meant to be delivered by a primary care physician [17]. A recent review of A-counseling found that patients want all counseling components conducted by their physician [81]. Our study is limited in that the PA counselor will provide all of the counseling. This study is also limited to more affluent individuals who can afford a smart device. However, if this study proves feasible, it will inform subsequent larger studies that will provide smart devices and counseling conducted by physicians. This study is also limited to the areas of greater Galveston and Harris Counties, TX. Although this study will not be nationally generalizable, we anticipate that it will include a diverse population.

Several potential limitations will be explicitly measured and addressed by the pilot study design. For example, the older adult participants may dislike aspects of the app or EAM, or compliance may be limited by misunderstandings. Furthermore, it may be insufficiently powered to detect all significant differences in study outcomes and it will not evaluate maintenance of PA.

Data Management

Participants will be thoroughly informed of study procedures and give informed consent prior to any data collection. All data and participant information will be kept in a locked file cabinet or stored as a deidentified file on a secured computer network. Data and participant information will be transported from the clinics to the office in a passcode protected folder or on an encrypted flash drive. Data will be linked with an identification number and will be stored separately from all personal information. Only authorized members of the research team will have access to data. Due to the small sample size, a data monitoring committee will not be utilized. Instead, the Principal Investigator will conduct data safety monitoring weekly.

Participants in the EAM group will be given deidentifiable accounts to be used by the UP app. The accounts will not provide names, images, or personal information of the participants. UP app accounts made by stakeholders, as part of their involvement in the focus groups, will not be deidentified and will include any personal information the individual discloses in the app (ie, name, images). Accounts will only be viewable by other study participants and the research team.

Results

TAME health is currently in the recruitment phase. Recruitment started in October and will continue until all participants are enrolled. As of December 3, 2015, a total of 8 participants have been enrolled. The intervention will start after January 1, 2016. The intervention component of TAME health is expected to be done by the end of June 2016. At that time, focus groups will be conducted and the results will be analyzed. The entire study is scheduled to be completed by October 2016. Any protocol modifications and study results will be updated on a website (NCT02554435).

Discussion

There is a need for scalable, relatively inexpensive, and low-intensity interventions that could be delivered across a large population [82]. After the completion of the study and focus groups, we will refine the intervention based upon findings as well as qualitative and quantitative participant feedback. This project will lay the groundwork and establish the infrastructure for a successful program of related research. Ultimately, we hope to use the results of our research program to implement health care programs that utilize technology to provide effective behavioral interventions on a public health scale, improving population CVD morbidity and mortality [10,16].

Acknowledgments

The authors would like to acknowledge Elizabeth Jaramillo, MD for acting as a consultant for this study. We would also like to acknowledge the assistance and coordination from the staff and physicians at the study clinics. The authors would also like to acknowledge the Preventive Medicine and Community Health department at UTMB for donating the pedometers for this study. Finally, the authors would like to acknowledge Eloisa Martinez, Demi Arnold, Kaitlin Dresser, and Yoel Kidane for aiding in the implementation of this project.

The intervention described, and ZHL, were supported by a Predoctoral Fellowship Grant from the AHA (16PRE27090012). The AHA had no role in the study design; data collection; management; analysis; interpretation; or preparation of the manuscript; and does not hold ultimate authority over these activities. The sponsor may be reached through the Principal Investigator, ZHL, at (409) 772-2576. A Mentored Research Scholar Grant in Applied and Clinical Research, MRSG-14-165-01-CPPB, from the American Cancer Society supported EJL, PhD. EJL was also supported by a Beginning Grant-in-Aid, 13BGIA17110021, from the AHA. MCS was supported by Comparative Effectiveness Research on Cancer in Texas from the Cancer Prevention Research Institute of Texas (RP140020). AFB was supported by NIH/NCATS Grant (UL1TR000124).

Authors' Contributions

ZHL was responsible for the conception of TAME health, secured funding, developed the protocol, and wrote the manuscript. KO, SF, and AB contributed to the protocol. KJ helped develop the analytic plan. MCS assisted with data collection for the preliminary studies and patient screening. EJL assisted with the development of the protocol and was the Principle Investigator for the preliminary studies.

Conflicts of Interest

While the AHA funded this study, MCS's spouse has an equity interest in Apple Inc, a company that may potentially benefit from the research results. UTMB’s Conflicts of Interest Committee has reviewed this equity interest and a management plan implemented to prevent any appearance of a conflict of interest. Any inquiries regarding this management plan can be directed to UTMB's Office of Institutional Compliance, (409) 747-8701.

Multimedia Appendix 1

SPIRIT Guideline Checklist.

[PDF File (Adobe PDF File), 62KB - resprot_v5i2e59_app1.pdf]

Multimedia Appendix 2

Feature within the UP app by Jawbone.

[PDF File (Adobe PDF File), 1MB - resprot_v5i2e59_app2.pdf]

Multimedia Appendix 3

Grant proposal reviewer comments.

[PDF File (Adobe PDF File), 31KB - resprot_v5i2e59_app3.pdf]

References

1. Mozaffarian D, Benjamin E, Go A. Heart disease and stroke statistics--. American: A report from the Heart Association. Circulation. 2015;131(4); 2015:e29-322.
2. Luckhaupt SE, Calvert GM, Centers for Disease Control and Prevention. Prevalence of coronary heart disease or stroke among workers aged <55 years--United States, 2008-2012. MMWR Morb Mortal Wkly Rep 2014 Aug 1;63(30):645-649 [FREE Full text] [Medline: 25078653]

3. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van HL, American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: The American Heart Association's strategic impact goal through 2020 and beyond. Circulation 2010 Feb 2;121(4):586-613 [FREE Full text] [doi: 10.1161/CIRCULATIONAHA.109.192703] [Medline: 20089546]
4. Ahmed HM, Blaha MJ, Nasir K, Rivera JJ, Blumenthal RS. Effects of physical activity on cardiovascular disease. Am J Cardiol 2012 Jan 15;109(2):288-295. [doi: 10.1016/j.amjcard.2011.08.042] [Medline: 22011559]
5. McGavock JM, Eves ND, Mandic S, Glenn NM, Quinney HA, Haykowsky MJ. The role of exercise in the treatment of cardiovascular disease associated with type 2 diabetes mellitus. Sports Med 2004;34(1):27-48. [Medline: 14715038]
6. Perez-Terzic CM. Exercise in cardiovascular diseases. PM R 2012 Nov;4(11):867-873. [doi: 10.1016/j.pmrj.2012.10.003] [Medline: 23174552]
7. Swift DL, Lavie CJ, Johannsen NM, Arena R, Earnest CP, O'Keefe JH, et al. Physical activity, cardiorespiratory fitness, and exercise training in primary and secondary coronary prevention. Circ J 2013;77(2):281-292 [FREE Full text] [Medline: 23328449]
8. Vanhees L, De SJ, Gelada S, Doyle F, Prescott E, Cornelissen V, EACPR. Importance of characteristics and modalities of physical activity and exercise in defining the benefits to cardiovascular health within the general population: Recommendations from the EACPR (Part I). Eur J Prev Cardiol 2012 Aug;19(4):670-686. [doi: 10.1177/2047487312437059] [Medline: 22637742]
9. Ströbl V, Knisel W, Landgraf U, Faller H. A combined planning and telephone aftercare intervention for obese patients: Effects on physical activity and body weight after one year. J Rehabil Med 2013 Feb;45(2):198-205 [FREE Full text] [doi: 10.2340/16501977-1095] [Medline: 23250000]
10. Spring B, Ockene JK, Gidding SS, Mozaffarian D, Moore S, Rosal MC, American Heart Association Behavior Change Committee of the Council on Epidemiology and Prevention, Council on Lifestyle and Cardiometabolic Health, Council for High Blood Pressure Research, Council on Cardiovascular and Stroke Nursing. Better population health through behavior change in adults: A call to action. Circulation 2013 Nov 5;128(19):2169-2176 [FREE Full text] [doi: 10.1161/01.cir.0000435173.25936.e1] [Medline: 24100544]
11. Sun F, Norman IJ, While AE. Physical activity in older people: A systematic review. BMC Public Health 2013;13:449 [FREE Full text] [doi: 10.1186/1471-2458-13-449] [Medline: 23648225]
12. Teixeira PJ, Carraça EV, Markland D, Silva MN, Ryan RM. Exercise, physical activity, and self-determination theory: A systematic review. Int J Behav Nutr Phys Act 2012;9:78 [FREE Full text] [doi: 10.1186/1479-5868-9-78] [Medline: 22726453]
13. Goldstein MG, Whitlock EP, DePue J, Planning Committee of the Addressing Multiple Behavioral Risk Factors in Primary Care Project. Multiple behavioral risk factor interventions in primary care. Summary of research evidence. Am J Prev Med 2004 Aug;27(2 Suppl):61-79. [doi: 10.1016/j.amepre.2004.04.023] [Medline: 15275675]
14. Jacobson DM, Strohecker L, Compton MT, Katz DL. Physical activity counseling in the adult primary care setting: Position statement of the American College of Preventive Medicine. Am J Prev Med 2005 Aug;29(2):158-162. [doi: 10.1016/j.amepre.2005.04.009] [Medline: 16005814]
15. Bock C, Diehl K, Schneider S, Diehm C, Litaker D. Behavioral counseling for cardiovascular disease prevention in primary care settings: A systematic review of practice and associated factors. Med Care Res Rev 2012 Oct;69(5):495-518. [doi: 10.1177/1077558712441084] [Medline: 22457269]
16. Berra K, Rippe J, Manson J. Making physical activity counseling a priority in clinical practice: The time for action is now. JAMA 2015;314(24):2617-2618. [doi: 10.1001/jama.2015.16244] [Medline: 26662069]
17. Whitlock EP, Orleans CT, Pender N, Allan J. Evaluating primary care behavioral counseling interventions: An evidence-based approach. Am J Prev Med 2002 May;22(4):267-284. [Medline: 11988383]
18. Fortier MS, Hogg W, O'Sullivan TL, Blanchard C, Reid RD, Sigal RJ, et al. The physical activity counselling (PAC) randomized controlled trial: Rationale, methods, and interventions. Appl Physiol Nutr Metab 2007 Dec;32(6):1170-1185. [doi: 10.1139/H07-075] [Medline: 18059592]
19. Vansteenkiste M, Williams GC, Resnicow K. Toward systematic integration between self-determination theory and motivational interviewing as examples of top-down and bottom-up intervention development: Autonomy or volition as a fundamental theoretical principle. Int J Behav Nutr Phys Act 2012;9:23 [FREE Full text] [doi: 10.1186/1479-5868-9-23] [Medline: 22385828]
20. Diehl K, Mayer M, Mayer F, Görig T, Bock C, Herr RM, et al. Physical activity counseling by primary care physicians: Attitudes, knowledge, implementation, and perceived success. J Phys Act Health 2015 Feb;12(2):216-223. [doi: 10.1123/jpah.2013-0273] [Medline: 24762394]
21. van AT, Huisman-de Waal Getty G J, Ketelaar Nicole A B M, Oostendorp RA, Jacobs JE, Wollersheim Hub C H. How to promote healthy behaviours in patients? An overview of evidence for behaviour change techniques. Health Promot Int 2011 Jun;26(2):148-162 [FREE Full text] [doi: 10.1093/heapro/daq050] [Medline: 20739325]
22. Michie S, Abraham C, Whittington C, McAteer J, Gupta S. Effective techniques in healthy eating and physical activity interventions: A meta-regression. Health Psychol 2009 Nov;28(6):690-701. [doi: 10.1037/a0016136] [Medline: 19916637]

23. Verwey R, van der Weegen Sanne, Spreeuwenberg M, Tange H, van der Weijden Trudy, de WL. A monitoring and feedback tool embedded in a counselling protocol to increase physical activity of patients with COPD or type 2 diabetes in primary care: Study protocol of a three-arm cluster randomised controlled trial. BMC Fam Pract 2014;15:93 [FREE Full text] [doi: 10.1186/1471-2296-15-93] [Medline: 24885096]
24. Knight E, Stuckey MI, Petrella RJ. Health promotion through primary care: Enhancing self-management with activity prescription and mHealth. Phys Sportsmed 2014 Sep;42(3):90-99. [doi: 10.3810/psm.2014.09.2080] [Medline: 25295771]
25. Thomas JG, Bond DS. Review of innovations in digital health technology to promote weight control. Curr Diab Rep 2014;14(5):485. [doi: 10.1007/s11892-014-0485-1] [Medline: 24664797]
26. Knight JA. Physical inactivity: Associated diseases and disorders. Ann Clin Lab Sci 2012;42(3):320-337. [Medline: 22964623]
27. Bravata DM, Smith-Spangler C, Sundaram V, Gienger AL, Lin N, Lewis R, et al. Using pedometers to increase physical activity and improve health: A systematic review. JAMA 2007 Nov 21;298(19):2296-2304. [doi: 10.1001/jama.298.19.2296] [Medline: 18029834]
28. Cayir Y, Aslan SM, Akturk Z. The effect of pedometer use on physical activity and body weight in obese women. Eur J Sport Sci 2015;15(4):351-356. [doi: 10.1080/17461391.2014.940558] [Medline: 25068676]
29. Richardson CR, Newton TL, Abraham JJ, Sen A, Jimbo M, Swartz AM. A meta-analysis of pedometer-based walking interventions and weight loss. Ann Fam Med 2008;6(1):69-77 [FREE Full text] [doi: 10.1370/afm.761] [Medline: 18195317]
30. Miyazaki R, Kotani K, Tsuzaki K, Sakane N, Yonei Y, Ishii K. Effects of a year-long pedometer-based walking program on cardiovascular disease risk factors in active older people. Asia Pac J Public Health 2015 Mar;27(2):155-163. [doi: 10.1177/1010539513506603] [Medline: 24174388]
31. Freak-Poli R, Wolfe R, Brand M, de CM, Peeters A. Eight-month postprogram completion: Change in risk factors for chronic disease amongst participants in a 4-month pedometer-based workplace health program. Obesity (Silver Spring) 2013 Sep;21(9):E360-E368 [FREE Full text] [doi: 10.1002/oby.20342] [Medline: 23408732]
32. Aittasalo M, Miilunpalo S, Kukkonen-Harjula K, Pasanen M. A randomized intervention of physical activity promotion and patient self-monitoring in primary health care. Prev Med 2006 Jan;42(1):40-46. [doi: 10.1016/j.ypmed.2005.10.003] [Medline: 16297442]
33. Bonomi AG, Westerterp KR. Advances in physical activity monitoring and lifestyle interventions in obesity: A review. Int J Obes (Lond) 2012 Feb;36(2):167-177. [doi: 10.1038/ijo.2011.99] [Medline: 21587199]
34. Aittasalo M, Miilunpalo S, Kukkonen-Harjula K, Pasanen M. A randomized intervention of physical activity promotion and patient self-monitoring in primary health care. Prev Med 2006 Jan;42(1):40-46. [doi: 10.1016/j.ypmed.2005.10.003] [Medline: 16297442]
35. Franklin NC, Lavie CJ, Arena RA. Personal health technology: A new era in cardiovascular disease prevention. Postgrad Med 2015 Mar;127(2):150-158 [FREE Full text] [doi: 10.1080/00325481.2015.1015396] [Medline: 25690685]
36. Danova T. Just 3 million fitness trackers were sold in the US in the past year. URL: http://www.businessinsider.com/33-million-fitness-trackers-were-sold-in-the-us-in-the-past-year-2014-5 [accessed 2016-02-24] [WebCite Cache ID 6fXokIyaC]
37. Lewis ZH, Lyons EJ, Jarvis JM, Baillargeon J. Using an electronic activity monitor system as an intervention modality: A systematic review. BMC Public Health 2015;15:585 [FREE Full text] [doi: 10.1186/s12889-015-1947-3] [Medline: 26104189]
38. Lyons EJ, Lewis ZH, Mayrsohn BG, Rowland JL. Behavior change techniques implemented in electronic lifestyle activity monitors: A systematic content analysis. J Med Internet Res 2014;16(8):e192 [FREE Full text] [doi: 10.2196/jmir.3469] [Medline: 25131661]
39. Michie S, Ashford S, Sniehotta FF, Dombrowski SU, Bishop A, French DP. A refined taxonomy of behaviour change techniques to help people change their physical activity and healthy eating behaviours: The CALO-RE taxonomy. Psychol Health 2011 Nov;26(11):1479-1498. [doi: 10.1080/08870446.2010.540664] [Medline: 21678185]
40. Normansell R, Smith J, Victor C, Cook DG, Kerry S, Iliffe S, et al. Numbers are not the whole story: A qualitative exploration of barriers and facilitators to increased physical activity in a primary care based walking intervention. BMC Public Health 2014;14:1272 [FREE Full text] [doi: 10.1186/1471-2458-14-1272] [Medline: 25511452]
41. Patel M, Asch D, Volpp K. Wearable devices as facilitators, not drivers, of health behavior change. JAMA 2015 Feb 3;313(5):459-460. [doi: 10.1001/jama.2014.14781] [Medline: 25569175]
42. Carroll JK, Winters PC, Sanders MR, Decker F, Ngo T, Sciamanna CN. Clinician-targeted intervention and patient-reported counseling on physical activity. Prev Chronic Dis 2014;11:E89 [FREE Full text] [doi: 10.5888/pcd11.130302] [Medline: 24874781]
43. Adams M, Sallis J, Norman G, Hovell M, Hekler E, Perata E. An adaptive physical activity intervention for overweight adults: A randomized controlled trial. PLoS One 2013;8(12):e82901 [FREE Full text] [doi: 10.1371/journal.pone.0082901] [Medline: 24349392]
44. Task Force on Community Preventive Services. Recommendations to increase physical activity in communities. Am J Prev Med 2002 May;22(4 Suppl):67-72. [Medline: 11985935]

45. Williams SL, French DP. What are the most effective intervention techniques for changing physical activity self-efficacy and physical activity behaviour--and are they the same? Health Educ Res 2011 Apr;26(2):308-322 [FREE Full text] [doi: 10.1093/her/cyr005] [Medline: 21321008]
46. Olander EK, Fletcher H, Williams S, Atkinson L, Turner A, French DP. What are the most effective techniques in changing obese individuals' physical activity self-efficacy and behaviour: A systematic review and meta-analysis. Int J Behav Nutr Phys Act 2013;10:29 [FREE Full text] [doi: 10.1186/1479-5868-10-29] [Medline: 23452345]
47. Warburton D, Jamnik V, Bredin S, Gledhill N. The physical activity readiness questionnaire (PAR-Q+) and electronic physical activity readiness medical examination (ePARmed-X+). Health Fitness Journal Canada. 2011. Collaboration P-QR URL: http://new-hfjc.library.ubc.ca/index.php/html/article/view/105 [WebCite Cache ID 6fw6i2A2o]
48. Smith A. 2014. Older adults and technology use URL: http://www.pewinternet.org/2014/04/03/older-adults-and-technology-use/ [accessed 2016-02-24] [WebCite Cache ID 6fXp2C500]
49. Yasunaga A, Togo F, Watanabe E, Park H, Park S, Shephard RJ, et al. Sex, age, season, and habitual physical activity of older Japanese: The Nakanojo study. J Aging Phys Act 2008 Jan;16(1):3-13. [Medline: 18212390]
50. Urbaniak G, Plous S. Research randomizer. 1999. Research randomizer URL: https://www.randomizer.org/ [accessed 2016-02-25] [WebCite Cache ID 6fZ4HCrWE]
51. Yamax. Accessed September 30. 2015. Digi-Walker CW-700/701 URL: http://www.yamaxx.com/digi/cw_700_e.html [accessed 2016-02-24] [WebCite Cache ID 6fXp7PlF5]
52. Dolan B. mobihealth news. 2014. Fitbit, Jawbone, Nike had 97 percent of fitness tracker retail sales in 2013 URL: http://mobihealthnews.com/28825/fitbit-jawbone-nike-had-97-percent-of-fitness-tracker-retail-sales-in-2013/ [accessed 2016-02-24] [WebCite Cache ID 6fXpDcg5j]
53. Jawbone. Jawbone. 2015. The UP system URL: https://jawbone.com/up [accessed 2016-02-23] [WebCite Cache ID 6fXpL95jR]
54. Vandelanotte C, De BI. Acceptability and feasibility of a computer-tailored physical activity intervention using stages of change: Project FAITH. Health Educ Res 2003 Jun;18(3):304-317 [FREE Full text] [Medline: 12828232]
55. Rovniak LS, Anderson ES, Winett RA, Stephens RS. Social cognitive determinants of physical activity in young adults: A prospective structural equation analysis. Ann Behav Med 2002;24(2):149-156. [Medline: 12054320]
56. D'Agostino R, Vasan R, Pencina M. 2015. Accessed October. 2015. Cardiovascular disease (10-year risk) URL: https://www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/10-year-risk.php [accessed 2016-02-25] [WebCite Cache ID 6fZ4WndB2]
57. Rikli R, Jones C. Journal of Aging and Physical Activity. 1998. The Reliability and validity of a 6-minute walk test as a measure of physical endurance in older adults URL: http://hdcs.fullerton.edu/csa/Research/documents/RikliJones1998TheReliabilityandValidityofa6MinuteWalk_000.pdf [WebCite Cache ID 6fw7QWDpO]
58. Kaminsky LA, Arena R, Beckie TM, Brubaker PH, Church TS, Forman DE, American Heart Association Advocacy Coordinating Committee, Council on Clinical Cardiology, Council on Nutrition, Physical Activity and Metabolism. The importance of cardiorespiratory fitness in the United States: The need for a national registry: A policy statement from the American Heart Association. Circulation 2013 Feb 5;127(5):652-662 [FREE Full text] [doi: 10.1161/CIR.0b013e31827ee100] [Medline: 23295916]
59. Widmer RJ, Collins NM, Collins CS, West CP, Lerman LO, Lerman A. Digital health interventions for the prevention of cardiovascular disease: A systematic review and meta-analysis. Mayo Clin Proc 2015 Apr;90(4):469-480. [doi: 10.1016/j.mayocp.2014.12.026] [Medline: 25841251]
60. D'Agostino R, Vasan R, Pencina M, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: The Framingham Heart Study. Circulation 2008 Feb 12;117(6):743-753 [FREE Full text] [doi: 10.1161/CIRCULATIONAHA.107.699579] [Medline: 18212285]
61. Rikli R. Senior fitness test manual. IL: Champaign, IL; Human Kinetics; 2013.
62. Berntsen S, Hageberg R, Aandstad A, Mowinckel P, Anderssen SA, Carlsen K, et al. Validity of physical activity monitors in adults participating in free-living activities. Br J Sports Med 2010 Jul;44(9):657-664. [doi: 10.1136/bjsm.2008.048868] [Medline: 18628358]
63. Seca. Accessed October 7. 2015. seca 213 URL: https://us.secashop.com/products/height-measuring-instruments/seca-213/2131821009 [accessed 2016-02-24] [WebCite Cache ID 6fXpaVPUA]
64. Tanita. Tanita. 2014. BWB-800S Doctors scale URL: http://www.tanita.com/en/bwb-800s/ [accessed 2016-02-24] [WebCite Cache ID 6fXpfD671]
65. NIH. Accessed October 7. 2015. Calculate your body mass index URL: http://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm [accessed 2016-02-24] [WebCite Cache ID 6fXpoCseC]
66. Taylor RW, Jones IE, Williams SM, Goulding A. Evaluation of waist circumference, waist-to-hip ratio, and the conicity index as screening tools for high trunk fat mass, as measured by dual-energy X-ray absorptiometry, in children aged 3-19 y. Am J Clin Nutr 2000 Aug;72(2):490-495 [FREE Full text] [Medline: 10919946]
67. Takahashi H, Yokoi T, Yoshika M. Validation of the OMRON M6 AC (HEM-7322-E) upper arm blood pressure monitor, in oscillometry mode, for clinic use and self measurement in a general population, according to the European Society of

Hypertension International Protocol revision. Dublin: dablEducational Trust; 2014. URL: http://www.omronhealthcare.ca/service-and-support/clinical-validation/ [accessed 2016-02-25] [WebCite Cache ID 6fZ5LzdW4]
68. Jenkinson C, Wright L, Coulter A. Criterion validity and reliability of the SF-36 in a population sample. Qual Life Res 1994 Feb;3(1):7-12. [Medline: 8142947]
69. Freiberger E, de VP, Schoene D, Rydwik E, Mueller V, Frändin K, et al. Performance-based physical function in older community-dwelling persons: A systematic review of instruments. Age Ageing 2012 Nov;41(6):712-721 [FREE Full text] [doi: 10.1093/ageing/afs099] [Medline: 22885845]
70. Cella D, Gershon R, Bass M, Rothrock N. Promis. 2013. Assessment center URL: http://www.nihpromis.org/Measures/availableinstruments?AspxAutoDetectCookieSupport=1 [accessed 2016-02-23] [WebCite Cache ID 6fXpw2f2s]
71. Markland D. BREQ-2 home; Accessed April 8. 2013. BREQ and BREQ-2 scoring URL: http://pages.bangor.ac.uk/~pes004/exercise_motivation/breq/breq.htm [accessed 2016-02-24] [WebCite Cache ID 6fXpzTSGw]
72. Wilson PM, Todd RW, Rodgers WM, Wild TC. Journal of Sport & Exercise Psychology. 2006. The psychological need satisfaction in exercise scale URL: http://journals.humankinetics.com/AcuCustom/Sitename/Documents/DocumentItem/6053.pdf [WebCite Cache ID 6fw8WxsE7]
73. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement. Open Med 2009;3(3):e123-e130 [FREE Full text] [Medline: 21603045]
74. Wadden TA, Volger S, Sarwer DB, Vetter ML, Tsai AG, Berkowitz RI, et al. A two-year randomized trial of obesity treatment in primary care practice. N Engl J Med 2011 Nov 24;365(21):1969-1979 [FREE Full text] [doi: 10.1056/NEJMoa1109220] [Medline: 22082239]
75. Harris T, Kerry SM, Victor CR, Ekelund U, Woodcock A, Iliffe S, et al. A primary care nurse-delivered walking intervention in older adults: PACE (pedometer accelerometer consultation evaluation)-Lift cluster randomised controlled trial. PLoS Med 2015 Feb;12(2):e1001783 [FREE Full text] [doi: 10.1371/journal.pmed.1001783] [Medline: 25689364]
76. Pfaeffli DL, Whittaker R, Jiang Y, Stewart R, Rolleston A, Maddison R. Text message and internet support for coronary heart disease self-management: Results from the Text4Heart randomized controlled trial. J Med Internet Res 2015;17(10):e237 [FREE Full text] [doi: 10.2196/jmir.4944] [Medline: 26490012]
77. Braun V, Clarke V. What can "thematic analysis" offer health and wellbeing researchers? Int J Qual Stud Health Well-being 2014;9:26152 [FREE Full text] [Medline: 25326092]
78. Thorpe KE, Zwarenstein M, Oxman AD, Treweek S, Furberg CD, Altman DG, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): A tool to help trial designers. J Clin Epidemiol 2009 May;62(5):464-475. [doi: 10.1016/j.jclinepi.2008.12.011] [Medline: 19348971]
79. Stevens J, Taber DR, Murray DM, Ward DS. Advances and controversies in the design of obesity prevention trials. Obesity (Silver Spring) 2007 Sep;15(9):2163-2170 [FREE Full text] [doi: 10.1038/oby.2007.257] [Medline: 17890483]
80. Kang M, Marshall SJ, Barreira TV, Lee J. Effect of pedometer-based physical activity interventions: A meta-analysis. Res Q Exerc Sport 2009 Sep;80(3):648-655. [doi: 10.1080/02701367.2009.10599604] [Medline: 19791652]
81. Sherson EA, Yakes JE, Katalanos N. A review of the use of the 5 A's model for weight loss counselling: Differences between physician practice and patient demand. Fam Pract 2014 Aug;31(4):389-398 [FREE Full text] [doi: 10.1093/fampra/cmu020] [Medline: 24891472]
82. Kwong EWY, Kwan AYH. Participation in health-promoting behaviour: Influences on community-dwelling older Chinese people. J Adv Nurs 2007 Mar;57(5):522-534. [doi: 10.1111/j.1365-2648.2006.04132.x] [Medline: 17284280]

Abbreviations

AHA: American Heart Association
app: application
BCT: behavioral change technique
BMI: body mass index
CVD: cardiovascular disease
EAM: electronic activity monitor
PA: physical activity
Par-Q+: Physical Activity Readiness Questionnaire Plus
TAME health: Testing Activity Monitors' Effect on health
USPSTF: United States Preventive Services Task Force
UTMB: University of Texas Medical Branch

Edited by G Eysenbach; submitted 17.12.15; peer-reviewed by S Santana, D Pfaeffli; comments to author 05.01.16; accepted 19.01.16; published 29.04.16.

Please cite as:
Lewis ZH, Ottenbacher KJ, Fisher SR, Jennings K, Brown AF, Swartz MC, Lyons EJ
Testing Activity Monitors' Effect on Health: Study Protocol for a Randomized Controlled Trial Among Older Primary Care Patients
JMIR Res Protoc 2016;5(2):e59
URL: http://www.researchprotocols.org/2016/2/e59/
doi:10.2196/resprot.5454
PMID:27129602

Protocol

An Internet-Based Intervention to Promote Alcohol-Related Attitudinal and Behavioral Change Among Adolescents: Protocol of a Cluster Randomized Controlled Trial

Patrick Ip[1], MBBS, MPH; Ko-Ling Chan[2], BSW, MA, PhD; Chun-Bong Chow[1], MBBS, MD; Tai-Hing Lam[3], MBBS, MSc, MD; Sai-Yin Ho[3], MPH, PhD; Wilfred Hing-Sang Wong[1], BSc, MMS; Margaret Fung-Yee Wong[4], BSW, MSocSc, MA, DSW

[1]The University of Hong Kong, Department of Paediatrics and Adolescent Medicine, Hong Kong, China (Hong Kong)

[2]The University of Hong Kong, Department of Social Work & Social Administration, Hong Kong, China (Hong Kong)

[3]The University of Hong Kong, School of Public Health, Hong Kong, China (Hong Kong)

[4]Tung Wah Group of Hospitals, Community Services Division, Hong Kong, China (Hong Kong)

Corresponding Author:
Patrick Ip, MBBS, MPH
The University of Hong Kong
Department of Paediatrics and Adolescent Medicine
1/F, New Clinical Building, Queen Mary Hospital, Pokfulam
Hong Kong,
China (Hong Kong)
Phone: 852 28198501
Fax: 852 22554089
Email: patricip@hku.hk

Abstract

Background: Underage drinking is a prevalent risk behavior and common public health problem. Research shows that alcohol abuse not only affects the quality of life of drinkers themselves. The problems resulting from underage drinking pose substantial costs to society as well. The proposed study will address underage drinking with the use of an Internet campaign, which is a cost-effective way of tackling the problem.

Objective: The aims of this study are to test the effectiveness of an online quiz competition in changing adolescents' alcohol-related attitudes and behavior and to explore the feasibility of using Internet viral marketing to reach a significant number of adolescents.

Methods: The study will constitute a cluster randomized controlled trial for 20 secondary schools (6720 Grade 7-9 students). Schools will be randomized to intervention or control arm with equal likelihood. Students in intervention schools will be invited to take part in the Internet campaign, whereas those in control schools will receive relevant promotional leaflets.

Results: Alcohol-related attitude and behavior will be the primary outcome measures. The results of the proposed study will provide evidence on the efficacy of an Internet intervention in modifying adolescents' attitudes and behavior and guide further investigation into the prevention of and intervention in such risk behaviors as underage drinking. The project was funded July 2015, enrollment started September 2015, and results are expected July 2017.

Conclusions: With the Internet increasingly being recognized as a practical and cost-effective platform for health information delivery, the proposed Internet-based intervention is expected to be more effective in altering adolescents' alcohol-related attitudes and behaviors than traditional health promotion.

ClinicalTrial: ClinicalTrials.gov NCT02450344; https://clinicaltrials.gov/ct2/show/NCT02450344 (Archived by WebCite at http://www.webcitation.org/6heB2zMBD)

(JMIR Res Protoc 2016;5(2):e103) doi:10.2196/resprot.5001

KEYWORDS

Internet viral marketing; attitude change; behavioural change; underage drinking; risk behaviour; Internet intervention

Introduction

Background

Underage drinking is a leading global public health problem. Each year, many underage drinkers die from motor vehicle crashes, homicide, suicide, falls, burns, and drowning [1]. Research shows that alcohol abuse not only affects the quality of life of drinkers themselves; the problems resulting from underage drinking pose substantial costs to society as well [2]. The proposed study will address underage drinking because, like many other behaviors that pose a health risk such as cigarette smoking and unprotected sex, excessive alcohol consumption habits acquired during adolescence can be tracked into adulthood, thereby harming both current health and health later in life [3]. Studies on the long-term health impacts attributable to alcohol use have found adolescents who start drinking at an early age are more likely to binge drink during adulthood [4]. Moreover, young people's susceptibility to peer influence peaks during the middle adolescent years, which renders that age group particularly vulnerable to underage alcohol use [5]. In light of these associations and risks, it is recommended that alcohol-related interventions and prevention strategies be initiated as early as during adolescence to obtain maximal benefits.

Underage Drinking and its Prevalence

Adolescence is a period of stress, during which feelings of insecurity are high and motivation is low [6]. Traditional intervention means may be inadequate to engage youths. As adolescents have been found more open than other age groups to the new possibilities offered by the Internet [7], this medium provides an innovative platform for an intervention program targeting this population. Viral marketing through the peer dissemination of information online may be particularly applicable to changing adolescents' perceptions and engagement in risk behaviors. The aim of the proposed study is therefore to investigate the extent to which an Internet viral marketing campaign can change drinking behavior and attitudes towards alcohol use among Chinese adolescents.

Underage drinking poses a multitude of risks for teens, their families, and society as a whole, and the prevalence of underage drinking among today's adolescents is widespread internationally [8]. In 2011, for example, the US National Survey on Drug Use and Health reported that 25% of American youths aged 12-20 drink alcohol, with 16% reporting binge drinking [9]. In Korea, a study of 2124 students attending junior and high schools in Seoul showed that 68% of those aged 12-16 were monthly drinkers and that 28% drank alcohol weekly [10].

The situation in Hong Kong is equally worrying, with the Child Health Survey of 2005/2006 reporting that a significant proportion of children aged 11-14 were current binge drinkers [11]. A more recent survey conducted by the Narcotics Division in 2008 showed that 64.9% of secondary school students had consumed alcohol at least once [12]. The abolition of beer and wine taxes in 2008 and subsequent fierce advertising by the alcohol industry and open endorsement of alcohol by top government officials have further aggravated the local underage drinking problem. School surveys have found a significant increase in monthly alcohol drinking in both adolescent boys (from 19.1% in 2006/7 to 30.4% in 2009/10) and girls (from 16.5% in 2006/7 to 27.5% in 2009/10) after the alcohol tax cut [13]. Hence, there is a pressing need for alcohol-related interventions to stop the growing trend of underage drinking in Hong Kong.

Transition From Traditional to Internet-Based Alcohol Interventions

Although traditional alcohol interventions by mail or health talks delivered by health care professionals have demonstrated efficacy, it remains difficult to engage adolescents with underage drinking problems who are unwilling or simply do not seek assistance through traditional health services or self-help groups. The Internet, because of its increasing usage among today's youth, can be an effective medium to engage this high-risk population. There is evidence to support the benefit of online alcohol intervention to reach groups less likely to access traditional alcohol-related services, such as young people, and the evidence also supports its potential to effect behavioral change in large numbers of people [14].

Internet Viral Marketing and its Efficacy

Internet viral marketing, or the electronic "word-of-mouth" dissemination of information, is one of the best-recognized forms of Internet-based marketing. Research shows that viral marketing is a more effective and efficient marketing tool than traditional media, and one that is characterized by its low cost and exponential transmission of information [15]. A recent prospective pilot study conducted by Ip and Chow assessed the efficacy of an online game-based viral marketing campaign in promoting antismoking attitudes among Chinese adolescents. During the 22-day campaign, the study observed an eightfold increase in the number of participants and a significant attitudinal change, with 73% holding a negative attitude towards smoking after the campaign compared to 57% before it [16]. These promising results suggest the potential effectiveness of adopting a similar viral marketing model to engage youth and promulgate alcohol-related health information among Chinese adolescents.

Attitudinal Change and its Effects on Behavior

The theory of reasoned action and theory of planned behavior are the most frequently tested models of attitude-behavior relations. Both models view a particular behavior as a function of salient information, or beliefs, relevant to that behavior [17]. Beliefs about the positive outcomes of a behavior lead people to favor and engage in that behavior, while beliefs about its undesirable consequences hinder them from doing so. Research also supports the correlation between attitudinal change and behavioral change [18]. Hence, interventions aimed at changing attitudes towards alcohol use have the potential to induce simultaneous changes in drinking behavior. The aims of this study are to test the effectiveness of an online quiz competition in changing adolescents' alcohol-related attitudes and behavior and to explore the feasibility of using Internet viral marketing to reach a significant number of adolescents.

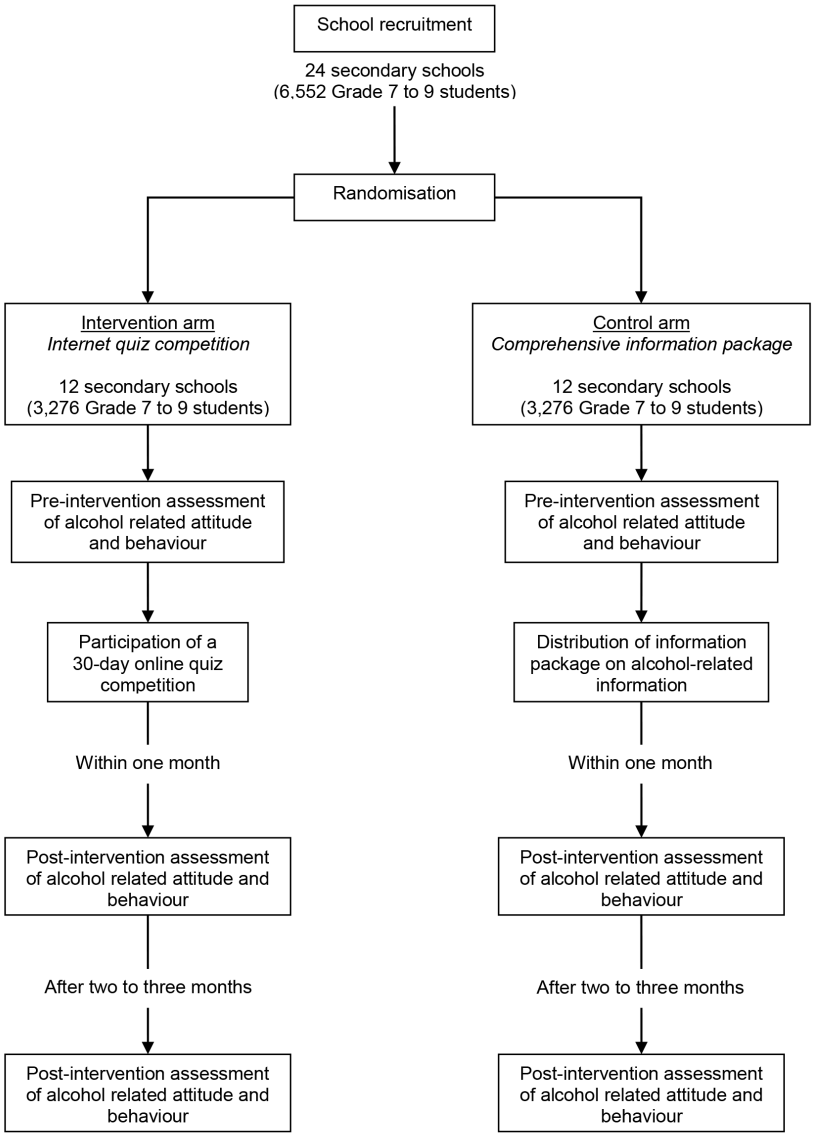
Methods

Study Design

The proposed study will consist of a cluster randomized controlled trial on the effectiveness of an Internet quiz competition in promoting healthy attitudes and behaviors towards alcohol use among adolescents. As the intervention website could be referred by participants, cluster randomization, instead of individual-level randomization, is chosen to minimize treatment contamination. The study will employ an Internet viral marketing strategy to maximize sample size. In total, 24 schools (6552 Grade 7-9 students) will be recruited with the collaboration of our community partners such as the Tung Wah Group of Hospitals. Considering that the average number of students in one secondary school class is 35 and that there are four classes in each grade, a total of 10,080 students (24×3×4×35) will be reached. Assuming a response rate of 65%, the number of effective campaign starters will be 6552. Students who cannot comprehend basic Chinese and Cantonese will be excluded.

Half the schools will be randomized for the Internet quiz competition campaign (intervention arm) and half will be randomized for an information package (control arm). Students in the intervention group will be given the opportunity to take part in the online quiz competition and refer others to join the campaign, whereas those in the control group will receive an electronic information package containing comparable information as the intervention arm. All participating students' demographics and change in attitude and behavior will be measured by questionnaire surveys before intervention, within 1 month, and between 2-3 months after intervention. A longer-term follow-up (12 months after intervention) will also be attempted if schools are willing to commit and resources allow. Weblog data will also be collected from website servers for subsequent analysis of the effectiveness of the Internet viral marketing strategy. Figure 1 is a flowchart of the proposed study.

Figure 1. Flowchart of the research design.



Power Analysis

Considering an attitude difference in 50% of the pooled standard deviation (SD) to be minimally satisfactory, we will need a sample size of 128 to examine, via a two-sample independent *t* test, whether the campaign is more effective than a traditional promotion strategy at a .05 significance level and 80% power [19]. Due to our cluster study design, intraclass correlation (ICC) needs to be addressed. It was reported that an ICC of attitude-related construct among schools was about 0.092 [20], which inflates the required sample size to N=n×[1+(K 1)×ICC]=128×[1+(3×4×35 1)×0.092]≈5063. Hence, the number of starters to be recruited (6552) will be sufficient to achieve the study's primary aim regardless of the number of referrals.

Intervention Arm: Internet Quiz Competition Campaign

The intervention is designed based on the Theory of Planned Behavior. Participants will gain alcohol-related knowledge through the participation of the intervention, which would in turn alter their attitude concerning drinking and alcohol use. According to the Theory of Planned Behavior, such knowledge and attitude improvement would reduce participants' intention to drink and thus change or prevent their drinking behavior [21]. To promote the intervention, we will conduct a briefing session and a demonstration session for all eligible students in participating schools in the intervention arm. Campaign promotion brochures and posters will be distributed within those schools.

Campaign Design

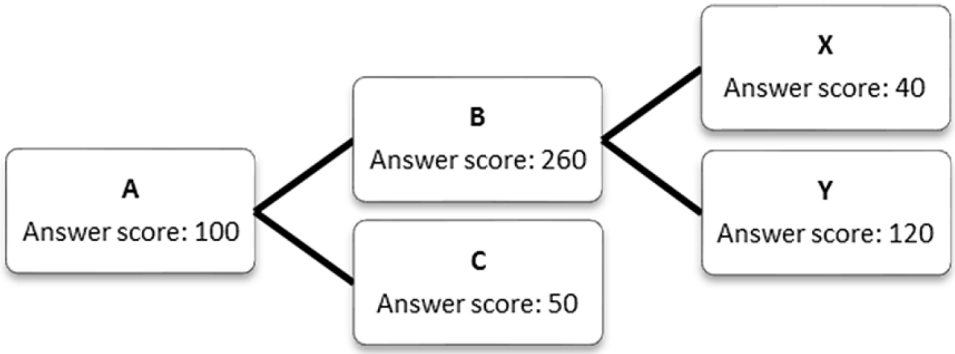
Participants of the campaign will receive a referral code from those who refer them to the online quiz website; starters of the campaigns will receive the code directly from the research team. These referral codes, sets of 8-digit numbers, will be unique to each user and used to track the referral process. During registration, participants will be asked to provide basic demographic information and their referral code. After registration, their baseline attitudes and behavior will be assessed using the Alcohol Attitudes and Behavior survey.

The campaign will last for 30 days, starting from the day of the school promotion session. The aim of the competition from the participants' perspective will be to obtain the highest score possible to win a prize. They will have two ways of doing so.

The first way will be to answer the online quiz questions. The points gained in this way will constitute the "answer score." Alcohol-related multiple-choice questions will be presented on the webpage one by one in random non-repeated order. Each correct answer will result in 10 points being awarded to the user's account. Giving an incorrect answer or skipping a question will not result in any points being deducted. Users will be shown the correct answer immediately after they have chosen their own. The purpose of this design is to promote correct alcohol-related knowledge and attitudes.

The second way of accruing points to obtain a high score will be to make referrals, a step designed to enhance the effectiveness of the Internet viral marketing strategy. Upon a successful referral, the referrer will receive all of the answer scores of their direct referrals (which will constitute their "referral score"). To minimize the chance of self-referrals, users will receive no points from making a successful referral. Furthermore, to ensure campaign competitiveness, the referral scores of lower-level users will not be added to starters' accounts. The answer score and referral score will be summed into a total score that will be used for prize distribution. Figure 2 illustrates the point system.

Figure 2. Example of the point system.



A's total score = A's answer score + A's referral score
= A's answer score + (B's answer score + C's answer score)
= 100 + 260 + 50 = 410

B's total score = B's answer score + B's referral score
= B's answer score + (X's answer score + Y's answer score)
= 260 + 40 + 120 = 420

C's total score = C's answer score = 50

Campaign Website and Quiz Questions

The campaign website will be based on our previous Internet viral marketing campaign, which has shown satisfactory user acceptance [16]. We will make necessary modifications such as enhancing the user interface and preventing duplicate registrations for our study.

Setting the quiz questions will be guided by the Elaboration Likelihood Model (ELM) of persuasion. The quiz questions will be designed by youth volunteers to convey accurate and interesting facts based on international and local sources such as World Health Organization and Hong Kong Department of Health reports and research articles from peer-reviewed journals. The questions will be concrete, specific, and of personal relevance to the participants so that they will be more likely to adopt a "central path" of message processing, which the ELM predicts will induce a more sustainable effect [22]. An experienced clinician and a research assistant will examine every set of 100 questions and discuss them with the question setters to ensure language accuracy and information reliability. This process will be repeated until a total of 1000 quiz questions are generated. Finally, all of the questions will be proofread, refined, and approved by a local alcohol research team from the School of Public Health, University of Hong Kong.

Incentive Scheme

An incentive scheme will be used to encourage active participation. The 10 highest scorers in each school will receive cash coupons of different values. Table 1 presents the detailed incentive scheme for each school.

Table 1. Prizes for the campaign winners in each school.

Rank of total score	Total number of prizes	Prize for each school	Value (HK$)
1	1	Cash coupon	500
2-3	2	Cash coupon	300
4-10	7	Cash coupon	200
Total			2500

Control Arm: Information Package

A comprehensive package on alcohol-related information will be distributed to all students in the control arm. The information package will contain both printed promotional leaflets from the Department of Health and an electronic guideline for understanding alcohol-related information. The electronic guideline sent through the school intranet system would serve as a unidirectional knowledge transfer medium, which would include a brief summary of the most recent research regarding alcohol and a comprehensive list of relevant website and information sources. We will use these relevant websites and information sources in setting the quiz questions for the intervention arm. As a result, both intervention and control arms could have comparable accessibility to alcohol-related information and the sole contrast between the two groups would be the method of presentation (interactive online quiz competition vs unidirectional information package).

Due to the referral nature of the Internet campaign, it is possible that a small portion of students in the control group school would be referred to participate in the quiz competition, which could in turn dilute the effect size estimate. As a result, we will ask the students in the control group in the postintervention survey whether they have participated in the Internet quiz competition campaign and exclude those who participate in subsequent data analysis.

Outcome Measure

Alcohol Use and Experience

Alcohol use and experience will be evaluated using the 17 items in the Alcohol Attitudes and Behavior survey before and after the intervention. These items are adapted from the Centers for Disease Control and Prevention's Behavioral Risk Factor Surveillance System Questionnaire and Global School-based Student Health Survey [23,24]. Alcohol use will be measured by an item on the 30-day recall dosage of alcohol consumption. Reasons for drinking, experience in drinking, and other relevant information will be surveyed with the rest of the 16 items. These items have been used in a national study in China [23,24].

Attitude Toward Alcohol Use

Attitude towards alcohol use will also be measured with the Alcohol Attitudes and Behavior survey, which includes 15 items adapted from the Scale for the Measurement of Attitudes Toward Alcohol designed to assess that attitude in three domains: sociability, personal unease, and economic aspects [25]. The scale has been validated among adolescents and has demonstrated good internal consistency (Cronbach alphas ranging from .79 to .91) and valid factor structures. Both domain-specific scores and the total score will be used in analysis. We have already gone through a standard procedure for piloting the questionnaire. To ensure the validity of the survey among Chinese adolescents, we have gone through a standard piloting procedure [26]. Briefly, we have invited professional Chinese translators with experience in public health to translate the questionnaire into traditional Chinese, which was then examined and back-translated into English by the research team. The back-translated version of the questionnaire was checked by the research team again to ensure the language accuracy. The Chinese version of the questionnaire was reviewed by a local expert panel using the Delphi process. The expert team included pediatricians, public health experts, parents of adolescents, and secondary school teachers. After reaching consensus with the expert team, the questionnaire was piloted to adolescents to fine-tune the wording and presentation.

Number of Successful Referrals per Participants

When making a referral, a participant will need to provide their unique referral code. The new participant who receives this

code will then input it during registration. Our website server will record all of these unique referral codes, which will allow us to subsequently analyze the referral pathways and calculate the number of successful referrals per participant.

Since the change in attitudes and behaviors could vary with age, the above analysis will also be carried out for each grade separately.

Covariates

Owing to randomization, the confounding effect should be minimized. However, we will still evaluate school-level covariates for data analysis. The covariates we will collect include the number of health education lessons related to alcohol, the school neighborhood socioeconomic factors as extracted from 2011 Hong Kong Population Census, and the school academic quality as operationalized by the university admission rate for each school.

Results

The project was funded by the Health and Medical Research Fund of the Food and Health Bureau, Hong Kong government, in July 2015. Enrollment started September 2015, and results are expected by July 2017.

Discussion

Principal Considerations

Alcohol consumption is prevalent among adolescents in Hong Kong. The prevalence of underage drinking is rising globally, according to the World Health Organization. The rise of underage drinking in Hong Kong has been particularly alarming since the alcohol duty reduction in 2008. It is therefore of the utmost importance that children and adolescents be informed of the harmful effects of excessive alcohol use, particularly at a young age.

The aim of the proposed study is to find a cost-effective way of tackling the problem. With the Internet increasingly being recognized as a practical and cost-effective platform for health information delivery, we expect our Internet-based intervention to significantly alter adolescents' attitudes towards alcohol. It is important to provide accurate alcohol-related knowledge early in adolescence. Research shows the correlation between attitudinal and behavioral changes. Promoting better attitudes toward alcohol use among adolescents may lead to changes in drinking behavior, thereby mitigating the local underage drinking problem.

Conclusion

The local resources available for school-based alcohol education are relatively minimal. The proposed study will offer an innovative, cost-effective method of raising adolescents' awareness of the harmful effects of excessive alcohol assumption. The project will be carried out in collaboration with an academic institution and a non-government organization and will involve shared resources, the exchange of best practices, and joint efforts towards sustainability. In the long term, the aim is for the online alcohol education platform to be funded on an ongoing basis and to be incorporated into Hong Kong's mainstream secondary school health education curriculum. The platform can also be adapted to deliver health-related information in other learning areas such as physical activities, drug use, and safe sex in the near future.

Conflicts of Interest

None declared.

References

1. US Department of Health & Human Services. 2006. Why do adolescents drink, what are the risks, and how can underage drinking be prevented? URL: http://pubs.niaaa.nih.gov/publications/AA67/AA67.pdf [accessed 2016-05-12] [WebCite Cache ID 6hRQH62L1]
2. Miller TR, Levy DT, Spicer RS, Taylor DM. Societal costs of underage drinking. J Stud Alcohol 2006 Jul;67(4):519-528. [Medline: 16736071]
3. Kelder SH, Perry CL, Klepp KI, Lytle LL. Longitudinal tracking of adolescent smoking, physical activity, and food choice behaviors. Am J Public Health 1994 Jul;84(7):1121-1126. [Medline: 8017536]
4. Jefferis BJMH, Power C, Manor O. Adolescent drinking level and adult binge drinking in a national birth cohort. Addiction 2005 Apr;100(4):543-549. [doi: 10.1111/j.1360-0443.2005.01034.x] [Medline: 15784069]
5. Cleveland MJ, Feinberg ME, Jones DE. Predicting alcohol use across adolescence: relative strength of individual, family, peer, and contextual risk and protective factors. Psychol Addict Behav 2012 Dec;26(4):703-713 [FREE Full text] [doi: 10.1037/a0027583] [Medline: 22390336]
6. National Institute of Open Schooling. Adolescence and its challenges URL: http://www.nios.ac.in/media/documents/secpsycour/English/Chapter-11.pdf [accessed 2016-05-12] [WebCite Cache ID 6hRQPSoL8]
7. Leung L. Impacts of Net-generation attributes, seductive properties of the Internet, and gratifications-obtained on Internet use. Telematics and Informatics 2003;20(2):107-129.
8. World Health Organization. 2004. Global Status Report on Alcohol 2004 URL: http://www.who.int/substance_abuse/publications/global_status_report_2004_overview.pdf [accessed 2016-05-12] [WebCite Cache ID 6hRQQ5fTK]

9. US Department of Health and Human Services. Results from the 2011 National Survey on Drug Use and Health: Summary of National Findings. 2012. URL: http://www.samhsa.gov/data/nsduh/2k11results/nsduhresults2011.htm [accessed 2016-05-12] [WebCite Cache ID 6hRQTSyEG]
10. World Health Organization. 2004. Global Status Report on Alcohol 2004 - Republic of Korea URL: http://www.who.int/substance_abuse/publications/en/republic_of_korea.pdf [accessed 2016-05-12] [WebCite Cache ID 6hRQsNRFb]
11. Department of Health of Hong Kong. Child Health Survey 2005-2006. 2010. URL: http://www.chp.gov.hk/files/pdf/chs_eng.pdf [accessed 2016-05-19] [WebCite Cache ID 6hdFLyGjR]
12. Narcotics Division of Security Bureau of Hong Kong. The 2008/2009 Survey of Drug Use among Students. 2009. URL: http://www.nd.gov.hk/pdf/survey_drug_use/2008-2009/Report.pdf [accessed 2016-05-19] [WebCite Cache ID 6hdFSbx84]
13. Ho D. Growing Trends and correlates of adolescent alcohol drinking in Hong Kong: Uncontrolled and Uncontrollable? 2011 Presented at: The 3rd Hong Kong Public Health Forum; 2011; Hong Kong.
14. Webb T, Joseph J, Yardley L, Michie S. Using the internet to promote health behavior change: a systematic review and meta-analysis of the impact of theoretical basis, use of behavior change techniques, and mode of delivery on efficacy. J Med Internet Res 2010;12(1):e4 [FREE Full text] [doi: 10.2196/jmir.1376] [Medline: 20164043]
15. Trusov M, Bucklin R, Pauwels K. Effects of word-of-mouth versus traditional marketing: findings from an internet social networking site. Journal of Marketing 2009 Sep;73(5):90-102.
16. Ip P, Lam T, Chan S, Ho F, Lo L, Chiu I, et al. Use of Internet viral marketing to promote smoke-free lifestyles among Chinese adolescents. PLoS One 2014;9(6):e99082 [FREE Full text] [doi: 10.1371/journal.pone.0099082] [Medline: 24911010]
17. Ajzen I. The theory of planned behavior. Organizational Behavior and Human Decision Processes 1991 Dec;50(2):179-211. [doi: 10.1016/0749-5978(91)90020-T]
18. Miller TE, Booraem C, Flowers JV, Iversen AE. Changes in knowledge, attitudes, and behavior as a result of a community-based AIDS prevention program. AIDS Educ Prev 1990;2(1):12-23. [Medline: 2386650]
19. Machin D, Campbell M, Tan SB, Tan SH. Sample size tables for clinical studies. New York: John Wiley & Sons; 2009.
20. Siddiqui O, Hedeker D, Flay BR, Hu FB. Intraclass correlation estimates in a school-based smoking prevention study. Outcome and mediating variables, by sex and ethnicity. Am J Epidemiol 1996 Aug 15;144(4):425-433 [FREE Full text] [Medline: 8712201]
21. Ajzen I. Theory of planned behavior. In: Van Lang P, Kruglanski A, Higgins E, editors. Handbook of Theories of Social Psychology, Volume One. Thousand Oaks, CA: Sage Publications; 2011:438.
22. Petty R, Cacioppo J. Communication and persuasion: Central and peripheral routes to attitude change. NY: Springer; 1986.
23. Centers for Disease Control and Prevention. Global School-based Student Health Survey. 2013. URL: http://www.cdc.gov/gshs/index.htm [accessed 2016-05-12] [WebCite Cache ID 6hRRIhNU2]
24. Centers for Disease Control and Prevention. Behavioral Risk Factor Surveillance System Questionnaire 2013. URL: http://www.cdc.gov/brfss/questionnaires/pdf-ques/2013%20BRFSS_English.pdf [accessed 2016-05-12] [WebCite Cache ID 6hRRJPIz0]
25. Francalanci C, Chiassai S, Ferrara G, Ferretti F, Mattei R. Scale for the measurement of attitudes towards alcohol. Alcohol Alcohol 2011;46(2):133-137 [FREE Full text] [doi: 10.1093/alcalc/agq094] [Medline: 21273299]
26. Demaio AR, Dugee O, Amgalan G, Maximenco E, Munkhtaivan A, Graeser S, et al. Protocol for a national, mixed-methods knowledge, attitudes and practices survey on non-communicable diseases. BMC Public Health 2011;11:961 [FREE Full text] [doi: 10.1186/1471-2458-11-961] [Medline: 22208645]

Abbreviations

ELM: Elaboration Likelihood Model
ICC: intraclass correlation

Edited by G Eysenbach; submitted 04.08.15; peer-reviewed by C Giraud-Carrier, G Kok; comments to author 09.10.15; revised version received 14.10.15; accepted 03.01.16; published 01.06.16.

Please cite as:
Ip P, Chan KL, Chow CB, Lam TH, Ho SY, Wong WHS, Wong MFY
An Internet-Based Intervention to Promote Alcohol-Related Attitudinal and Behavioral Change Among Adolescents: Protocol of a Cluster Randomized Controlled Trial
JMIR Res Protoc 2016;5(2):e103
URL: http://www.researchprotocols.org/2016/2/e103/
doi:10.2196/resprot.5001
PMID:27252072

Protocol

Using Behavioral Intervention Technologies to Help Low-Income and Latino Smokers Quit: Protocol of a Randomized Controlled Trial

Ricardo F Muñoz[1], PhD; Eduardo L Bunge[1], PhD; Alinne Z Barrera[1], PhD; Robert E Wickham[1], PhD; Jessica Lee[2], BA

[1]Palo Alto University, Palo Alto, CA, United States

[2]i4health, Palo Alto, CA, United States

Corresponding Author:
Ricardo F Muñoz, PhD
Palo Alto University
1791 Arastradero
Palo Alto, CA,
United States
Phone: 1 800 818 6136
Fax: 1 650 433 3888
Email: rmunoz@paloaltou.edu

Related Article:

This is a corrected version. See correction statement: http://www.researchprotocols.org/2016/3/e189/

Abstract

Background: The Institute for International Internet Interventions for Health at Palo Alto University proposes to develop digital tools specifically to help low-income English- and Spanish-speaking smokers to quit. Individuals from lower-income countries and those with lower social status quit at lower rates than those from high-income countries and those with higher social status.

Objective: We plan to launch a project designed to test whether a mobile-based digital intervention designed with systematic input from low-income English- and Spanish-speaking smokers from a public-sector health care system can significantly improve its acceptability, utilization, and effectiveness.

Methods: Using human-centered development methods, we will involve low-income patients in the design of a Web app/text messaging tool. We will also use their input to improve our recruitment and dissemination strategies. We will iteratively develop versions of the digital interventions informed by our human-centered approach. The project involves three specific aims: (1) human-centered development of an English/Spanish smoking cessation web app, (2) improvement of dissemination strategies, and (3) evaluation of resulting smoking cessation web app. We will develop iterative versions of a digital smoking cessation tool that is highly responsive to the needs and preferences of the users. Input from participants will identify effective ways of reaching and encouraging low-income English- and Spanish-speaking smokers to use the digital smoking cessation interventions to be developed. This information will support ongoing dissemination and implementation efforts beyond the grant period. We will evaluate the effectiveness of the successive versions of the resulting stop smoking Web app by an online randomized controlled trial. Increased effectiveness will be defined as increased utilization of the Web app and higher abstinence rates than those obtained by a baseline usual care Web app.

Results: Recruitment will begin January 2016, the study is intended to be completed by summer 2018, and the results should be available by fall 2019.

Conclusions: This study will provide useful knowledge in developing, testing, and disseminating mobile-based interventions for low-income smokers.

ClinicalTrial: ClinicalTrials.gov NCT02666482; https://clinicaltrials.gov/ct2/show/NCT02666482 (Archived by WebCite at http://www.webcitation.org/6gtcwaT28)

(JMIR Res Protoc 2016;5(2):e127) doi:10.2196/resprot.5355

KEYWORDS

smoking cessation; Web app; human-centered design; recruitment; dissemination

Introduction

Background

Smoking is a major health problem. Globally, it is the number one preventable cause of premature death. The World Health Organization estimates as many as 1 billion tobacco-related deaths will occur in this century if smoking trends remain stable [1]. Smoking has a disproportionate impact on low-income populations. Most of the predictable deaths due to smoking are expected to occur in populations from middle- and low-income countries [2]. The state of California has a large proportion of immigrants and descendants of immigrants from such countries, with the largest proportion being from Latin America [3]. As of March 2014, California residents of Latino ethnicity became the largest ethnic group in the state (39% of the total); white residents accounted for 39% of the population [4]. It is estimated that 29% of Californians speak Spanish [5]. Given that Latinos are now the largest ethnic group in California and they are overrepresented in the low-income population of the state, efforts to reach low-income individuals in California must take into account the preferences of Spanish- and English-speaking Latinos.

Low-income populations in the United States have higher smoking rates than high-income populations [6]. Although the overall smoking rate in California is now one of the lowest in the country (14% vs 21%), low-income groups have higher rates. In California, smoking prevalence is 4 times higher among low socioeconomic status (SES) populations than high SES populations (17% vs 4%, respectively) [7]. Safety-net hospitals that serve more low SES patients also reflect disproportionately high smoking rates among their patients. According to Benowitz et al [8], 40% of inpatients surveyed at San Francisco General Hospital, the hospital serving the San Francisco Health Network (SFHN), were active smokers, and 32% of those who denied smoking were found to have had significant exposure. Spanish-speaking groups in California have intermediate rates (13%) [9]; however, Spanish-speaking smokers have lower rates of utilization of smoking cessation aids [10,11]. In a recent paper by our group reviewing 10 years of global online studies [12], we found that nicotine replacement therapies were used by 41.70% of English-speaking smokers but only 20.61% of Spanish-speaking smokers. The nicotine patch was used by 19.50% of English speakers versus 7.70% of Spanish speakers. The same is true for smoking cessation groups: only 2.10% of English speakers and 1.70% of Spanish speakers used them. The lower utilization among this sample of Spanish-speakers could be attributed to limited access to smoking cessation aids in other countries. In the United States, however, access to such aids is widespread, yet utilization remains low among this disproportionally impacted population. A systematic approach that explicitly addresses this well-documented instance of disparities in utilization of smoking cessation tools is called for. We propose to address this issue by systematically involving low-income English- and Spanish-speaking smokers in the development and testing of a new smoking cessation Web app. We intend to eventually disseminate the resulting Web app to low-income smokers in other regions of the country and the world.

Prior Research and Interventions

Our work on smoking cessation with Spanish speakers began in the 1990s. With support from a grant from the National Cancer Institute (NCI) (Eliseo J. Pérez-Stable, principal investigator), we attempted to carry out a traditional smoking cessation study involving face-to-face group interventions. Initial attempts to engage smokers in traditional face-to-face cessation groups were not successful. However, an alternative strategy of using surface mail was far more successful in reaching smokers. We found that our smoking cessation guide (*Guía Para Dejar de Fumar*) yielded 11% quit rates at 3 months, and adding a brief mood management intervention doubled the quit rate to 23% [13]. Our experience with this study highlighted the importance of finding alternate means of reaching Latino smokers and providing them with resources that could be effective when used at home and could be offered to the community at no charge. Seeing the possibilities for reaching people at home using the Internet, we submitted a grant to California's Tobacco-Related Disease Research Program (TRDRP) in 1997 proposing developing and testing an online intervention to help Spanish- and English-speaking smokers in California stop smoking. Our team has received three TRDRP grants which have resulted in 19 publications to date. Below we summarize our studies and list several lessons learned from our experience. The current grant proposal is intended to implement the logical next steps in our research program based on what we have learned thus far.

Our studies have yielded proof of concept that efficacy of Internet interventions for smoking cessation are higher than those reported for placebo patches (9% at 6 months [14]) and can approach those reported for the nicotine patch (6-month quit rates of 22% [14]) and smoking cessation groups (6-month quit rates of 27% for American Lung Association groups and 24% for American Cancer Society groups [15]). Our most robust missing=smoking abstinence data (a conservative convention in which all participants with missing data at any follow-up are presumed to be smoking which allows us to include all randomized participants in outcome analyses, similar to intention-to-treat approaches) at 12 months are 20% for Spanish speakers and 21% for English speakers for smokers with mean Fagerström scores of 5.2 [16], similar to those scores found in face-to-face smoking cessation trials by Hall et al [17].

One of our surface mail interventions was labeled *Tomando Control de su Vida* (*Taking Control of Your Life*) which led to the TC designation for the series of studies that followed. TC1 was the NCI-funded randomized controlled trial (RCT) conducted via surface mail (entirely in Spanish) in which we

found that a smoking cessation guide together with a mood management intervention significantly improved quit rates [13]. In order to increase the number of smokers we could potentially reach, we obtained TRDRP funding to adapt our materials into an automated self-help Internet intervention, the San Francisco Stop Smoking website. This site was used in several online randomized controlled and participant preference trials (TC2, TC3, and TC4).

The TC2 studies [18] involved over 4000 smokers from 74 countries and examined outcome (self-reported 7-day abstinence) and mechanisms related to outcome (the impact of major depressive episodes on the likelihood of quitting). It included four substudies. Substudies 1 and 2 evaluated the online version of the smoking cessation guide, and substudies 3 and 4 were randomized trials comparing the guide plus ITEMs (individually timed educational messages) to the guide plus ITEMs and a mood management course. At 6 months, self-reported 7-day abstinence rates using the missing=smoking convention varied from 5.60% (39/702, study 2) to 25.56% (38/146, study 4) in the four substudies. The guide plus ITEMs condition tended to have higher quit rates. The best missing=smoking abstinence rate (28.10%, 41/146; study 4) at 3 months was found in a sample of Spanish-speaking smokers.

The TC3 studies [18,19] consisted of a totally automated self-help smoking cessation site programmed to randomly assign participants who signed consent to one of four conditions. Each condition added new elements: condition 1 consisted of the static smoking cessation guide, condition 2 consisted of the guide plus email reminders to return to the site, condition 3 added cognitive behavioral mood management lessons, and condition 4 added a virtual group (an asynchronous bulletin board). The first phase of the trial included the first 1000 participants recruited (from 68 countries); 500 Spanish-speaking and 500 English-speaking adult Internet users were randomized to the four study conditions and, in order to reduce attrition at follow-up, were contacted by phone if they did not provide 1-, 3-, 6-, and 12-month follow-up data online. With the addition of phone follow-ups, we obtained follow-up rates of 73.50% (735/1000), 66.10% (661/1000), 57.30% (573/1000), and 69.20% (692/1000) at 1-, 3-, 6-, and 12-month follow-ups, respectively. There were no significant differences among the four conditions. However, the overall 12-month 7-day missing=smoking abstinence rates were 20.20% (101/500) for Spanish speakers and 21.00% (105/500) for English speakers.

After recruiting the first 1000 participants, we maintained the TC3 website online, and we conducted a totally automated RCT (that is, we did not follow participants via the phone) in which 16,430 participants from 165 countries were recruited and followed entirely via automated emails [19]. The totally automated trial had, as expected, a much greater attrition rate than the initial TC3 trial. For month 1 follow-up, 39.95% (6563/16,430) of participants provided data. This number was reduced to 30.38% (4992/16,430), 23.21% (3813/16,430), and 21.95% (3606/16,430) for follow-ups at months 3, 6, and 12, respectively. These numbers were comparable with those obtained in the earlier TC3 study, in which 36.37% (4952/13,617), 26.92% (3666/13,617), 20.77% (2828/13,617), and 18.98% (2585/13,617) of participants who never received any live follow-up returned at months 1, 3, 6, and 12, respectively. The self-reported 7-day observed quit rates ranged from 36.18% (2239/6189) at 1 month to 41.34% (1361/3292) at 12 months. The 7-day missing=smoking abstinence rates ranged from 13.63% (2239/16,430) at 1 month to 8.28% (1361/16,430) at 12 months.

In the TC4 studies [20] we morphed the site into a participant preference site. The Spanish/English San Francisco Stop Smoking site was designed to be open. Specifically, any Spanish- or English-speaking smoker 18 years of age or older anywhere in the world could enter the study and select (rather than be randomized to) any of the intervention elements tested in our previous studies. Our intent was to demonstrate that Internet interventions tested in RCTs can be readily adapted to serve as universal health care resources. During the first year of the study, 94,158 individuals from 152 countries and territories visited the site. The participant preference design allowed us to examine quit rates obtained when users could choose from all elements tested in previous RCTs. Participants were able to personalize the site by choosing among 9 site elements (e.g., stop smoking guide, reminder emails, journal, mood management intervention, virtual group). Results from the first year of recruitment yielded higher observed quit rates (odds ratio 1.30) than the previous RCT (TC3) when controlled for individual demographic and smoking characteristics [20]. Of note, the utility of this version of the site as an adjunct to traditional health care has been tested by an independent research group. Gallego and colleagues [21] used the San Francisco Stop Smoking site with smokers at a clinic in Spain as an adjunct to standard pharmacological treatment and report posttreatment abstinence rates of 78.13% (25/32) and 1-year follow-up abstinence rates of 53.13% (17/32). This study suggests that our digital tools can serve as adjuncts to usual primary care, motivating us to involve the SFHN as described below.

Our latest study was on a new sample of participants who were recruited for 18 additional months to the San Francisco Stop Smoking site. A total of 164,182 individuals from 168 countries visited the site during this period: 27,163 were screened for eligibility; 9348 signed consent; 7407 completed the baseline survey; and 1431, 901, 595, and 318 left 1-, 3-, 6-, and 12-month data, respectively. Observed quit rates were 39.20% (561/1431), 43.51% (392/901), 45.71% (272/595), and 50.31% (160/318), respectively. The TC4 studies show that Internet interventions can yield quit rates similar to those found in earlier RCTs and can be disseminated to literally thousands of users across the world with minimal additional costs. We have begun thinking of them as MOOIs (massive open online interventions) [22], similar to the well-known MOOCs (massive open online courses). The current proposal will help us design a MOOI with greater reach than our previous website by incorporating preferences that take into account demographic trends in technology access and use [23]. Specifically, we will recruit smokers with lower income and educational levels to help us design a Web app that is more accessible and acceptable to them.

Clinical Problem

We have argued that Internet interventions can help reduce health disparities by reaching those who do not have access to smoking cessation aids. Concerns have been raised that, although this approach may be increasing the reach of evidence-based smoking cessation interventions across large segments of the population and thus reducing health disparities across countries, digital interventions may actually increase health disparities. The reason for this concern is that more highly educated people may be more likely to use these interventions and perhaps more likely to benefit from them. To address this concern, we have compared quit rates for participants with differential socioeconomic standing as well as for participants from countries with different gross domestic products. We tested whether smokers in richer countries and smokers higher in self-reported SES are more likely to quit. Our results show that, indeed, our Internet interventions preferentially benefit individuals from countries with higher gross domestic products and/or with higher individual socioeconomic standing [24]. This may be due to reasons other than the availability of technology because all participants had access to the online intervention. It may be that the ways in which we have designed the interventions do not take into account the characteristics of smokers with lower incomes and lower educational levels. These findings are the motivation for the current study. We have received TRDRP funding to revise our smoking cessation digital tools so that they address the unique interests and needs of low-income and Latino smokers in California with the hope that the modifications made will generalize to other smokers from similar socioeconomic levels. We conceptualize the SFHN, described in the next paragraph, as serving as a "magnifying glass" that will allow us to learn how to best serve this population with our digital tools so that when we make the tools available worldwide, the range of smokers we will be able to reach and be effective with will be greater.

The SFHN is the city's only complete care system. It consists of 14 primary care clinics throughout the city as well as San Francisco General and Laguna Honda hospitals. Between July 1, 2013, and June 30, 2014, the SFHN served 72,379 unduplicated patients who had 354,445 outpatient visits. Almost all were covered by Medi-Cal and/or Medicare (251,616/354,4445, 71.00%) or were uninsured (101,466/354,445, 28.60%). Only 60.10% (43,460/72,379) reported English as their primary language; 22.01% (15,905/72,379) reported Spanish as theirs. The next largest language group was Cantonese (8042/72,357, 11.10%) followed by an additional 37 language groups, all at 1.20% (853/72,357) or less. Latinos are the largest ethnic group being served, at 32.60% (23,575/72,357) of the total, followed by Asians (25.20%, 18,206/72,357), whites (19.01%, 13,721/72,357), African Americans (18.30%, 13,214/72,357), and other groups accounting for less than 2.20% (1585/72,357) each. Slightly more than half of the patients are women (53.10%, 38,398/72,357). Those between the ages of 18 and 64 years (the group most likely to participate in our studies) compose 69.40% (50,355/72,357) of the population. Smoking rates are likely higher than for the general San Francisco population (13%), but rates are not available for the SFHN as a whole. Benowitz et al [8] have found that 40% of San Francisco General Hospital inpatients were active smokers, and of those who denied smoking, an additional 32% were found to have significant exposure to nicotine. Thus the smoking rate in primary care patients is likely higher than 13% but less than 40%. Assuming a 20% smoking rate, there are likely to be 8247 smokers who are aged 18 to 64 years and speak English or Spanish.

Estimates of how many SFHN patients use digital technology stem from a published report by Schickedanz et al [25] who surveyed 416 patients in waiting rooms of SFHN clinics and report that 71% were interested in using electronic communication with health care providers and 19% were already doing so. The survey was conducted in English, Spanish, Cantonese, and Mandarin; 87% (52/60) of Spanish speakers were interested in using email to communicate with their health care provider compared to 77% (164/213) of English speakers, 38% (23/61) of Cantonese speakers, and 75% (38/51) other. It appears, then, that interest in digital tools is high even in this low-income population. We have chosen to recruit SFHN patients who own smartphones because we believe that by 2018 most will do so and we want our intervention to be relevant for that time.

We propose to recruit the following number of SFHN smokers who use smartphones: face-to-face field studies (ethnographies and usability tests), 30 in year 1 and 30 in year 2 and online studies, 50 in year 1, 100 in year 2, and 200 in year 3. We believe recruiting 410 out of more than 8000 smokers over a 3-year period is feasible.

We will also be doing open recruitment of smokers who own smartphones throughout California at the following rate: 100 in year 1, 200 in year 2, and 800 in year 3. This effort will provide a large enough sample to carry out adequately powered outcome studies as described in the Methods section.

The proposed study is based on the premise that we cannot presume to know what would be best for our intended users without engaging them. To build a smoking cessation intervention that will be used and be effective with low-income smokers aged 18 years and older, including Spanish-speaking smokers, we must build a deep understanding of their needs and values.

We propose to carry out a research study inspired by the "rapid, responsive, relevant (R3) research" approach described by Riley and colleagues [26]. The R3 approach urges researchers to consider shifting away from a narrowly focused and long-term RCT approach and to instead use techniques that reflect and integrate stakeholder needs, use innovative designs and methods for evaluation, and emphasize widespread immediate implementation. A successful R3 research approach is scientifically rigorous and a good fit for addressing mental health disparities in underserved communities such as low-income Latino smokers, where uptake of empirically supported interventions has failed or is not relevant to the cultural or technological characteristics of the target population.

Lessons Learned From a 16-Year Online Research Program

There are more than 1.1 billion smokers worldwide [27]. We will never train enough health care providers to administer adequate health care for all who need it if we continue our reliance on consumable interventions (ie, interventions that once used cannot be used again). For example, the nicotine patch can only be used once, and the time spent counseling a patient to quit smoking cannot be used again to help another patient. To reduce health disparities, we need interventions which can be used again and again without losing their therapeutic power, can reach people even if local health care systems cannot or will not provide them with needed health care, and can be shared widely without taking resources away from the populations for whom the interventions were developed.

A major advantage of fully automated self-help digital interventions is their low cost. Bringing a medication to market costs hundreds of millions of dollars [28], while developing a digital intervention may cost as little as a few thousand dollars for a simple site. Costs of testing a site in RCTs may run in the hundreds of thousands of dollars but generally cost less per trial participant than face-to-face interventions. The differences in per-person costs of administering the intervention are even more impressive: a dose of a medication has a minimal cost even when bought in large quantities, but the marginal cost of providing a self-help automated Internet intervention to one additional user eventually approaches zero. The cost of hosting the site remains steady once the server has made the site available to say, 50,000 users, and the cost of serving one more user becomes negligible. This makes it possible to share the site with people worldwide. We have shown that, with TRDRP funding, we have been able to help California smokers and, at no additional cost, smokers all over the world.

Our research group has shown that unguided interventions focused on depression have significantly reduced depressive symptoms [29]. Our TC studies were all conducted as self-help automated interventions. Thus, we propose to continue to focus on automated interventions, moving from desktop- or laptop-accessible websites to mobile devices (mostly smartphones) which can access Web apps and text messaging throughout the smoker's day. It is true that digital interventions do not need to be fully automated. For example, Internet interventions can employ staff to provide support, information, and encouragement to users. However, such guided interventions involve staff time, which places them in the category of consumable interventions. Such interventions are generally limited to the geographical area that provides the salary for the support staff; offices, equipment, and communication tools; and organizational infrastructure to provide the guidance. Once grant funding ends, the guided intervention has to end. By focusing our work on self-help automated interventions, we increase the likelihood that we will be able to keep these interventions available to people beyond the grant period and beyond the geographical area covered by the grant.

When the principal investigator first began to work at San Francisco General Hospital in 1977, he believed that, given ten years of recruiting and training new Spanish-speaking health care providers, we would be able to hire enough Spanish speakers to meet the demand for services in our hospital. More than 39 years later, we are still having difficulty recruiting Spanish-speaking providers. We are often forced to either not provide Spanish speakers needed services or to use interpreters to communicate with them. Smoking cessation groups in Spanish are hard to maintain. Our group has made the development of interventions in both English and Spanish (and, whenever possible, in other languages) one of its major priorities. Thus, this proposal focuses on low-income Latino smokers, most of whom speak Spanish and have low English proficiency.

When we began our work with online smoking cessation tools, we used skeuomorphic designs. A skeuomorph is a physical ornament or design on an object made to resemble another material or technique. The lights of an electric candelabra are fashioned in the shape of traditional candles, but the candle shape is not necessary to provide light. The shutter sound on cameras built into mobile devices and the floppy disk icons used on computers to save documents are, likewise, skeuomorphs. We included an 8-session mood management intervention modeled after face-to-face clinical appointments, and few people actually completed the sessions. In this proposal, we are attempting to be mindful of not limiting our designs using skeuomorphic thinking [30]. We propose to observe how digital tools are used by the population we are choosing to serve in their day-to-day lives and design our interventions in ways that are likely to fit the behavioral patterns we observe.

In a recent paper on rapid, responsive, relevant research [26], Riley and colleagues point out that a National Institutes of Health research grant designed in 2005 and awarded in 2006 would miss at least six important consumer technology advancements between its award and its publication in 2012, including the Wii, iPhone, iPad, and Siri. In our earlier projects, we designed a website, kept it as originally designed for the length of the RCT, and continued to use it beyond the grant period. There are advantages to that strategy, of which the most obvious is cost. Keeping the site originally developed with TRDRP funding awarded in 1998 still operational in 2014 was a rather remarkable example of good use of funds. However, the site eventually looked outdated, and technology is moving at a much faster rate than it did in 1998. It is important that our digital interventions be much more flexible than they were in the late 1990s. We propose an agile development process that will allow us to shape our intervention so that it is not frozen at the start of the grant period and can become increasingly responsive to the needs and preferences we discover in our population of interest. We intend for the Web app we develop to have a current look and feel when the grant ends in 2018. Specifically, we will engage stakeholders (low-income and Latino smokers and their health care providers in a large urban public-sector health network) in the development of the smoking cessation interventions with the goal of increasing follow-up retention and disseminating results so that other communities can take advantage of our interventions.

Objectives

Aim 1: Human-Centered Development of an English/Spanish Smoking Cessation Web App

We will develop iterative versions of a digital smoking cessation tool (a Web app with text messaging components) that is highly responsive to the needs and preferences of low-income English- and Spanish-speaking smokers. Development will take place with systematic input from patients who are part of the SFHN, which serves 70,000 mostly low-income individuals.

Aim 2: Improvement of Dissemination Strategies

Input from SFHN patients will identify effective ways of reaching and encouraging low-income English- and Spanish-speaking smokers to use the digital smoking cessation interventions that are developed. This information will support ongoing dissemination and implementation efforts beyond the grant period.

Aim 3: Evaluation of Resulting Smoking Cessation Web App

We will evaluate the effectiveness of the successive versions of the resulting stop smoking Web app by recruiting smokers at two levels—within the SFHN and throughout the state of California—culminating in an online RCT. Increased effectiveness will be defined as increased use of the Web app and higher abstinence rates than those obtained by a baseline (usual care) Web app.

Hypotheses

H1: Utilization of the final smoking cessation Web app (number of screens viewed, time spent using app, and amount of data entry) will be significantly higher than that of the baseline Web app.

H2: Recruitment based on dissemination strategies derived from ethnographic interviews will reach a significantly higher number of participants for successive online studies.

H3: Abstinence rates (7-day self-reported abstinence) will be significantly greater for the final Web app than for the baseline Web app.

Methods

Conceptual Foundations of the Research Design

Design Thinking and Health Care

Design thinking is a user-centered approach to innovation that considers and integrates the needs of people within the possibilities and reach of technology [31,32]. Design thinking is not just for designers—it is a mindset and process of problem solving that aims to identify the core tenets that drive a specific behavior. This knowledge is then used to solve complex problems and find desirable solutions. The emerging trend of applying user-centered design to health care problems has generated promising results [33]. Skinner et al [34] employed a user-centric approach in developing a youth smoking prevention and cessation website and demonstrated in a large-scale RCT that the intervention yielded positive effects. The Center for Innovation at the Mayo Clinic uses design thinking as a core process in creative problem solving that goes beyond process analysis and quality improvement [35]. The Innovation Consultancy at Kaiser Permanente used design thinking to improve the quality of patient care during nursing shift changes [36]. The Venice Family Clinic, a community health care center in California, used the design thinking process to redesign their clinic and patient experience for low-income families [37].

Design Thinking Processes

There are many variations of user-centered design processes, but they all uphold the same core tenets of being human-centered, prototype-centric, and iterative. The design thinking model presented by Kembel [38], notably different for its explicit treatment of empathy, is most relevant for the goals of this study. In this model, empathy arises from a deep understanding of the stakeholders and their needs and requires an anthropological approach to understanding users and their environments. In this study, we will leverage the design thinking process presented by Kembel to create and distribute a digital intervention for English- and Spanish-speaking low-income smokers. The model consists of a 5-step cyclic process.

- Empathize: fully understand the experience of the intended user via observation, interaction, and immersion in their experiences. This entails understanding their lifestyle, physical and emotional needs, how and why they do things, and what is meaningful to them as it relates to their smoking behavior. The goal is to uncover insights that will guide design and distribution of our digital intervention.
- Define: process and synthesize data collected from the Empathize step to outline connections and patterns of our target users. The goal is to develop a defined, meaningful, actionable problem statement that will provide focus when developing and evaluating proposed solutions.
- Ideate: generate a variety of possible solutions to provide source material for building prototypes. It is critical during this step to defer judgment and push for a wide range of ideas, allowing us to think beyond obvious existing solutions. The best solution is eventually determined during the prototyping and testing steps. We propose to systematically involve smokers and their health care providers in this step.
- Prototype: transform ideas into physical forms so users can interact with them. Initial low-fidelity prototypes (eg, sketch drawings, storyboards) are quick and inexpensive ways for the team to learn how well a solution aligns with the user needs. Each iteration moves the team closer to a final, user-defined solution.
- Test: observe and elicit feedback to learn more about the user, refine prototypes, and gain clarity on how well the solution addresses the problem statement.

Research Design and Methods

Framework

Human-Centered Development

We will develop iterative versions of digital interventions for smoking cessation in Spanish and English that are highly responsive to the needs and preferences of low-income and

Latino smokers. Development will take place with user input from patients who are part of the SFHN. We will use the 5-step cyclic design thinking process described above to understand low-income smokers and iteratively develop and refine an effective digital smoking cessation Web app that they will use.

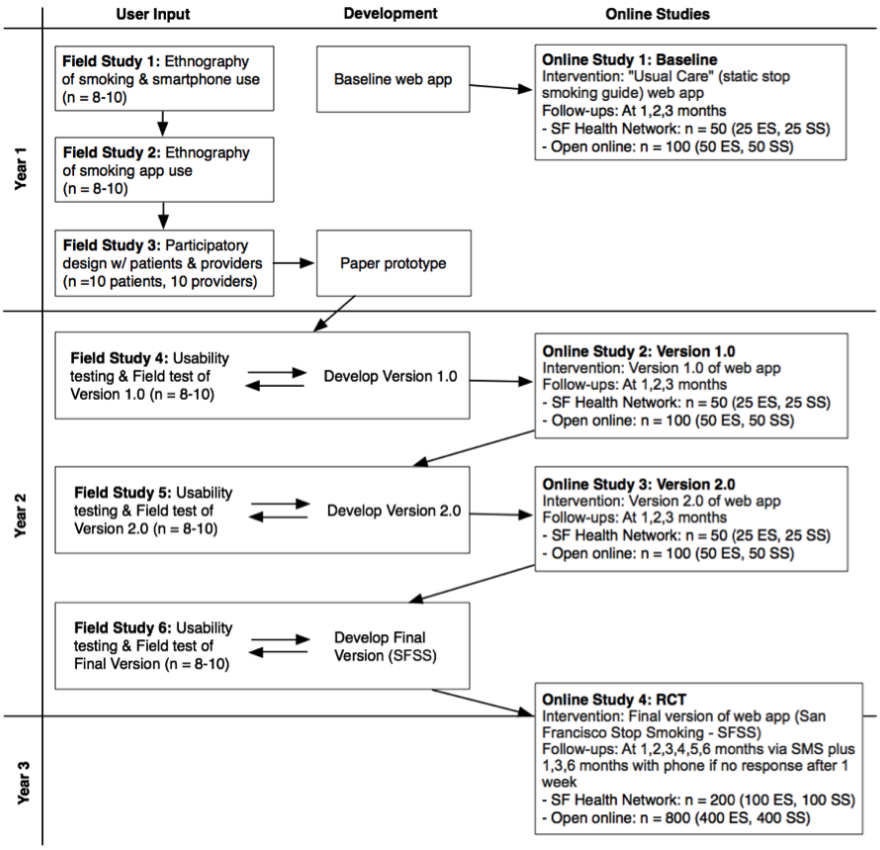
Dissemination Strategies

We will include in the ethnographic semistructured interviews questions regarding how the users found out about Web apps installed on their phones, how they use text messaging, and which digital smoking cessation tools they have used the most (if any). This information will guide the development of our recruitment and dissemination strategies both at the SFHN and at the state level.

Evaluation of the San Francisco Stop Smoking Web App

We will develop a baseline Web app and 3 successive versions of the user-centered Web app, the last of which will be evaluated in an RCT.

Figure 1. Flow of research study.



Methods

To ensure that our solution is based on a solid foundation, we will invest significant efforts during the initial Empathy step to understand our users. We will employ ethnographic methods to build a deep understanding of low-income English- and Spanish-speaking smokers. Research assistants will receive ethnography training (manuals and mock interviews) prior to going out into the field. We will conduct semistructured interviews pertaining to our themes of interest. Short interviews are hour-long semistructured interviews where research assistants will recruit patients from SFHN clinic waiting rooms to ask a set of questions related to their lifestyle and smoking habits. In-depth interviews will include a short interview plus a follow-up interview after a quit attempt and shadowing period of 3 hours in a natural location for the participant. Relevant themes include behaviors related to smoking, technology usage, personal lifestyle and social circles, how they get information (informing dissemination strategies), and personal values and motivations. All interviews will be audiorecorded and sent to third-party services for transcription.

Initial Ethnography (Empathy Step)

Recruitment

We will recruit 60 low-income participants aged 18 years or older who are members of the SFHN, use smartphones, and have been advised by their care providers to quit smoking or have tried to quit smoking at least once. They will be divided into four target groups (15 English-speaking men, 15 English-speaking women, 15 Spanish-speaking men, 15 Spanish-speaking women). These 60 participants will be asked to sign consent to participate in the shadowing process and short or in-depth interviews conducted by research assistants. We will also recruit 10 health care providers from the SFHN (eg, smoking cessation counselors, nurses, physicians) to contribute to the Ideate step by taking part in a prototyping exercise (see Figure 1, Field Study 3).

Outputs and Qualitative Analysis

Our ethnographic methods will yield a large amount of transcribed material, screenshots, and other photographs showing the use of apps. Our qualitative analysis will involve developing and refining our themes, identifying quotes from participants that support each theme, and developing a coding system that will help us identify behavior patterns and draw conclusions that will inform the next step in the design process.

Implementing the User-Centered Design

Recruitment

SFHN patients will be recruited by research assistants at outpatient clinics. We will seek patients who own smartphones and intend to quit smoking in the next 3 months who either have been advised to quit smoking by their care provider or have tried to quit smoking at least once. Patients will be paid $25 per hour for their time for interviews as described in face-to-face studies below.

Procedures

User-centered design, development, and testing will be carried out as shown on Figure 1, with two interconnected processes running in parallel: face-to-face user input from SFHN smokers via ethnographic and field test methods and online studies that will include samples recruited from the SFHN and open online recruitment. In all studies, half of the participants will be English-speaking and half Spanish-speaking.

Field Studies

Recruitment

For every field study the eligibility criteria are 18 years of age and older, current smoker (any number of cigarettes per day), and English or Spanish speaker. We plan to recruit low-income participants (ie, those who have Medicare and/or Medi-Cal, the California state equivalent, or are uninsured). Six face-to-face field studies are planned.

Year 1

Field Study 1: Ethnographic Study of Naturalistic Smoking, Smoking Cessation Attempts, and Smartphone Use

We will use shadowing methods (observing smokers' actual behavior in their natural environment) plus semistructured interviews to learn how smokers think about their smoking behavior, how they attempt to quit, and how they use their smartphones (ie, how they find, download, install, and begin using apps).

Field Study 2: Ethnographic Study of Smoking Cessation App Use

We will recruit SFHN patients who have installed at least one smoking cessation app on their smartphones. We will use shadowing and semistructured interviews to study the use of smoking cessation apps participants have installed on their own. We will ask participants to install the baseline version of our Web app and use it for one week, scheduling follow-up interviews to learn about use patterns and reactions to the baseline Web app.

Field Study 3: Participatory Design Field Test

We will schedule two meetings, one in English and one in Spanish, with 5 SFHN smokers each, with the purpose of jointly working on the design of an ideal app to help them stop smoking. Groups will be facilitated by research staff familiar with Web apps to keep the group focused on the intended product. The result will be a paper prototype and sample screens developed on tablets to ensure that we are accurately rendering the patients' suggestions. In addition, we will schedule two meetings, one in English and one in Spanish, with 5 SFHN providers each (smoking cessation counselors, nurses, physicians), using the same procedure. The results of the four meetings will be shared with the development team as part of the creation of version 1.0.

Year 2

Field Study 4: Usability Field Testing for Version 1.0

Once the developers begin the design process, we will engage in iterative usability testing with 4 or 5 SFHN English speakers and 4 or 5 Spanish speakers. Their input will be incorporated in version 1.0, which will be subjected to limited online testing (Online Study 2).

Field Study 5: Usability Field Testing for Version 2.0

We will engage in iterative usability testing as version 2.0 is being developed to ensure that SFHN smokers have input into the new version, which will then be subjected to limited online testing (Online Study 3).

Field Study 6: Usability Field Testing for the Final Version of the San Francisco Stop Smoking Web App

We will carry out iterative usability testing of the final version to ensure that SFHN smokers have input. The final version will be tested in an RCT.

Online Studies

Online Study 1: Baseline (Usual Care) Web App

A Web app will be developed to test the data-gathering infrastructure for the subsequent apps and generate baseline information on four variables: recruitment rates, utilization of the app, follow-up completion rates, and quit rates. Usual care is described in the Intervention section. We will engage in focused recruitment of smokers from the SFHN (up to 25 English speakers and 25 Spanish speakers) as well as open online recruitment with California as our main target (up to 50 English speakers and 50 Spanish speakers). We will implement follow-up interviews to examine quit rates at 1, 2, and 3 months after enrollment in the study. We will use 3 text messages (identified as coming from the Stop Smoking Study) 2 days apart. The first question will ask "Have you smoked 1 or more cigarettes in the last seven days?" A no response will be interpreted as 7-day point prevalence abstinence. Additional questions will address 30-day abstinence, number of cigarettes smoked daily if not abstinent, and use of other smoking cessation tools.

Online Study 2: Version 1.0

We will implement the same procedure as Online Study 1. We will obtain suggestions from our field test participants as to how

to increase recruitment rates, for example, by modifying the wording in our social media announcements, the themes we touch upon in our radio and television interviews, the flavor of our public service announcements, word-of-mouth recruitment, the use of text messages to encourage enrollment, the wording of our search engine ads, and so on. We will use "tokens," as described below, to identify how the participant heard about the Web app. We will examine which of these sources yield the greatest increases in recruitment. We will also track overall recruitment, as measured by the speed with which we meet our recruitment goals.

Online Study 3: Version 2.0

We will repeat the procedure as in Online Studies 1 and 2.

Online Study 4: Randomized Controlled Trial

We will carry out an RCT comparing the final version of the San Francisco Stop Smoking Web App with the baseline Web app. The RCT will be powered to detect differences in utilization rates and 7-day point prevalence quit rates, as described in the Data Analysis section. We will carry out open online recruitment, with a target of 800 smokers (400 English speakers and 400 Spanish speakers), as well as focused SFHN recruitment, with a target of 200 smokers (100 English speakers and 100 Spanish speakers).

Open recruitment will focus on California smokers. We will target English- and Spanish-speaking smokers searching for information on smoking cessation online using social media recruitment efforts, appearances on radio and television shows (especially those likely to be watched by Latinos), and a limited amount of search engine ads. To target the latter, we will use information reported by Graham and others [39] in terms of the most cost-effective online sites to recruit Latinos. We will focus our recruitment advertising resources on areas of California that have large proportions of Latinos in order to oversample Spanish-speaking smokers.

SFHN recruitment involves providing fliers for patients in waiting rooms at the San Francisco General Hospital clinics. Waiting room staff will also be given the fliers so they can inform smoking patients about the study. Primary care physicians will be provided with Post-It–like prescription pads which will have information regarding how to obtain the smoking cessation Web app. We will provide tokens (code numbers) to be entered when the Web app is installed that will indicate the source of the referral in order to determine whether physician recommendations to use the Web app result in greater utilization and higher quit rates than standard fliers. These tokens will also distinguish SFHN users from users recruited via open online recruitment.

Digital Interventions

Baseline (Usual Care) Web App

Online Study 1 will test the data gathering aspects of the proposed Web app using a baseline usual care intervention consisting of a static smoking cessation guide, *Guía Para Dejar de Fumar*, tested in printed form in the Muñoz et al study [13]. The print version of the guide yielded an 11% quit rate at 3 months. We will upload the content of the guide to the baseline app, and it will serve to estimate baseline utilization and quit rates.

The San Francisco Stop Smoking Web App

This Web app will be developed with input from the SFHN population. Thus, we are not able to provide a concrete description of the app at this time. However, our work to date has been guided by social learning/social cognitive theory and uses cognitive behavioral principles that will guide our thinking. Based on our experience with Web-based apps, we have found a number of features are valued by users. Users want information provided in a number of ways (text, graphics, audio, video, *telenovela*-type stories). Goal setting is important, so we will be looking for ideas for interactive goal-setting tools. Notifications are useful for bringing people back to the site or Web app, and we will ask our informants if they prefer them via text messaging or triggered by the app itself. We know that small behavior change steps can be encouraged using reinforcement, so we will be on the lookout for gaming ideas such as winning points and earning badges. We will ask for specific skills that our informants see as most useful (eg, saying no when offered cigarettes) and teach these skills using models. We will also consider social interaction tools (eg, smoking cessation buddies). However, the specific instantiation of these principles will stem from the participatory design process as defined by input from SFHN patients and health care providers. The exact structure of the intervention will be guided by participant input. Recent reports suggest using a hierarchical taxonomy to describe the active components of behavioral change intervention protocols [40]. We anticipate that active components of the intervention will include goal setting (behavior and outcome), self-monitoring, social support (practical and emotional), prompts/cues and cue signaling rewards, and behavioral practice/rehearsal.

Measures

Field Studies

User-centered design and usability testing aims to determine whether people can use the tools and features (ease of use) and how they like using them (usefulness). These questions will be addressed using a mix of qualitative (semistructured interview) and quantitative (satisfaction, acceptability, and perceived usefulness ratings) methods. Furthermore, during usability testing participants will be audio- and videotaped while interacting with the tools and features. Participants will report their overall satisfaction, as well as satisfaction with the design, content, functionality, and features. Participants will report what they liked best and least about the tools and features as well as strengths and weaknesses of the tools. Participants will rate the perceived usefulness of each aspect and the acceptability of using the program in the future.

Online Studies

To reduce participant burden, we will use reduced versions of the baseline and follow-up questionnaires we used in our earlier website-centered studies. Being asked to respond to long surveys on a mobile device is likely to result in high dropout rates. Therefore, we propose the following:

- Eligibility: age, current smoker, speak English or Spanish.

- Baseline (obtained on the Web app when the smokers installs the app and gives consent to enter the study): demographics (age, sex, race, ethnicity, marital status, employment status, income, and educational level), smoking history (age first cigarette, age regular smoker, cigarettes per day, quit attempts, and methods used to quit), the Fagerström Test for Nicotine Dependence (6 items) [41], and rating of quit confidence.
- Follow-ups (brief and obtained using text messaging to increase completion rates): smoking status (7-day and 30-day point prevalence abstinence rates, operationalized as a "no" response to "Have you smoked 1 or more cigarettes in the last seven days?" and, if "no" to the previous question, "Have you smoked 1 or more cigarettes in the last 30 days?"); number of cigarettes per day smoked in the last week (if still smoking); and rating of confidence that the user will remain quit (if not smoking) or be able to quit in the next 30 days (if smoking).

Data analysis

Ethnographic and Field Testing Phases

Mixed-methods data analysis will incorporate qualitative data from patient and therapist feedback; quantitative data from the satisfaction, acceptability, and usefulness ratings; and audio recordings from the field tests. Although quantitative ratings can highlight possible usability concerns, qualitative data provide answers to why those features might cause problems in ways that can guide development. Qualitative data will be interpreted following a grounded theory approach in which results from the semistructured interview will be analyzed using a series of codes to determine patterns in topics related to patients' and therapists' needs, concerns, and impressions of the prototype. Grounded theory was selected because it is a useful methodology for determining common topics within qualitative data to inform future practices and research. For the usability phase, we believe the users will raise unanticipated concerns and needs and thus we selected an approach that is flexible. Mean values of ratings from individual tools and features will be computed to identify those that require further refinement. Any tool or feature that is given the lowest value on a quantitative rating scale will be flagged for more intensive review in the video recordings and screen captures. Audio recordings and screen captures will address ease of use and be coded to determine three types of errors: navigation errors refer to instances when users cannot locate a function or have difficulty with aspects of the screen flow, content errors refer to instances of problems due to labeling or information presented, and usage errors refer to improper tool use or data field entry. Qualitative and quantitative data will be integrated through linking categories identified using the grounded theory approach with ratings on tools and features. Tools and features must score a mean value in the satisfactory range to be included in the next version. We will consider developing additional tools and features for other categories identified by users. Consistent with principles of constant comparative analysis, the principal investigator will make final decisions regarding tools and features.

Online Studies 1, 2, and 3

These studies are intended to provide continuous quality improvement data as a baseline smoking cessation intervention (a static stop smoking guide) moves through two iteratively designed versions of a user-centered Web app. The final version of the Web app will be evaluated in comparison to the baseline app. We will examine successive changes in recruitment rates, utilization of the app, follow-up rates, and quit rates. We will use observed changes or lack thereof to pinpoint areas that need improvement; this will help prioritize changes in recruitment media and messages, Web app functionality, text messaging issues, and elements of the Web app likely to increase quit rates.

Online Study 4

Participants will be randomly assigned to use either the baseline app or the final version of the San Francisco Stop Smoking Web app. We will focus our analysis on quit rates and use of the app. Latency (time spent) on content pages will be compared across the two versions of the app using independent samples *t* tests. Based on a Cohen designation of a small effect size for group mean comparisons of 0.2, a priori power analyses revealed a necessary sample size of N=800 (400 per version) to achieve a power of .80. Quit rates (smoking cessation status at 7- and 30-days) will be evaluated at 1, 3, and 6 months following registration, with individuals lost to follow-up treated as still smoking. To examine quit rate as a function of website version and demographic characteristics, logistic regression analyses will be conducted with quit status as the criterion variable; website version as the focal predictor; and gender, age, ethnicity, race, and income entered as covariates. Prior research suggests a usual care quit rate of 10% based on the 11% quit rate finding for the printed version of the *Guía Para Dejar de Fumar* in the Muñoz et al [13] study and missing=smoking rates ranging from 6.0% to 14.5% in our online studies [16,18,20]. We have estimated the quit rate of the improved, user-centered Web app at 20% based on the 23% quit rate found for the combined intervention in a later Muñoz et al study [13] and the best estimates of our online website, which yielded a missing=smoking rate of 20.2% for Spanish speakers and 21% for English speakers [16]. We estimate an increase of 10% (ie, improved website will result in 20% quit rate compared to a 10% quit rate for the baseline app), which results in an odds ratio of 2.25. This odds ratio was used as the effect size estimate in an a priori power analysis that yielded a total sample size of N=550 (225 per site version) to achieve power of .80.

We estimate needing a minimum of 800 participants to detect small effect sizes in utilization and 550 to detect clinically significant differences in quit rates. We therefore propose to recruit 800 participants via the open online recruitment process (to reach the minimum sample size estimated in our power analysis) and an additional 200 SFHN participants to increase our sample size and carry out secondary subgroup analyses to determine whether utilization and quit rates for the SFHN patients appear similar to those recruited outside the SFHN.

Results

The project was funded in July 2015. Enrollment is currently underway and is expected to be finished by 2018. The first results are expected to be submitted for publication in 2019.

Discussion

Dissemination Plan

Our research team is committed to the dissemination of our research products. We disseminated the findings supported by our three earlier TRDRP grants (7RT-0057, 10RT-0326, and 13RT-0050) to the tobacco research community via 19 published articles and many additional posters and papers presented at local, national, and international venues. We plan to do the same with the research findings stemming from this project. In addition we actively sought continuous funding to extend the reach and duration of the intervention resulting from our three previous TRDRP grants. Since we were first funded in 1998, we have documented 347,000 visitors from more than 200 countries and territories and 52,268 consented participants in several online smoking cessation trials. For the participant preference trials, we made the *Guía Para Dejar de fumar* stop-smoking guide available on our home page to all who visited the site, whether or not they chose to proceed beyond the landing page. They were allowed to click on the link to the guide to download it without registering or having to pay for it. More than 258,340 visitors were given access to the guide. And, if our best estimates of quit rates are accurate, 20% of the 52,268 who registered, consented, and used our online interventions may have quit smoking, a total of more than 10,000 individuals. The research site remained active for 16 years after our initial grant was awarded. We intend to make the San Francisco Stop Smoking Web app resulting from the proposed project available to smokers worldwide after the project period terminates. For a complete timeline of the research study see Figure 2.

Figure 2. Timeline. Note: D=Development, R=Recruitment, F=Follow-ups

	Year 1				Year 2				Year 3			
Quarter	1	2	3	4	1	2	3	4	1	2	3	4
Phase 1: User Input												
Ethnography: smoking and smartphones												
Ethnography: smoking app usage												
Participatory design sessions												
Phase 2: Design & Development												
Baseline web app Dev & Online Study 1	D	R	F									
Version 1.0 Dev & Online Study 2				D	R	F						
Version 2.0 Dev & Online Study 3						D	R	F				
Final Version Development							D					
Phase 3: RCT												
Recruitment/ Intervention								R	R	F	F	
Data analysis												
Manuscript preparation												
Prepare dissemination for public use												
Prepare next grant applications												

Human Subjects and Ethical Considerations

The project received approval from the institutional review board at Palo Alto University in January 2016. Many of the study materials have been widely distributed and are well validated, and we do not anticipate any negative physical, mental, emotional, legal, or social consequences stemming from this study that are beyond what an individual would encounter in daily life. The Web app is presented to potential participants as a self-help automated research intervention (similar to a self-help book) and as neither counseling nor therapy. Therefore, use of the app does not involve a therapeutic contract. Participants are not compensated for interacting with the app, but they may receive indirect benefits such as a reduction in smoking behavior. Participants may withdraw from the study at any time and may refuse to answer any questions. During the study enrollment process, participants are informed that they may refuse to have their data used for official research reports but may still use the app. Their data will still be collected and

used solely for the research team's ongoing Web app development.

All participants are informed that under no circumstances will their information be shared with their doctor or anyone outside the research team without their consent and that any published data will be aggregated and deidentified. All components of the Web application are provided in English and Spanish, and the previously validated stop-smoking guide has been shortened and simplified to a sixth-grade reading level. The project aims to sample equal numbers of male and female participants as well as English and Spanish speakers.

The first year of the current protocol has been registered at ClinicalTrials.gov Protocol Registration and Results System [NCT02666482].

Conclusion

This study is intended to increase the range of utilization and effectiveness of a smoking cessation Web app beyond well-educated users. English- and Spanish-speaking low-income primary care patients of a public-sector health network will be asked to contribute to the development of the new Web app via ethnographic interviews and focus groups. After several iterations of the Web app, an RCT will be conducted to determine whether the final version of the Web app is superior to the baseline version in terms of acceptance, utilization, and higher abstinence rates.

Acknowledgments

This project was partially supported by funds provided by The Regents of the University of California, Tobacco-Related Diseases Research Program, Grant Number No. 24RT-0027. The opinions, findings, and conclusions herein are those of the authors and not necessarily represent those of The Regents of the University of California, or any of its programs. Programming and development of the web app for this project is being carried out by the Center for Behavioral Intervention Technologies at Northwestern University Feinberg School of Medicine.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Reviews of TRDRP grant.

[PDF File (Adobe PDF File), 40KB - resprot_v5i2e127_app1.pdf]

References

1. Report on the global tobacco epidemic, 2008. Geneva, Switzerland: World Health Organization; 2008. URL: http://whqlibdoc.who.int/publications/2008/9789241596282_eng.pdf?ua=1 [accessed 2016-04-25] [WebCite Cache ID 6h2MTxyVu]
2. Management of substance abuse: tobacco. Geneva, Switzerland: World Helath Organization; 2014. URL: http://www.who.int/substance_abuse/facts/tobacco/en/ [accessed 2016-04-25] [WebCite Cache ID 6h2MY719E]
3. Cuellar Mejia M, Johnson H. Public Policy Institute of California. 2013 May. Immigrants in California URL: http://www.ppic.org/content/pubs/jtf/JTF_ImmigrantsJTF.pdf [accessed 2016-04-25] [WebCite Cache ID 6h2NKnx8J]
4. Lopez MH. Fact Tank.: Pew Research Center; 2014 Jan 24. In 2014, Latinos will surpass whites as largest racial/ethnic group in California URL: http://www.pewresearch.org/fact-tank/2014/01/24/in-2014-latinos-will-surpass-whites-as-largest-racialethnic-group-in-california/ [accessed 2016-04-25] [WebCite Cache ID 6h2NR5hFx]
5. Percent of people 5 years and over who speak Spanish at home.: United States Census Bureau; 2014. URL: http://factfinder2.census.gov/faces/tableservices/jsf/pages/productview.xhtml?pid=ACS_13_1YR_GCT1602.ST04&prodType=table [accessed 2016-05-12] [WebCite Cache ID 6hS8VkNda]
6. Desilver D. Who smokes in America?. Washington, DC: Pew Research Center; 2014 Feb 07. URL: http://www.pewresearch.org/fact-tank/2014/02/07/who-smokes-in-america/ [accessed 2016-04-25] [WebCite Cache ID 6h2NfJxL5]
7. Behavioral Risk Factor Surveillance System. Atlanta, GA: Centers for Disease Control and Prevention; 2014. URL: http://www.cdc.gov/brfss/ [accessed 2016-04-25] [WebCite Cache ID 6h2NjVXUV]
8. Benowitz N, Schultz K, Haller C, Wu A, Dains K, Jacob P. Prevalence of smoking assessed biochemically in an urban public hospital: a rationale for routine cotinine screening. Am J Epidemiol 2009:215. [Medline: 19713287]
9. Max W, Sung H, Tucker L, Stark B. The cost of smoking for California's Hispanic community. Nicotine Tob Res 2011 Apr;13(4):248-254. [doi: 10.1093/ntr/ntq245] [Medline: 21330281]
10. Kaplan RC, Bangdiwala SI, Barnhart JM, Castañeda SF, Gellman MD, Lee DJ, et al. Smoking among US Hispanic/Latino adults: the Hispanic Community Health Study/Study of Latinos. Am J Prev Med 2014 Nov;46(5):496-506. [doi: 10.1016/j.amepre.2014.01.014]

11. Levinson AH, Borrayo EA, Espinoza P, Flores ET, Pérez-Stable EJ. An exploration of Latino smokers and the use of pharmaceutical aids. Am J Prev Med 2006 Aug;31(2):167-171. [doi: 10.1016/j.amepre.2006.03.022] [Medline: 16829334]
12. Muñoz R, Chen K, Bunge E, Bravin J, Shaughnessy E. Reaching Spanish-speaking smokers online: a 10-year worldwide research program. Pan Am J Public Health 2014;35:407-414. [Medline: 25211569]
13. Muñoz RF, Marín BV, Posner SF, Pérez-Stable EJ. Mood management mail intervention increases abstinence rates for Spanish-speaking Latino smokers. Am J Community Psychol 1997 Jun;25(3):325-343. [Medline: 9332966]
14. Fiore MC, Smith SS, Jorenby DE, Baker TB. The effectiveness of the nicotine patch for smoking cessation. A meta-analysis. JAMA 1994;271(24):1940-1947. [Medline: 8201739]
15. Lando HA, McGovern PG, Barrios FX, Etringer BD. Comparative evaluation of American Cancer Society and American Lung Association smoking cessation clinics. Am J Public Health 1990 May;80(5):554-559. [Medline: 2327531]
16. Muñoz RF, Barrera AZ, Delucchi K, Penilla C, Torres LD, Pérez-Stable EJ. International Spanish/English Internet smoking cessation trial yields 20% abstinence rates at 1 year. Nicotine Tob Res 2009 Sep;11(9):1025-1034. [Medline: 19640833]
17. Hall SM, Humfleet GL, Reus VI, Muñoz RF, Hartz DT, Maude-Griffin R. Psychological intervention and antidepressant treatment in smoking cessation. Arch Gen Psychiatry 2002 Oct;59(10):930-936. [Medline: 12365880]
18. Muñoz RF, Lenert LL, Delucchi K, Stoddard J, Perez JE, Penilla C, et al. Toward evidence-based Internet interventions: A Spanish/English Web site for international smoking cessation trials. Nicotine Tob Res 2006 Feb;8(1):77-87. [Medline: 16497602]
19. Leykin Y, Aguilera A, Torres LD, Pérez-Stable EJ, Muñoz RF. Interpreting the outcomes of automated internet-based randomized trials: example of an International Smoking Cessation Study. J Med Internet Res 2012;14(1):e5 [FREE Full text] [doi: 10.2196/jmir.1829] [Medline: 22314016]
20. Muñoz RF, Aguilera A, Schueller SM, Leykin Y, Pérez-Stable EJ. From online randomized controlled trials to participant preference studies: morphing the San Francisco Stop Smoking site into a worldwide smoking cessation resource. J Med Internet Res 2012 Jan;14(3):e64-e64. [Medline: 22739225]
21. Gallego MJ, Modesto M, Muñoz MA, Almajano MJ, Modolell E, Peris CP. Tratamiento via Internet con contactos semanales por e-mail utilizado en una Unidad de Tabaquismo: utilidad clinica y predictores de exito. Behav Psychol Conduct 2014;22(1).
22. Muñoz RF, Bunge EL, Chen K, Schueller SM, Bravin JI, Shaughnessy EA, et al. Massive open online interventions: a novel model for delivering behavioral health services worldwide. Clin Psychol Sci 2016;4(2):194-205. [doi: 10.1177/2167702615583840]
23. Perrin A, Duggan M. Americans' Internet access: 2000-2015. Washington, DC: Pew Internet and American Life Project; 2015 Jun 26. URL: http://www.pewinternet.org/files/2015/06/2015-06-26_internet-usage-across-demographics-discover_FINAL.pdf [accessed 2016-04-25] [WebCite Cache ID 6h2Qu80RE]
24. Bravin JI, Bunge EL, Evare B, Wickham RE, Pérez-Stable EJ, Muñoz RF. Socioeconomic predictors of smoking cessation in a worldwide online smoking cessation trial. Internet Interv 2015 Nov;2(4):410-418. [doi: 10.1016/j.invent.2015.10.001]
25. Schickedanz A, Huang D, Lopez A, Cheung E, Lyles CR, Bodenheimer T, et al. Access, interest, and attitudes toward electronic communication for health care among patients in the medical safety net. J Gen Intern Med 2013 Jul;28(7):914-920 [FREE Full text] [doi: 10.1007/s11606-012-2329-5] [Medline: 23423453]
26. Riley WT, Glasgow RE, Etheredge L, Abernethy AP. Rapid, responsive, relevant (R3) research: a call for a rapid learning health research enterprise. Clin Transl Med 2013;2(1):10 [FREE Full text] [doi: 10.1186/2001-1326-2-10] [Medline: 23663660]
27. Management of substance abuse. Geneva, Switzerland: World Health Organization; 2014. URL: http://www.who.int/substance_abuse/facts/tobacco/en/ [accessed 2016-04-25] [WebCite Cache ID 6h2Q0V9Cl]
28. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. J Health Econ 2003 Mar;22(2):151-185. [doi: 10.1016/S0167-6296(02)00126-1] [Medline: 12606142]
29. Leykin Y, Muñoz RF, Contreras O, Latham MD. Results from a trial of an unsupported internet intervention for depressive symptoms. Internet Interv 2014 Oct 1;1(4):175-181 [FREE Full text] [doi: 10.1016/j.invent.2014.09.002] [Medline: 25485233]
30. Schueller SM, Pérez-Stable EJ, Muñoz RF. A mood management intervention in an Internet stop smoking randomized controlled trial does not prevent depression: a cautionary tale. Clin Psychol Sci 2013;1:401-412. [doi: 10.1177/2167702613484717]
31. Beyer H, Holtzblatt K. Contextual Design: Defining Customer-Centered Systems. San Francisco: Elsevier; 1997.
32. Brown T, Katz B. Change by design. J Prod Innov Manag 2011;28(3):381-383. [doi: 10.1111/j.1540-5885.2011.00806.x]
33. Brennan MD, Duncan AK, Armbruster RR, Montori VM, Feyereisn WL, LaRusso NF. The application of design principles to innovate clinical care delivery. J Health Qual 2009;31(1):5-9. [Medline: 19343895]
34. Skinner HA, Maley O, Norman CD. Developing Internet-based eHealth promotion programs: the Spiral Technology Action Research (STAR) model. Health Promot Pract 2006 Oct;7(4):406-417. [doi: 10.1177/1524839905278889] [Medline: 16840770]
35. Salter C. FastCompany. 2006 Apr 01. The Mayo SPARC program: a prescription for innovation! URL: http://www.fastcompany.com/56032/prescription-innovation [accessed 2016-04-25] [WebCite Cache ID 6h2PUp7Z9]

36. McCreary L. Harvard Business Review. 2010 Sep. Kaiser Permanente's innovation on the front lines URL: https://hbr.org/2010/09/kaiser-permanentes-innovation-on-the-front-lines/ [accessed 2016-04-25] [WebCite Cache ID 6h2SWQLpC]
37. Doss H. Forbes. 2014 May 23. Design thinking in healthcare: one step at a time URL: http://www.forbes.com/sites/henrydoss/2014/05/23/design-thinking-in-healthcare-one-step-at-a-time/ [accessed 2016-04-25] [WebCite Cache ID 6h2ScCvni]
38. Kembel G. Fora.tv. 2009 Aug 14. Awakening creativity URL: http://library.fora.tv/2009/08/14/George_Kembel_Awakening_Creativity [accessed 2016-04-25] [WebCite Cache ID 6h2SnkVZe]
39. Graham AL, Cobb NK, Papadonatos GD, Moreno JL, Kang H, Tinkelman DG, et al. A randomized trial of Internet and telephone treatment for smoking cessation. Arch Intern Med 2011;17(1):46-53. [doi: 10.1001/archinternmed.2010.451]
40. Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. Ann Behav Med 2013 Aug;46(1):81-95. [doi: 10.1007/s12160-013-9486-6] [Medline: 23512568]
41. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br J Addict 1991 Sep;86(9):1119-1127. [Medline: 1932883]

Abbreviations

ITEM: individually timed educational message
NCI: National Cancer Institute
R3: rapid, responsive, relevant
TC: Taking Control of Your Life
TRDRP: Tobacco-Related Disease Research Program
RCT: randomized controlled trial
SES: socioeconomic status
SFHN: San Francisco Health Network

Edited by G Eysenbach; submitted 21.11.15; peer-reviewed by M Hassandra, K Antypas; comments to author 16.12.15; accepted 17.01.16; published 14.06.16.

Please cite as:
Muñoz RF, Bunge EL, Barrera AZ, Wickham RE, Lee J
Using Behavioral Intervention Technologies to Help Low-Income and Latino Smokers Quit: Protocol of a Randomized Controlled Trial
JMIR Res Protoc 2016;5(2):e127
URL: http://www.researchprotocols.org/2016/3/e189/
doi:10.2196/resprot.5355
PMID:27302623

Protocol

A Cognitive Behavioral Therapy–Based Text Messaging Intervention Versus Medical Management for HIV-Infected Substance Users: Study Protocol for a Pilot Randomized Trial

Suzette Glasner-Edwards[1], PhD; Kevin Patrick[2], MS, MD; Michele L Ybarra[3], PhD; Cathy J Reback[1,4], PhD; Richard A Rawson[1], PhD; Helene Chokron Garneau[1], MPH; Kathryn Chavez[1], BA; Alexandra Venegas[1], BSc

[1]Integrated Substance Abuse Programs, Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, CA, United States

[2]University of California at San Diego, La Jolla, CA, United States

[3]Center for Innovative Public Health Research, San Clemente, CA, United States

[4]Friends Research Institute, Los Angeles, CA, United States

Corresponding Author:
Suzette Glasner-Edwards, PhD
Integrated Substance Abuse Programs
Semel Institute for Neuroscience and Human Behavior
University of California Los Angeles
11075 Santa Monica Blvd, Suite 200
Los Angeles, CA,
United States
Phone: 1 310 267 5206
Fax: 1 310 312 0538
Email: sglasner@ucla.edu

Abstract

Background: Evidence-based psychosocial interventions for addictions and related conditions such as cognitive behavioral therapy (CBT) are underutilized. Obstacles to implementation of CBT in clinical settings include limited availability of quality training, supervision, and certification in CBT for clinicians; high rates of clinician turnover and high caseloads; and limited qualifications of the workforce to facilitate CBT expertise.

Objective: Mobile phone–based delivery of CBT, if demonstrated to be feasible and effective, could be transformative in broadening its application and improving the quality of addiction treatment. No experimental interventions that deliver CBT targeting both drug use and medication adherence using text messaging have been previously reported; as such, the objective of this study is to develop and test an SMS-based treatment program for HIV-positive adults with comorbid substance use disorders.

Methods: With user input, we developed a 12-week CBT-based text messaging intervention (TXT-CBT) targeting antiretroviral (ART) adherence, risk behaviors, and drug use in a population of HIV-infected substance users.

Results: The intervention has been developed and is presently being tested in a pilot randomized clinical trial. Results will be reported later this year.

Conclusions: This investigation will yield valuable knowledge about the utility of a cost-effective, readily deployable text messaging behavioral intervention for HIV-infected drug users.

(JMIR Res Protoc 2016;5(2):e131) doi:10.2196/resprot.5407

KEYWORDS

SMS; medication adherence; HIV; relapse prevention; text messaging; CBT; ART

Introduction

Injection Drug Use and HIV

Injection drug use is a major risk factor for HIV infection, and people who inject drugs (PWID) account for a substantial proportion of new HIV infections in the Unites States and more than one-third of new AIDS cases (a proportion nearly double that of 10 years ago) [1]. This is not surprising given that the risk of infection after injection with an HIV-contaminated syringe is estimated to be 0.4% to 2.4% (median 0.8%; approximately 1 in 125 injections) [2].

Sharing contaminated needles and other injection equipment among PWID is a known source of the increased incidence of HIV transmission in this population, and PWID with sexual risk behaviors are at heightened risk for HIV [3,4]. New and easily deployable interventions targeting the most vulnerable individuals are urgently needed to reduce HIV transmission [5]. The goal of the present research is to develop and evaluate a cost-effective and novel technology-based approach for treating drug dependence and associated HIV risk and treatment adherence problems.

Reducing HIV Risk Behaviors and Improving HIV Treatment Regimen Adherence

ART Adherence Among HIV Positive Drug Users

Among the most promising interventions to address drug dependence, associated HIV risk behaviors, and injection-related HIV transmission are counseling to decrease the number of injections by treating the underlying drug dependence [6] and antiretroviral treatment (ART) to reduce viral load and diminish the likelihood of HIV transmission in the face of exposure for those who are HIV infected [7].

There is ample evidence suggesting that HIV-infected PWID are less likely to access HIV treatment and that once treatment is initiated, they are less likely to be adherent than former and nondrug users [8,9]. ART adherence is critically important; suboptimal dosing can contribute to the development of medication resistance and result in negative consequences including rebounding of HIV RNA levels, sometimes to above baseline levels [10,11]. Less than 5% of PWID receive CD4 cell count monitoring at a frequency consistent with clinical recommendations [12]. Nevertheless, PWID who adhere to antiretroviral therapies have HIV outcomes that are comparable to non-PWID [7]. Preliminary studies suggest that cognitive behavioral therapy (CBT)–based ART adherence counseling (Life-Steps) [11,13,14] is effective among HIV-positive drug users [15].

Cognitive Behavioral Therapy for Substance Use Disorders

Both behavioral and cognitive-behavioral treatment approaches have therapeutic effects on a range of functional outcomes among adults with drug use disorders [16]. Although CBT has been evaluated empirically for the treatment of drug users, no studies to date have used mobile phone technology to deliver this intervention to drug-dependent populations.

CBT is among the most widely studied psychosocial interventions for substance users in well-controlled randomized trials. The therapeutic effects of CBT are robust and have been well established across various substance using populations, including those who are dependent on opioids [17-20], marijuana [21], alcohol [22], and stimulants [23]. Based upon social learning theory, a central assumption of CBT treatment is that substance dependence emerges from a process whereby the individual learns through experience about the reinforcement value of the substance [24]. Anticipated reinforcement is thought to drive continued and problematic behavioral patterns of substance use. CBT therefore focuses on the goal of facilitating abstinence from substance use by teaching new alternative, reinforcing behaviors.

In addition to its efficacy in reducing substance use, effects of CBT on HIV risk behaviors have also been reported [6,25]. Pinkerton [25] compared the effectiveness of a 7-session CBT group emphasizing motivation, skills, and self-efficacy related to HIV risk reduction relative to a single video-based HIV/AIDS education session in 3706 high-risk men and women. Both interventions were effective in reducing sexual risk behaviors, but the reduction was much higher with CBT on a number of indices. In particular, CBT participants reduced their mean number of acts of unprotected sexual intercourse from 24.7 at baseline to 12.0 at one-year follow-up, whereas those in the video intervention condition reduced from a mean of 23.9 acts to 16.7 at follow-up. Schroeder [26] reported comparable reductions in sexual and drug-related HIV risk behaviors among cocaine users receiving opioid substitution therapy (OST) concurrently with CBT or contingency management. In both of the psychosocial conditions, participants received education concerning HIV transmission and risk reduction practices. These results suggest broad beneficial effects of OST augmented with behavioral interventions for reducing HIV risk behaviors. As such, the experimental CBT-based text messaging intervention to be evaluated in this study will maximize effects on HIV risk behaviors by incorporating HIV educational content.

Advances in Technology-Based Interventions for Substance Use and HIV

Mobile phones have the potential to provide an important new delivery medium for behavioral support programs to individuals with drug use disorders. By the end of 2014, the rate of mobile-cellular telephone subscriptions was 98.4 per 100 inhabitants in the United States [27]. There has been a rapid expansion in the use of text messaging, with about 1.92 trillion text messages sent globally in 2014 [28]. The literature describing the use of text messaging as a clinical intervention is rapidly expanding. Text messaging has been used with numerous clinical populations including those with diabetes, obesity, and HIV [29-34], yet the use of these approaches in the treatment of drug users has so far been limited [35,36].

Several studies of text messaging and multimedia intervention programs incorporating text messaging with cigarette smokers have shown improvements in quit rates and attempts and decreases in tobacco use [37-39]. A large randomized trial examined the efficacy of a fully automated digital multimedia smoking cessation intervention which included an intensive text

messaging component compared with a control group receiving a self-help booklet; this study found higher point abstinence rates and improved adherence to nicotine replacement therapy relative to the control group [40], with long-term benefits extending through 1-year postintervention.

Mobile phones have been used to disseminate several promising HIV prevention and intervention programs including a text messaging–based sexually transmitted infection and HIV prevention program for adolescents (SEXINFO) [41] and a pilot program employing mobile phone call reminders to improve medication adherence for HIV-infected individuals [34]. Studies to date are typically pilot interventions with small sample sizes, and there is presently little known about the effectiveness of text messaging for HIV-infected populations. Nevertheless, among PWID, a computer-based educational intervention concerning HIV/AIDS was found to have comparable effects on HIV risk behaviors relative to that of a counselor-delivered intervention, and it produced greater retention of HIV-related information [42]. More recently, a text messaging intervention delivering health education and social support in real time to high-risk men who have sex with men effectively reduced methamphetamine use and risky sexual behaviors [36]. Taken together, these data provide reason for optimism that utilizing mobile phone technology could be a promising next step to broadening the availability of cost-effective behavioral interventions for high-need populations such as HIV-infected drug users.

Aims

This paper describes the methodology leading to the development and pilot testing of a CBT-based text messaging intervention (TXT-CBT) targeting ART adherence and drug use. Although there are features of CBT such as direct therapist feedback concerning therapy homework, for example, that cannot be replicated using a predominantly automated text messaging platform, the TXT-CBT program transports the essential features of CBT for relapse prevention to the technology-assisted platform, with recognition of these inherent limitations. Some of the limitations imposed by a technology-based approach are mitigated by the involvement of a clinician in the TXT-CBT intervention program.

The purpose of this study was to develop, with user feedback, a 12-week CBT-based text messaging treatment program targeting ART adherence and drug use and test its efficacy through a pilot randomized clinical trial. The specific aims of the study were to (1) test the impact of TXT-CBT over and above usual care for HIV on substance use and health care outcomes, (2) evaluate the differential effect of TXT-CBT versus usual HIV care on HIV risk behavior and ART adherence, and (3) examine potential mechanisms of action of TXT-CBT.

The following hypotheses addressed the goals of the study:

- Among substance-dependent adults receiving HIV care, TXT-CBT would yield superior clinical outcomes relative to usual care in reducing substance use and health service utilization during and after treatment. In particular, while some health care utilization may increase among those who benefit from TXT-CBT (eg, use of routine HIV care services), we anticipate reductions in hospitalizations and emergency care services secondary to substance use.
- TXT-CBT would have superior effects on ART adherence and HIV risk behaviors relative to usual HIV care.
- TXT-CBT would have a direct effect on psychological variables that are recognized mechanisms of change in CBT treatment for addicted populations (negative affect, self-efficacy, social support). Specifically, we predicted that reductions in negative affect and cravings and increases in self-efficacy and social support would be positively associated with retention in TXT-CBT and inversely related to substance use during and after treatment.

Methods

Study Design

The study began with formative research to develop the intervention. This was followed by a 2-group randomized controlled trial (RCT) in which individuals receiving usual care for HIV were randomly assigned to receive either TXT-CBT or an informational pamphlet concerning HIV and substance use. The trial was conducted and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines [43]. Face-to-face assessments were conducted at baseline and weeks 4, 8, 12, and 24. Phone-based assessments of ART adherence were also conducted at each of these timepoints.

All study procedures were approved by the University of California, Los Angeles Institutional Review Board. This trial is registered at ClinicalTrials.gov [NCT01884233].

Target/Study Population

Inclusion criteria were (1) age 18 years or older, (2) Diagnostic and Statistical Manual of Mental Disorders, 4th. Edition (DSM-IV) diagnosis of opioid or stimulant dependence, (3) HIV-infected and currently taking ART prescribed within the past 30 days, and (4) currently own a cell phone that can send and receive text messages. Exclusion criteria were (1) lack of proficiency in English; (2) currently homeless (unless residing in a recovery home for which contact information can be provided); (3) dependence on an illicit substance for which medical detoxification is imminently needed; or (4) presence of clinically significant psychiatric symptoms as assessed by the M.I.N.I. International Neuropsychiatric Interview such as psychosis, acute mania, or suicide risk that would require immediate treatment or make study compliance difficult.

Procedures

Participants were recruited through advertising, word of mouth, study announcement fliers posted in treatment programs and community locations, infectious disease clinics in the community, referrals from local substance abuse treatment and outreach programs, outpatient and inpatient alcohol and drug abuse clinics, primary care providers, local mental health centers, crisis clinics, public service announcements, hospital emergency rooms, and self-referrals. All recruitment materials referred interested persons to clinic phones, which were answered by trained research staff who provided the caller with information about the study and scheduled interested persons

for an interview. Interested individuals received a study description and a prescreening prior to an initial interview to begin the informed consent process. Those who wished to participate provided informed consent and began the baseline assessment procedures to confirm eligibility to participate.

Randomization

Following the prescreening, baseline assessment phase, and confirmation of study eligibility, participants were randomly assigned to group 1, a treatment-as-usual (TAU) condition in which participants received usual care (ie, medical management) for HIV plus a Substance Abuse and Mental Health Services Administration informational pamphlet concerning HIV and substance use (see Multimedia Appendix 1 for the pamphlet content), or group 2, a TAU plus a CBT text messaging condition (TAU+TXT-CBT). Those who were assigned to the TXT-CBT received $20 gift cards monthly over the 3-month intervention phase to offset the costs of an unlimited text messaging plan. Randomization was conducted by a research assistant using a Web-based, automated program implemented by the University of California, Los Angeles, Integrated Substance Abuse Programs Data Management Center. Neither the research staff nor participants were blinded.

Sample Size

Determination of sample size (proposed n=25 per group) was guided by feasibility and appropriateness to achieve pilot study objectives rather than by statistical power estimates [44,45]. Pilot studies play an important role in providing information for the planning and justification of RCTs in terms of feasibility of intervention protocols and recruitment strategies, feasibility and comprehensiveness of data management and analysis procedures, and exploration of potential effect sizes [46-48]. We anticipated that the sample size (N=50) would provide representativeness of a diversity of HIV-infected substance user characteristics for examining intervention feasibility and produce data characteristics/distributions appropriate to examining data- and analysis-related procedures, variability, and potential effect sizes.

Intervention Development

The TXT-CBT intervention development process included CBT expert groups, focus groups, and community partners meetings conducted to obtain input for the content of the intervention and a logic model for the TXT-CBT intervention developed based upon rules that supported tailoring the intervention content over the 12-week period. Concurrently, text messages for the TXT-CBT library were written and categorized by outcome target (substance use, HIV risk behaviors, ART adherence). Written materials provided to the participants were also developed. A participant TXT-CBT manual was developed including instructions on how to use the text messaging system and detailing the specific psychological skills to be learned and rehearsed upon participation in the intervention. The beta version of the TXT-CBT text messaging system was developed and a pilot study of the beta version was conducted among HIV-positive, opioid-dependent adults (n=10) receiving HIV care. For this pilot test, all planned measures for the randomized trial were collected to determine feasibility of the protocol. Participants received qualitative data collection calls weekly during their participation in TXT-CBT to gather information concerning the functionality of the program, address any technical difficulties they might experience, and determine whether any of the messaging content was unacceptable or in need of revision. Based upon the pilot study findings, the intervention was refined and accompanying materials finalized in preparation for the pilot RCT.

Intervention Content

The intervention comprised one CBT-based face-to-face counseling session with a master's level clinician followed by 12 weeks of daily text messages. The messages included medication reminders plus 2 or 3 additional messages on the topic of addiction recovery and associated risk behaviors. Participants selected the desired frequency and time at which to receive their medication reminder messages. Participants enrolled thus far typically require 1 or 2 medication reminders daily. As such, participants receive 4 or 5 text messages daily. Of the 14 to 21 messages per week that are not medication reminders, approximately half of the message content pertains to CBT skills for drug relapse prevention with the remaining half split evenly between content concerning common HIV risk behaviors and ways to reduce them and the importance of ART adherence coupled with behavioral strategies to promote adherence.

During the clinician-delivered CBT session, a number of variables upon which the intervention was tailored or individualized were identified, including the top 3 barriers to ART adherence for the individual, with corresponding coping skills training; the participant's first name; specific times of day at which medication reminders are needed; and motives for quitting substance use.

Content had both informational and interactive components to model the balance between psychoeducation and counseling in traditional clinician-delivered CBT. The remaining texts provided psychoeducation, tips, suggestions, and reminders to facilitate the use of cognitive and behavioral strategies to prevent substance relapse, improve ART adherence, and reduce HIV risk behaviors. Relapse prevention messages comprised 50% of those sent to participants each week (see Textbox 1). The 12-week intervention is staged such that each week a new specific coping skill was introduced:

1. Behavioral techniques such as scheduling and engaging in alternative rewarding activities to prevent boredom and maintain a sober lifestyle

2. Opioid withdrawal symptoms, similarities between stress and withdrawal symptoms, and coping techniques to prevent relapse in the face of these symptoms

3. Stress as a relapse precipitant, with descriptions of stress management techniques in the form of easy-to-implement tips

4. Common triggers to opioid relapse with suggestions on how to eliminate or minimize triggers

5. Relapse analysis practice, in which an example of a prior relapse is described to identify its precipitants

6. Goal-setting with interactive messages used to help participants specify goals that are incompatible with substance use

7. Family and social support for abstinence; emphasizing avoiding isolation

8. Impact of addiction and the recovery process on important relationships, with suggestions and tips regarding family roles in treatment

9. Behavioral lifestyle changes that support recovery

10. Decisions about other drug use (eg, marijuana)

11. Motivation to remain abstinent

12. Individualized relapse prevention planning, with interactive messages to identify components of a personalized relapse prevention plan (eg, contact information for support, preferred behavioral strategies such as exercise, and cognitive techniques such as reviewing reasons for quitting).

Textbox 1. Behavioral targets and examples of text messages.

ART adherence

- Taking ur medicine exactly as prescribed will help u 2 get the most benefit from it.
- By taking ur meds on schedule, ur keeping ur viral load low and ur CD4 count right where it needs 2 be! It's worth the effort!!
- If u slip up, the best choice is 2 get right back 2 taking ur meds ASAP!

Relapse prevention

- Which feelings R triggers 4 U? Txt them to us. Text EXAMPLE for examples of common ones.
- Keep ur life in balance! Have fun with family or friends, be kind to yourself, and always fill in free time with activities!
- Relapse is a slow process that begins long b4 U actually pick up or start drinking. It helps to watch 4 early signs. Do u know ur signs?

HIV risk behaviors

- Even if u r taking meds and lower ur viral load, there's still a risk that u will transmit HIV to a partner during unprotected sex. Always use a condom!
- If U get infected with a different strain of HIV, this is called "superinfection." It can make u sicker bc it may b harder 4 ur immune system 2 control.
- Safe sex takes two! Make sure 2 talk to ur partner about using condoms beforehand.

HIV Risk Reduction Content

Text messages targeting HIV risk reduction were developed based on key constructs in the Cognitive-Social Health Information Processing model [49] coupled with a recently developed text messaging–based intervention targeting HIV risk behaviors among methamphetamine users [35]. Psychoeducational messages regarding HIV transmission, medical consequences, treatments, risky drug use behaviors, sexual risk behaviors, and ways to prevent transmission were included. HIV risk reduction messages comprised 25% of those sent to users each week.

Adherence Content

Messages concerning HIV medication adherence were based on the CBT program Life-Steps [13], which comprised education, problem solving, and rehearsal strategies to help patients develop better skills for adhering to HIV treatment. Content following the Life-Steps model was tailored to each individual based on the top 3 barriers to adherence identified in a meeting with a CBT clinician at baseline. Content may have included education about adherence, scheduling, cue control strategies including the use of the mobile phone alarm, adaptive thoughts about adherence, and improving communication with medical providers [11]. Adherence messages comprised 25% of those sent to each user weekly.

Text CRAVE

In addition to the programmed delivery of daily messages, participants had the option to send a CRAVE text that generated programmed feedback in the form of advice or suggestions when they experienced a craving [50]. In this regard, the TXT-CBT intervention provided a near real-time medium to facilitate the use of social support and feedback, key elements of CBT model, for coping with the craving without using. To keep the messages novel and nonrepetitive, participants rarely (if ever) received the exact same message more than once throughout the duration of the study.

Treatment As Usual

All participants were receiving usual care for HIV, which comprised pharmacological management by a physician in an infectious disease clinic setting. Generally, participants were scheduled for monthly visits with their physician and quarterly assessment of viral load and CD4 counts.

Clinician Involvement

Apart from the single face-to-face CBT session, TXT-CBT participants may have had contact with the CBT clinician in one of two contexts. In the text CALL function, participants were prompted to text the word CALL if they needed more instruction about how to implement a particular coping skill that they had planned to use to facilitate ART adherence. When a text CALL was received, a clinician called the participant

back and provided counseling to assist with the specific skill for which guidance was needed. In the text LIFELINE function, participants could text the word LIFELINE if they needed to speak to a clinician during business hours. All participants were able to use this function a total of three times during the 12-week intervention. For both text CALL and text LIFELINE functions, prior to receiving a call back from a clinician, participants received an automated response to remind them of the hours during which the clinician is available and were instructed to call 911 or go to an emergency room for any urgent matters beyond these hours or that required an immediate response. If the text was received during business hours, the clinician called the participant on the same day. For any participant who used the LIFELINE function three times or more, the protocol specified that a licensed clinician on the research team was to be consulted to determine whether a treatment referral was indicated and/or whether the participant could continue to participate in the study.

Technical Support

Participants received weekly calls from the research staff to collect qualitative data concerning the perceived helpfulness of the TXT-CBT intervention and address any technical difficulties they may have been experiencing. A research assistant reviewed the text messaging logs regularly to monitor whether text messages were being sent on time and whether participants were engaging in texting. If participants wished to disenroll from the study they could text the keyword STOP.

Outcome Measures

See Table 1 for an overview of the outcome measures. Primary outcomes included ART adherence, substance use, and HIV risk behaviors. ART adherence was assessed by phone using an unannounced pill count (UPC) procedure. All other outcome measures were administered in face-to-face interviews, with some clinician-administered measures and the majority of the assessments conducted using a Web-based data entry system. Participants were compensated in gift cards as follows: $40 for the baseline assessment, $20 for each monthly face-to-face assessment, and $20 for each phone-based pill count procedure. Additionally, for bringing in photocopies of viral load and CD4 count assay reports from their primary HIV care provider, participants were compensated $20 at baseline (BL), treatment end, and follow-up.

Primary Outcomes

Substance Use

Substance use was assessed using urine drug screens, the Addiction Severity Index, and the Timeline Followback (TLFB) method. Urine drug screens were collected at baseline and weeks 4, 8, 12, and 24 using temperature-controlled test cups. A US Food and Drug Administration–approved one-step, rapid dip drug test is used (CLIAwaived Inc). The urine drug screens tested for the presence of amphetamines, benzodiazepines, methadone, cocaine, methamphetamine, barbiturates, oxycotin, opiates, and marijuana.

The Addiction Severity Index [51], collected at baseline, treatment end, and follow-up, was used to assess psychiatric and substance use disorder severity and other domains of functioning. Composite scores (alcohol and drug, psychiatric, legal, family, and employment) will be contrasted between groups at baseline to evaluate the effectiveness of randomization. Drug use severity composite scores will be used as a covariate in the analysis of differential treatment effects on outcomes.

The TLFB, a calendar-assisted structured interview [52] with demonstrated validity in substance treatment samples [53], was used to assess drug use in the preceding 90-day period at baseline and follow-up and preceding 30-day drug use at weeks 4, 8, and 12. The TLFB was used to calculate self-report substance outcome variables including percent days abstinent as reported in Project MATCH [54]. Time to first relapse was also evaluated using the TLFB. As in prior work [55], relapse was defined as the first drug use following 7 consecutive days of abstinence after the initiation of treatment.

HIV Risk Behavior

The Behavioral Risk Assessment [56] measured HIV risk behavior. This instrument recorded data on participants' sociodemographic characteristics (gender identity, sexual identity, age, race/ethnicity, HIV status, educational attainment, housing status), substance use in the previous 30 days (injection and noninjection drug use and safe needle use protocol), number and gender of sexual partners in the previous 30 days (main, casual, anonymous, exchange and male, female, male-to-female preoperative transgender, female-to-male preoperative transgender), and details about the participants' three most recent sexual encounters within the previous 12 months (partner type, number of partners in the encounter, HIV status of partner[s], sexual activities during the encounter, substance use by participant and partner[s], location of sexual encounter).

ART Adherence

ART adherence was assessed using both phone-based UPCs and viral load data. Both home- and phone-based UPCs have been shown to be reliable and valid measures of HIV treatment adherence, yielding comparable data to electronic medication monitoring [57,58] and significant correspondence with plasma viral load [59]. At the initial research visit, participants were trained by an intake assessor and a phone-based pill counter on the telephone in procedures for conducting UPCs. Training focuses on instructing participants to organize and count their pills. The first UPC was conducted within 1 week of the training, with subsequent monthly UPCs at unannounced times during and after the intervention through follow-up at week 24. All UPCs were conducted for each ART medication the participant is taking. Pharmacy information from pill bottles was also collected to verify the number of pills dispensed between calls. A medication adherence score was then calculated as the ratio of pills counted to pills prescribed, taking into account the number of pills dispensed. Using this method, the adherence score represents the percentage of pills taken as prescribed averaged across medications [60].

Viral load served as a biological indicator of adherence. Consistent with the typical frequency with which viral load is assessed in clinical settings, data concerning viral load was

collected at baseline, treatment end, and follow-up. Participants either provided us with a copy of their latest viral load results or signed a medical release of information allowing us to obtain their viral load results directly from their medical provider.

Table 1. Key variables and measurements.

	Variables	Measurements	Screen	BL	Week 4	Week 8	Week 12	Follow-up
Primary outcomes								
	Substance use	Addiction Severity Index[b]		x			x	x
		Urine drug screen[b]		x	x	x	x	x
		Timeline Followback[b]		x	x	x	x	x
	HIV risk behavior	Reback Behavioral Risk Assessment[c]		x			x	x
	ART adherence	Unannounced pill counts[b]		x	x	x	x	x
		Viral load/CD4[b]		x			x	x
Secondary outcomes								
	Medication compliance	Self-report[c]		x	x	x	x	x
	Behavioral strategies	Self-report[c]		x				x
	Depression	PHQ-9[c,d]		x	x	x	x	x
	Anxiety	OASIS[c,e]		x	x	x	x	x
	Drug-taking self-efficacy	Drug-Taking Confidence Questionnaire[c]		x			x	x
	Health-related quality of life	SF-12[c,f]		x			x	x
	Readiness for change	SOCRATES-D[c,g]		x				
Covariates								
	Demographics	Self-report[c]	x					
	Psychiatric diagnosis	M.I.N.I. International Neuropsychiatric Interview[b]	x					
	Concomitant medications	Self-report[b]		x	x	x	x	x
	Ancillary treatments	Self-report[c]		x	x	x	x	x
Participant satisfaction [a]								
	Participant satisfaction	Weekly qualitative calls[b]			x	x	x	
	Participant adherence	Message exposure[b]			x	x	x	

[a]Only for participants randomized to the TXT-CBT group.

[b]Research assistant–administered.

[c]Participants used a Web-based data entry system.

[d]Patient Health Questionnaire.

[e]Overall Anxiety Severity and Impairment Scale.

[f]Short Form Health Survey.

[g]Stages of Change Readiness and Treatment Eagerness Scale.

Secondary Outcomes

Self-Reported Medication Adherence

Self-reported adherence was assessed monthly using a brief 3-item adherence survey developed by Kalichman et al [61]. Using a visual analogue rating scale, participants were asked to indicate their best guess, ranging between 0% and 100%, about how much of their HIV medication they have taken in the past week and in the past month. They were also asked how confident they were that they can take all of their HIV medications in the next week.

Behavioral Strategies for Adherence

From a 25-item behavioral strategies checklist developed by Kalichman et al [60], participants were asked to indicate how often they have used these strategies during the past 3 months. Answer choices are never, sometimes, often, very often, and always. Examples of strategies included in the questionnaire are "used a pill box organized by day of the week" and "used bedtime as a reminder to take medications."

Depression

The Patient Health Questionnaire (PHQ-9) [62,63] is a self-administered, 9-item questionnaire used to assess depression. It includes DSM-IV depression criteria as well as other major depressive symptoms. The PHQ-9 is a reliable and valid measure of depression [62,63]. Participants were asked to report "how often they have been bothered by any of the following problems" with response choices ranging from "not at all" to "nearly every day."

Anxiety

The Overall Anxiety Severity and Impairment Scale (OASIS) was used to assess severity and impairment associated with anxiety [64]. It is a 5-item measure that is valid across anxiety disorders, for multiple anxiety disorders, and with subthreshold symptoms [64]. Participants were asked to identify which answer best describes what they have been feeling in the past week. Three questions have answer choices that range from "none" to "extreme," and two range from "none" to "constant" anxiety.

Drug Taking Self-Efficacy

Drug taking self-efficacy was measured using the Drug-Taking Confidence Questionnaire [65], which measures confidence in avoiding alcohol and other drugs (abstinence goal) or heavy use (moderation goal) across the 8 high-risk categories in Marlatt's taxonomy of relapse precipitants [66]. Participants imagined themselves in 8 specific situations and rated confidence in resisting the urge to drink heavily or use a specific drug.

Health-Related Quality of Life

The health status questionnaire [67,68] measures mental and physical functioning as well as overall health-related quality of life. All 12 questions come from the 36-item Short Form Health Survey (SF-36) [67,68]. Participants were asked whether their daily activities are impacted as a result of their physical health or emotional problems.

Readiness for Change

The Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES-D) is a 19-item scale used to assess readiness and motivation for change in drug users [69]. The SOCRATES instrument has 3 subscales: Recognition, Ambivalence and Taking Steps. Participants are asked to rate how much they agree or disagree with a statement "right now." Possible answers range from "strongly disagree" to "strongly agree." Examples of statements are "I really want to make changes in my use of drugs," "sometimes I wonder if I am in control of my drug use," and "I am actively doing things now to cut down or stop my use of drugs."

Covariates

Demographic variables, psychiatric diagnosis, ancillary treatments, and message exposure (participant adherence to TXT-CBT) were examined as potential moderating or mediating variables.

Participant Satisfaction With TXT-CBT

Participant satisfaction with the TXT-CBT intervention was assessed using qualitative weekly phone-based interviews in which those assigned to the experimental group were asked a series of scripted questions concerning the perceived helpfulness of the intervention in that week. Participants were queried concerning any messages that stood out as particularly helpful or that they might have disliked and whether and how the intervention helped them to change behaviors in the key domains of interest (ie, ART adherence, drug use, and/or other risk behaviors).

Statistical Analyses

Analyses in the pilot study will allow basic description of the sample in terms of distributional characteristics, variability, and missing data as well as examination of possible effect sizes in comparing the groups. Preliminary analyses will include descriptive statistics and confidence intervals, computation of scale scores, and assessment of reliability. Exploratory analyses will use a random effects regression approach to examine group differences across the repeated observations (baseline, treatment end, and follow-up) as specified in each of the study aims. This type of model accommodates the (potentially correlated) repeated measures and allows for inclusion of covariates (ie, subject characteristics on which the groups differ at admission) and additional repeated observations for some measures (eg, viral load at baseline, treatment end, and follow-up). The pilot sample size of 25 per group should allow detection of an effect size of approximately d=.7 in differential change in outcomes from baseline to follow-up, assuming a moderate correlation of 0.50 over time and allowing attrition of up to 20% (power=.80, one-tailed alpha=.05). This detectable effect size would translate to a differential change of about 19 points on the ART adherence composite score assuming an average (across time) pooled (across groups) standard deviation of about 27, as found by Safren [11] for a specialized CBT intervention for HIV-infected individuals. Safren et al found a differential change of approximately 25 points.

Separate analyses will address each measure in aims 1, 2, and 3. For example, analyses for aim 2 will include as dependent variables urine toxicology results for opioids and stimulants, ART adherence scores, health-related quality of life scores from the SF-12, and select items from the ASI indicating number of days in the past month utilizing health services. Analyses for aim 3 will include correlations between changes in self-efficacy (Drug-Taking Confidence Questionniare) and treatment retention and substance use during and after treatment.

Results

Currently, data collection is ongoing and is expected to be completed in July 2016. We expect that analysis and results will be available by September 2016.

Discussion

Principal Findings

In this clinical trial protocol, we present the study design of a two-phase intervention development and evaluation project in which we (1) developed, with user input, a 12-week CBT-based text messaging intervention targeting ART adherence and drug use in an adult addicted population with HIV and (2) pilot tested the intervention in an RTC. We hypothesize that TXT-CBT will directly impact ART adherence and substance use, over and above the effect of usual care for HIV, relative to those who receive usual HIV care in conjunction with an informational pamphlet concerning HIV, ART adherence, and substance use. Exploratory analyses will be conducted to examine process changes in TXT-CBT and their associations with outcomes. We expect that mechanisms of action demonstrated in prior work examining the key ingredients of face-to-face CBT (eg, self-efficacy) will also account, at least in part, for any therapeutic effects of TXT-CBT on the target clinical outcomes in this study.

Limitations

The major limitation of the study design is the absence of a control condition matched for time and attention. Likewise, data collection procedures that are specific to the active TXT-CBT condition, such as qualitative data collection efforts to ascertain perceived acceptability and helpfulness of the intervention, were not balanced between conditions and could potentiate the effects of the TXT-CBT intervention. Nevertheless, this initial investigation is designed to establish the acceptability and preliminary outcomes of the TXT-CBT intervention; if the current hypotheses are supported, a text messaging control condition will be developed as part of a larger, fully powered RCT. Likewise, the sample size limits the statistical power for detecting effects of the intervention; nevertheless, as a pilot trial, the proposed N is appropriate for meeting the study objectives.

Strengths

This is the first trial to our knowledge that uses a theory-based intervention approach to the treatment of addiction via a text messaging platform. As such, rather than implementing a single behavioral strategy (eg, reminders or motivational sayings), the TXT-CBT provides a therapy program that draws its content from evidence-based addiction and medication adherence interventions. Second, we focus on a well-defined population (ie, HIV-infected adults with substance use disorders) with an urgent need for accessible, low-cost intervention approaches to reduce risk factors for the spread of HIV infection (including drug use and poor ART adherence). Third, we involved the users closely in the intervention development process to optimize the likelihood of acceptability and participant retention in TXT-CBT. Finally, by investigating mechanisms of action of TXT-CBT, this study is expected to advance our understanding of the psychological processes by which text messaging interventions effect behavior change.

Conclusions

We present the methodology germane to the development and pilot testing of TXT-CBT, a theory-based intervention using a technology-based text messaging platform for HIV-infected adults with substance use disorders. By providing support to maximize HIV treatment regimen adherence and reinforce coping skills to prevent relapse to substance use, TXT-CBT may provide a promising, cost-effective, and easily deployable strategy for the treatment of substance users who are HIV-infected.

Acknowledgments

The research presented in this paper was supported by grant R34 DA033196 from the National Institute on Drug Abuse. We are thankful to Seth Kalichman for his valuable input concerning ART adherence measurement. We thank Anne Bellows Lee, Vanessa Novoa, and Robert Veliz for their assistance with data collection.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Substance Abuse and Mental Health Services Administration Pamphlet. Drugs, Alcohol and HIV/AIDS: A Consumer Guide.

[PDF File (Adobe PDF File), 1MB - resprot_v5i2e131_app1.pdf]

References

1. HIV in the United States. Atlanta, GA: Centers for Disease Control and Prevention; 2011 Nov. URL: http://www.cdc.gov/hiv/resources/factsheets/PDF/us.pdf [accessed 2016-05-27] [WebCite Cache ID 6hoJcHtNo]
2. Degenhardt L, Mathers B, Vickerman P, Rhodes T, Latkin C, Hickman M. Prevention of HIV infection for people who inject drugs: why individual, structural, and combination approaches are needed. Lancet 2010 Jul 24;376(9737):285-301. [doi: 10.1016/S0140-6736(10)60742-8] [Medline: 20650522]
3. Arasteh K, Des Jarlais DC, Perlis TE. Alcohol and HIV sexual risk behaviors among injection drug users. Drug Alcohol Depend 2008 May 1;95(1-2):54-61 [FREE Full text] [doi: 10.1016/j.drugalcdep.2007.12.008] [Medline: 18242009]

4. Mathers BM, Degenhardt L, Phillips B, Wiessing L, Hickman M, Strathdee SA, 2007 Reference Group to the UN on HIV and Injecting Drug Use. Global epidemiology of injecting drug use and HIV among people who inject drugs: a systematic review. Lancet 2008 Nov 15;372(9651):1733-1745. [doi: 10.1016/S0140-6736(08)61311-2] [Medline: 18817968]
5. World Drug Report 2010. Vienna, Austria: United Nations Office on Drugs and Crime (UNODC); 2010. URL: https://www.unodc.org/documents/wdr/WDR_2010/World_Drug_Report_2010_lo-res.pdf [accessed 2016-05-27] [WebCite Cache ID 6hoK3yFTu]
6. Shoptaw S, Reback CJ, Peck JA, Yang X, Rotheram-Fuller E, Larkins S, et al. Behavioral treatment approaches for methamphetamine dependence and HIV-related sexual risk behaviors among urban gay and bisexual men. Drug Alcohol Depend 2005 May 9;78(2):125-134. [doi: 10.1016/j.drugalcdep.2004.10.004] [Medline: 15845315]
7. Wood E, Montaner JSG, Yip B, Tyndall MW, Schechter MT, O'Shaughnessy MV, et al. Adherence and plasma HIV RNA responses to highly active antiretroviral therapy among HIV-1 infected injection drug users. CMAJ 2003 Sep 30;169(7):656-661 [FREE Full text] [Medline: 14517122]
8. Palepu A, Tyndall MW, Joy R, Kerr T, Wood E, Press N, et al. Antiretroviral adherence and HIV treatment outcomes among HIV/HCV co-infected injection drug users: the role of methadone maintenance therapy. Drug Alcohol Depend 2006 Sep 15;84(2):188-194. [doi: 10.1016/j.drugalcdep.2006.02.003] [Medline: 16542797]
9. Vlahov D, Celentano DD. Access to highly active antiretroviral therapy for injection drug users: adherence, resistance, and death. Cad Saude Publica 2006 Apr;22(4):705-718 [FREE Full text] [Medline: 16612417]
10. Katzenstein DA. Adherence as a particular issue with protease inhibitors. J Assoc Nurses AIDS Care 1997;8 Suppl:10-17. [Medline: 9356957]
11. Safren SA, O'Cleirigh C, Tan JY, Raminani SR, Reilly LC, Otto MW, et al. A randomized controlled trial of cognitive behavioral therapy for adherence and depression (CBT-AD) in HIV-infected individuals. Health Psychol 2009 Jan;28(1):1-10 [FREE Full text] [Medline: 19210012]
12. Wood E, Kerr T, Zhang R, Guillemi S, Palepu A, Hogg RS, et al. Poor adherence to HIV monitoring and treatment guidelines for HIV-infected injection drug users. HIV Med 2008 Aug;9(7):503-507 [FREE Full text] [Medline: 18484977]
13. Safren S, Otto M, Worth J. Life-Steps: Applying cognitive-behavioral therapy to patient adherence to HIV medication treatment. Cognitive and Behavioral Practice 1999(6):332-341.
14. Safren SA, Otto MW, Worth JL, Salomon E, Johnson W, Mayer K, et al. Two strategies to increase adherence to HIV antiretroviral medication: life-steps and medication monitoring. Behav Res Ther 2001 Oct;39(10):1151-1162. [Medline: 11579986]
15. Soroudi N, Perez G, Gonzalez JS, Greer JA, Pollack MH, Otto MW, et al. CBT for medication adherence and depression (CBT-AD) in HIV-infected patients receiving methadone maintenance therapy. Cognitive and Behavioral Practice 2008;15(1):93-106 [FREE Full text] [doi: 10.1016/j.cbpra.2006.11.004]
16. Copenhaver MM, Bruce RD, Altice FL. Behavioral counseling content for optimizing the use of buprenorphine for treatment of opioid dependence in community-based settings: a review of the empirical evidence. Am J Drug Alcohol Abuse 2007;33(5):643-654 [FREE Full text] [doi: 10.1080/00952990701522674] [Medline: 17891657]
17. Church SH, Rothenberg JL, Sullivan MA, Bornstein G, Nunes EV. Concurrent substance use and outcome in combined behavioral and naltrexone therapy for opiate dependence. Am J Drug Alcohol Abuse 2001 Aug;27(3):441-452. [Medline: 11506261]
18. McAuliffe WE. A randomized controlled trial of recovery training and self-help for opioid addicts in New England and Hong Kong. J Psychoactive Drugs 1990;22(2):197-209. [Medline: 2197394]
19. Pollack MH, Penava SA, Bolton E, Worthington JJ, Allen GL, Farach FJ, et al. A novel cognitive-behavioral approach for treatment-resistant drug dependence. J Subst Abuse Treat 2002 Dec;23(4):335-342. [Medline: 12495795]
20. Stein MD, Herman DS, Solomon DA, Anthony JL, Anderson BJ, Ramsey SE, et al. Adherence to treatment of depression in active injection drug users: the minerva study. J Subst Abuse Treat 2004 Mar;26(2):87-93. [Medline: 15050085]
21. Roffman RA, Stephens RS, Simpson EE, Whitaker DL. Treatment of marijuana dependence: preliminary results. J Psychoactive Drugs 1988;20(1):129-137. [Medline: 3392627]
22. Annis H, Davis C. Relapse prevention. In: Hester RK, Miller WR, editors. Handbook of alcoholism treatment approaches: Alternative approaches. New York: Pergamon Press; 1989:170-182.
23. Carroll KM, Nich C, Ball SA, McCance E, Frankforter TL, Rounsaville BJ. One-year follow-up of disulfiram and psychotherapy for cocaine-alcohol users: sustained effects of treatment. Addiction 2000 Sep;95(9):1335-1349. [Medline: 11048353]
24. Monti P, Abrams D, Kadden R, Rohsenow D, Cooney N. Treating alcohol dependence: A coping skills therapy guide. New York: Guilford; 1989.
25. Pinkerton S, Holtgrave D, Johnson-Masotti A, Turk M, Hackl K, DiFranceisco W. Cost-effectiveness of the NIMH Multisite HIV Prevention intervention. AIDS and Behavior, 6 2002:83-96.
26. Schroeder JR, Epstein DH, Umbricht A, Preston KL. Changes in HIV risk behaviors among patients receiving combined pharmacological and behavioral interventions for heroin and cocaine dependence. Addict Behav 2006 May;31(5):868-879. [Medline: 16085366]

27. ICT facts and figures: the world in 2015, aggregate data. Mobile-cellular subscriptions. Geneva, Switzerland: International Telecommunication Union (ITU); 2015. URL: https://www.itu.int/en/ITU-D/Statistics/Pages/stat/default.aspx [accessed 2016-06-02] [WebCite Cache ID 6hyB0WAwY]
28. CTIA's semi-annual wireless industry survey. Washington, DC: CTIA: The Wireless Association; 2015. URL: http://www.ctia.org/your-wireless-life/how-wireless-works/annual-wireless-industry-survey [accessed 2016-06-12] [WebCite Cache ID 6iCcC2utj]
29. Patrick K, Raab F, Adams MA, Dillon L, Zabinski M, Rock CL, et al. A text message-based intervention for weight loss: randomized controlled trial. J Med Internet Res 2009;11(1):e1 [FREE Full text] [Medline: 19141433]
30. Patrick K, Norman GJ, Davila EP, Calfas KJ, Raab F, Gottschalk M, et al. Outcomes of a 12-month technology-based intervention to promote weight loss in adolescents at risk for type 2 diabetes. J Diabetes Sci Technol 2013 May;7(3):759-770 [FREE Full text] [Medline: 23759410]
31. Shapiro JR, Koro T, Doran N, Thompson S, Sallis JF, Calfas K, et al. Text4Diet: a randomized controlled study using text messaging for weight loss behaviors. Prev Med 2012 Nov;55(5):412-417. [Medline: 22944150]
32. Franklin VL, Waller A, Pagliari C, Greene SA. A randomized controlled trial of Sweet Talk, a text-messaging system to support young people with diabetes. Diabet Med 2006 Dec;23(12):1332-1338. [Medline: 17116184]
33. Hurling R, Catt M, Boni MD, Fairley BW, Hurst T, Murray P, et al. Using internet and mobile phone technology to deliver an automated physical activity program: randomized controlled trial. J Med Internet Res 2007;9(2):e7 [FREE Full text] [doi: 10.2196/jmir.9.2.e7] [Medline: 17478409]
34. Puccio JA, Belzer M, Olson J, Martinez M, Salata C, Tucker D, et al. The use of cell phone reminder calls for assisting HIV-infected adolescents and young adults to adhere to highly active antiretroviral therapy: a pilot study. AIDS Patient Care STDS 2006 Jun;20(6):438-444. [doi: 10.1089/apc.2006.20.438] [Medline: 16789857]
35. Reback CJ, Ling D, Shoptaw S, Rohde J. Developing a text messaging risk reduction intervention for methamphetamine-using MSM: research note. Open AIDS J 2010;4:116-122 [FREE Full text] [doi: 10.2174/1874613601004030116] [Medline: 20657827]
36. Reback C, Grant D, Fletcher J, Branson C, Shoptaw S, Bowers J, et al. Text messaging reduces HIV risk behaviors among methamphetamine-using men who have sex with men. AIDS and Behavior 2012;16(7):1993-2002.
37. Ybarra ML, Holtrop J, Prescott TL, Rahbar MH, Strong D. Pilot RCT results of stop my smoking USA: a text messaging-based smoking cessation program for young adults. Nicotine Tob Res 2013 Aug;15(8):1388-1399 [FREE Full text] [doi: 10.1093/ntr/nts339] [Medline: 23348969]
38. Whittaker R, McRobbie H, Bullen C, Borland R, Rodgers A, Gu Y. Mobile phone-based interventions for smoking cessation. Cochrane Database Syst Rev 2012:CD006611. [doi: 10.1002/14651858.CD006611.pub3] [Medline: 23152238]
39. Free C, Phillips G, Galli L, Watson L, Felix L, Edwards P, et al. The effectiveness of mobile-health technology-based health behaviour change or disease management interventions for health care consumers: a systematic review. PLoS Med 2013 Jan;10(1):e1001362 [FREE Full text] [doi: 10.1371/journal.pmed.1001362] [Medline: 23349621]
40. Brendryen H, Kraft P. Happy ending: a randomized controlled trial of a digital multi-media smoking cessation intervention. Addiction 2008 Mar;103(3):478-484. [doi: 10.1111/j.1360-0443.2007.02119.x] [Medline: 18269367]
41. Levine D, McCright J, Dobkin L, Woodruff AJ, Klausner JD. SEXINFO: a sexual health text messaging service for San Francisco youth. Am J Public Health 2008 Mar;98(3):393-395. [doi: 10.2105/AJPH.2007.110767] [Medline: 18235068]
42. Marsch LA, Bickel WK. Efficacy of computer-based HIV/AIDS education for injection drug users. Am J Health Behav 2004;28(4):316-327. [Medline: 15228968]
43. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. J Pharmacol Pharmacother 2010 Jul;1(2):100-107 [FREE Full text] [doi: 10.4103/0976-500X.72352] [Medline: 21350618]
44. Jairath N, Hogerney M, Parsons C. The role of the pilot study: a case illustration from cardiac nursing research. Appl Nurs Res 2000 May;13(2):92-96. [Medline: 10842905]
45. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. J Eval Clin Pract 2004 May;10(2):307-312. [doi: 10.1111/j.2002.384.doc.x] [Medline: 15189396]
46. Becker PT. Publishing pilot intervention studies. Res Nurs Health 2008 Feb;31(1):1-3. [doi: 10.1002/nur.20268] [Medline: 18183570]
47. Kraemer HC, Kupfer DJ. Size of treatment effects and their importance to clinical research and practice. Biol Psychiatry 2006 Jun 1;59(11):990-996. [doi: 10.1016/j.biopsych.2005.09.014] [Medline: 16368078]
48. Stewart P. Cincinnati Childrens Hospital Medical Center. 2007. Protocol submission: Small and/or pilot studies URL: http://www.cincinnatichildrens.org/research/cincinnati/support/ctrc/default/ [accessed 2016-06-02] [WebCite Cache ID 6hyAhqrmc]
49. Miller WR, Tonigan JS. Assessing drinkers motivation for change: The Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES). Psychology of Addictive Behaviors 1996;10:81-89.
50. Rodgers A, Corbett T, Bramley D, Riddell T, Wills M, Lin R, et al. Do u smoke after txt? Results of a randomised trial of smoking cessation using mobile phone text messaging. Tob Control 2005 Aug;14(4):255-261 [FREE Full text] [doi: 10.1136/tc.2005.011577] [Medline: 16046689]

51. McLellan AT, Kushner H, Metzger D, Peters R, Smith I, Grissom G, et al. The Fifth Edition of the Addiction Severity Index. J Subst Abuse Treat 1992;9(3):199-213. [Medline: 1334156]
52. Sobell LC, Sobell MB. Timeline follow-back: A technique for assessing self-reported ethanol consumption. In: Allen J, Litten RZ, editors. Measuring Alcohol Consumption: Psychosocial and Biological Methods. Totowa, NJ: Humana Press; 1992:41-72.
53. Fals-Stewart W, O'Farrell TJ, Freitas TT, McFarlin SK, Rutigliano P. The timeline followback reports of psychoactive substance use by drug-abusing patients: psychometric properties. J Consult Clin Psychol 2000 Feb;68(1):134-144. [Medline: 10710848]
54. Project MATCH Research Group. Matching alcoholism treatments to client heterogeneity: Project MATCH posttreatment drinking outcomes. J Stud Alcohol 1997 Jan;58(1):7-29. [Medline: 8979210]
55. Cornelius JR, Maisto SA, Martin CS, Bukstein OG, Salloum IM, Daley DC, et al. Major depression associated with earlier alcohol relapse in treated teens with AUD. Addict Behav 2004 Jul;29(5):1035-1038. [doi: 10.1016/j.addbeh.2004.02.056] [Medline: 15219354]
56. Reback C. Behavioral Risk Assessment (unpublished instrument). Friends Research Institute, Inc 2005.
57. Kalichman SC, Amaral CM, Cherry C, Flanagan J, Pope H, Eaton L, et al. Monitoring medication adherence by unannounced pill counts conducted by telephone: reliability and criterion-related validity. HIV Clin Trials 2008;9(5):298-308 [FREE Full text] [doi: 10.1310/hct0905-298] [Medline: 18977718]
58. Kalichman SC, Amaral C, Swetsze C, Eaton L, Kalichman MO, Cherry C, et al. Monthly unannounced pill counts for monitoring HIV treatment adherence: tests for self-monitoring and reactivity effects. HIV Clin Trials 2010;11(6):325-331. [doi: 10.1310/hct1106-325] [Medline: 21239360]
59. Giordano TP, Guzman D, Clark R, Charlebois ED, Bangsberg DR. Measuring adherence to antiretroviral therapy in a diverse population using a visual analogue scale. HIV Clin Trials 2004;5(2):74-79. [doi: 10.1310/JFXH-G3X2-EYM6-D6UG] [Medline: 15116282]
60. Kalichman SC, Kalichman MO, Cherry C, Swetzes C, Amaral CM, White D, et al. Brief behavioral self-regulation counseling for HIV treatment adherence delivered by cell phone: an initial test of concept trial. AIDS Patient Care STDS 2011 May;25(5):303-310 [FREE Full text] [doi: 10.1089/apc.2010.0367] [Medline: 21457056]
61. Kalichman SC, Amaral CM, Swetzes C, Jones M, Macy R, Kalichman MO, et al. A simple single-item rating scale to measure medication adherence: further evidence for convergent validity. J Int Assoc Physicians AIDS Care (Chic) 2009;8(6):367-374 [FREE Full text] [doi: 10.1177/1545109709352884] [Medline: 19952289]
62. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA 1999 Nov 10;282(18):1737-1744. [Medline: 10568646]
63. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001 Sep;16(9):606-613 [FREE Full text] [Medline: 11556941]
64. Norman SB, Cissell SH, Means-Christensen AJ, Stein MB. Development and validation of an Overall Anxiety Severity And Impairment Scale (OASIS). Depress Anxiety 2006;23(4):245-249. [doi: 10.1002/da.20182] [Medline: 16688739]
65. Sklar SM, Annis HM, Turner NE. Development and validation of the drug-taking confidence questionnaire: a measure of coping self-efficacy. Addict Behav 1997;22(5):655-670. [Medline: 9347068]
66. Marlett GA, Gordon JR, editors. Relapse Prevention: Maintenance Strategies in the Treatment of Addictive Behaviors. New York: Guilford; 1985.
67. Ware J, Kosinski M, Turner-Bowker D, Gandek B. User's manual for the SF-12v2 Health Survey. Lincoln, RI: QualityMetric Incorporated; 2002.
68. Ware J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996 Mar;34(3):220-233. [Medline: 8628042]
69. Miller W. Form 90: A structured assessment interview for drinking and related behaviors: Test manual. Rockville, MD: National Institute on Alcohol Abuse and Alcoholism; 1996. URL: http://pubs.niaaa.nih.gov/publications/ProjectMatch/match05.pdf [accessed 2016-06-12] [WebCite Cache ID 6iCbDhZnw]

Abbreviations

ART: antiretroviral treatment
CBT: cognitive behavioral therapy
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
OASIS: Overall Anxiety Severity and Impairment Scale
OST: opioid substitution therapy
PHQ-9: Patient Health Questionnaire–9
PWID: people who inject drugs
RCT: randomized controlled trial
SEXINFO: Sexually Transmitted Infection and HIV Prevention Program for Adolescents

SF-36: 36-item Short Form Health Survey
SOCRATES-D: Stages of Change Readiness and Treatment Eagerness Scale
TAU: treatment-as-usual
TLFB: Timeline Followback
TXT-CBT: cognitive behavioral therapy–based text messaging intervention
UPC: unannounced pill counts

Edited by G Eysenbach; submitted 03.12.15; peer-reviewed by N Shah, K Kaipainen, A Baumel; comments to author 07.01.16; revised version received 15.02.16; accepted 20.02.16; published 24.06.16.

Please cite as:
Glasner-Edwards S, Patrick K, Ybarra ML, Reback CJ, Rawson RA, Chokron Garneau H, Chavez K, Venegas A
A Cognitive Behavioral Therapy–Based Text Messaging Intervention Versus Medical Management for HIV-Infected Substance Users: Study Protocol for a Pilot Randomized Trial
JMIR Res Protoc 2016;5(2):e131
URL: http://www.researchprotocols.org/2016/2/e131/
doi:10.2196/resprot.5407
PMID:27341852

Protocol

Developing a Video-Based eHealth Intervention for HIV-Positive Gay, Bisexual, and Other Men Who Have Sex with Men: Study Protocol for a Randomized Controlled Trial

Sabina Hirshfield[1], PhD; Martin J Downing Jr[1], PhD; Jeffrey T Parsons[2], PhD; Christian Grov[3], MPH, PhD; Rachel J Gordon[4], MPH, MD; Steven T Houang[1], BA; Roberta Scheinmann[1], MPH; Patrick S Sullivan[5], PhD, DVM; Irene S Yoon[1], MSc; Ian Anderson[6], BA; Mary Ann Chiasson[1], DrPH

[1]Public Health Solutions, Research and Evaluation, New York, NY, United States

[2]Center for HIV/AIDS Educational Studies and Training (CHEST), Department of Psychology, and the Graduate Center of the City University of New York (CUNY), Hunter College, New York, NY, United States

[3]Center for HIV/AIDS Educational Studies and Training (CHEST), Graduate School of Public Health and Health Policy, City University of New York, New York, NY, United States

[4]Division of Infectious Diseases, Departments of Medicine and Epidemiology, Columbia University, New York, NY, United States

[5]Rollins School of Public Health, Department of Epidemiology, Emory University, Atlanta, GA, United States

[6]Smart + Strong, New York, NY, United States

Corresponding Author:
Sabina Hirshfield, PhD
Public Health Solutions
Research and Evaluation
40 Worth Street, 5th Floor
New York, NY, 10013
United States
Phone: 1 6466196676
Fax: 1 6466196777
Email: SHirshfield@healthsolutions.org

Abstract

Background: Gay, bisexual, and other men who have sex with men (GBMSM) accounted for 67% of new US human immunodeficiency virus (HIV) infections in 2012; however, less than 40% of HIV-positive GBMSM are virally suppressed. Preventing transmission from virally unsuppressed men who have condomless anal sex (CAS) with serodiscordant partners is a public health imperative. New HIV infections in GBMSM are attributed in part to online access to sex partners; therefore, low-cost eHealth interventions are a unique opportunity to reach men where they meet partners.

Objective: To describe the protocol of a randomized controlled trial evaluating whether video-based messaging delivered online may lead to reductions in serodiscordant CAS and increased HIV disclosure.

Methods: Sex Positive![+] is a two-arm, phase III, video-based randomized controlled trial delivered online to GBMSM living with HIV. Participants in the intervention arm receive 10 video vignettes grounded in social learning and social cognitive theories that are designed to elicit critical thinking around issues of HIV transmission and disclosure. Participants in the attention control arm receive 10 video vignettes that focus on healthy living. All videos are optimized for mobile viewing. The study protocol includes five online assessments conducted over a 1-year period among 1500 US white, black, or Hispanic/Latino GBMSM living with HIV who report suboptimal antiretroviral therapy (ART) adherence or a detectable viral load in the past 12 months and recent CAS (past 6 months) with HIV-negative or unknown status male partners. Compared to the control arm, we hypothesize that men who watch the intervention videos will report at 12-month follow-up significantly fewer serodiscordant CAS partners, increased HIV disclosure, and improved social cognition (eg, condom use self-efficacy, perceived responsibility).

Results: Participant recruitment began in June 2015 and ended in December 2015.

Conclusions: This protocol describes the underlying theoretical framework and measures, study design, recruitment challenges, and antifraud measures for an online, video-based randomized controlled trial that has the potential to decrease HIV transmission risk behaviors among HIV-positive GBMSM who struggle with ART adherence. The Sex Positive![+] intervention allows for

participation through multiple Internet-based mediums and has the potential to reach and engage a broader population of HIV-positive GBMSM who are virally unsuppressed.

ClinicalTrial: ClinicalTrials.gov NCT02023580; https://clinicaltrials.gov/ct2/show/NCT02023580 (Archived by WebCite at http://www.webcitation.org/6iHzA8wRG)

(JMIR Res Protoc 2016;5(2):e125) doi:10.2196/resprot.5554

KEYWORDS

eHealth interventions; GBMSM; HIV prevention; HIV disclosure; randomized controlled trial; videos

Introduction

Gay, bisexual, and other men who have sex with men (GBMSM) accounted for 67% of new human immunodeficiency virus (HIV) infections in the United States in 2012 [1]. Although antiretroviral therapy (ART) has improved survival with HIV, the low level of ART adherence presents a significant public health challenge in terms of the potential to transmit HIV [2]. Further, only three of the 96 evidence-based interventions defined by the Centers for Disease Control and Prevention have been designed for GBMSM living with HIV [3]. Among GBMSM with diagnosed HIV in the United States and Puerto Rico in 2010, it was estimated that 74% of men aged 18 to 24 years were virally unsuppressed compared to less than 40% in men aged 55 years and older. By race/ethnicity, the highest proportion of virally unsuppressed cases were among black GBMSM (63%), followed by Hispanic/Latino (58.5%), and white men (56%) [4]. This is particularly concerning because a recent study found that, compared to heterosexual males with HIV, GBMSM living with HIV who had unsuppressed viral loads had eight times the odds of engaging in serodiscordant condomless sex [5].

Preventing transmission in virally unsuppressed GBMSM who have condomless anal sex (CAS) with serodiscordant partners can have a great public health impact. Nationally, white, black, and Hispanic GBMSM continue to account for approximately 95% of newly diagnosed HIV infections among men [6]. Further, black and Hispanic men are also overrepresented as being virally unsuppressed [5,7,8]. Interventions designed to reduce CAS among GBMSM should be cost-effective and scalable, which are goals of the National HIV/AIDS Strategy [9]. Because new infections in GBMSM have been attributed in part to increased access to sex partners online [10,11], it is critical to deliver online behavioral interventions to GBMSM living with HIV to reach many high-risk men at a relatively low cost [12], engage men where they meet sex partners [13], and enable men to participate privately on a computer, tablet, or mobile phone with smartphone capabilities on their own schedule versus in a structured clinical setting [14].

Users of Technology

Primarily because of the anonymity and accessibility of online spaces (websites, mobile apps), GBMSM have been early adopters of technologies designed for sexual partnering [15]. However, as promising as technology may be for HIV prevention and because Hispanic/Latino and black populations are more likely to own mobile phones and use mobile apps compared to white populations [16,17], HIV prevention technology also introduces often-overlooked methodological pitfalls such as low engagement of racial/ethnic minorities and recruitment bias. Historically, online HIV prevention work has had low representation of minority GBMSM [18-20]. There are two likely explanations for this disparity. First, black men constitute 13% of the US male population [21], which may account for the smaller proportion who complete online surveys. Second, online recruitment bias may occur, such that researchers may not be using targeted language or graphics, or recruiting from sites that cater to minority GBMSM [22].

eHealth Interventions

Electronic health (eHealth) interventions have the potential to reach and engage GBMSM living with HIV from diverse racial/ethnic groups and socioeconomic statuses. These interventions are critical for risk-reduction efforts [23,24], can reach geographically dispersed men [12,25], and can adapt offline interventions [26]. However, few interventions have demonstrated efficacy in reducing HIV transmission from GBMSM who are HIV-positive. Recent eHealth and mobile health (mHealth) interventions for HIV-positive populations have focused on ART adherence [27,28], rather than sexual risk [29], and have been delivered through text messaging and on computers [30-33]. eHealth assessments of GBMSM living with HIV have been used to tailor provider-delivered interventions to decrease CAS with serodiscordant partners. Nevertheless, a recent provider-delivered eHealth intervention had low participation and retention, due mainly to factors such as time commitment and clinical setting [34]. Other eHealth interventions address HIV disclosure and condom use among GBMSM who are HIV-positive but are still in early stages of implementation (eg, Miranda et al [35]).

Cost-Effectiveness of eHealth Interventions

There is a great need for cost-effective HIV prevention strategies for HIV-positive populations, particularly GBMSM who constitute the majority of those living with HIV [36,37]. Even modest intervention effects can have a significant public health impact because the two most important factors that determine cost-effectiveness are (1) the HIV prevalence of the target population (preventing transmission from men who are HIV-positive rather than preventing acquisition by men who are HIV-negative) and (2) the cost per person reached [38]. Effective HIV prevention interventions that use digital media are also likely to be highly cost-effective because they can be easily replicated after development, require minimal staffing, and have unlimited geographic reach [31,38-40].

Aims and Objectives

The aim of this paper is to describe the study protocol of a randomized controlled trial (RCT) evaluating the effectiveness of a video-based messaging intervention delivered online, by comparing intervention and attention control groups on reductions in serodiscordant CAS and increases in HIV disclosure to sex partners. Through our prior work [18,19,41], we have identified a risk-reduction intervention approach for GBMSM living with HIV. The Sex Positive![+] study is conducted over a 1-year period among 1500 US white, black, and Hispanic/Latino GBMSM who were virally unsuppressed at some point during the past year, or who report suboptimal adherence to ART, and report recent CAS with serodiscordant male partners. Sex Positive![+] encompasses many characteristics found to reduce risk among HIV-positive populations in that it is theory-driven, has intervention content focused on HIV transmission behaviors, uses videos that demonstrate risk reduction and health behaviors through modeling, is delivered in an intensive manner, and is delivered over a 1-year period [42].

Methods

Trial Design

Sex Positive![+] is a two-arm randomized controlled phase III clinical trial with a 1:1 allocation ratio.

Ethics Statement

The Institutional Review Board at Public Health Solutions in New York, NY, approved all study procedures. A waiver of documentation of written consent was obtained given the Internet-based research approach. Although Federal regulation requires that researchers obtain written informed consent for research on human subjects, under 45 CFR § 46.117(c) [43], written consent can be waived for research that involves minimal risk to participants and involves no procedures for which written consent is normally required outside of the research context. This research meets that criterion and we use an alternative approach where participants click a button signifying that they have read the informed consent page and agree to participate in the study. An advantage of online studies is that the consent form is available for the participant to review and/or print at any time. This strategy complies with the requirement of 45 CFR § 46.117(c) that participants are given a written statement describing the research and risks.

A Data and Safety Monitoring Board has been established to conduct semiannual reviews of study activities and to ensure participant safety, validity, and integrity of the data. The Board is comprised of experts, independent of the trial or funding agency, in RCTs, Internet research, Web design, and HIV-positive populations. Furthermore, a Certificate of Confidentiality has been obtained from the National Institute of Mental Health to help protect the privacy of HIV-positive participants enrolled in this health-related study.

Participants

The target sample is 1500 high-risk, virally unsuppressed or less than 90% ART-adherent, US white, black, and Hispanic/Latino GBMSM living with HIV. Individuals participating in any aspect of the study must (1) be biologically male, (2) be age 18 or older, (3) be able to read and respond in English, (4) reside within the United States or a US territory, (5) report CAS with any HIV-negative or unknown status (serodiscordant) male partners in the past 6 months, (6) identify as HIV-positive, (7) report a detectable viral load, not being on ART and not knowing their viral load in the past year, or an undetectable viral load but less than 90% ART-adherent in the past 30 days, (8) identify as white, black, or Hispanic/Latino, (9) be willing to participate in an online intervention study for 12 months, and (10) have a working email address and mobile phone for intervention follow-up. We use quota sampling and targeted recruitment to ensure balanced representation of white (n=500), black (n=500), and Hispanic/Latino (n=500) men. Further, we include the following black racial/ethnic categories: black, African American, Caribbean, African, or multiethnic black [44]. In addition, we use targeted recruitment to ensure that 20% of the sample are men between the ages of 18 and 29 years. This group is overrepresented in the current HIV epidemic, particularly young men of color, and is less likely to be adherent to HIV medications or in care [4]. Men who meet study criteria, consent, and register to participate are automatically randomized into one of the two study arms.

Recruitment

Men are identified for the study through social networking websites and gay-oriented sexual networking websites, dating websites, global positioning system (GPS)-based mobile phone apps that utilize targeted recruitment by city, race, and ethnicity, and online bulletin boards. By recruiting from different types of websites and mobile phone apps, we increase our chances of reaching a broader, more diverse pool of men with HIV. The goals of recruitment are to identify eligible participants online who are willing to participate in an online, longitudinal HIV risk-reduction intervention. Based on previous research findings [22], study banner advertisements mirror the racial/ethnic composition of each study subgroup. One of our sources of recruitment is POZ Personals, the dating site for *POZ Magazine*, which distributes internal system messages to a defined subset of US male members who are HIV-positive, at least 18 years of age, and self-identify as gay or bisexual.

Primary Outcome Measures

Both HIV status disclosure to sex partners and serodiscordant CAS are assessed at each of five survey time points (baseline, 3-, 6-, 9-, and 12-month follow-up). The recall period for the primary outcome measures is the past 3 months for each of the five online assessments (Table 1).

Table 1. Survey instrument summary of primary outcomes assessed at baseline and at 3-, 6-, 9-, and 12-month follow-ups.

Primary outcomes measures	Description or lead question	Items
Serodiscordant condomless anal sex	Past 3 months, three most recent male sexual partners in one-on-one encounters	Sexual behavior by partner type (eg, one-time, repeat, exchange): insertive and/or receptive oral sex with or without condoms and ejaculation (y/n), insertive and/or receptive anal sex with or without condoms and ejaculation (y/n), drug and/or alcohol use prior to or during sex (y/n), total number of anal sex acts (with or without condoms) for each sex partner
HIV disclosure	Past 3 months, HIV disclosure with three most recent sex partners in one-on-one encounters	Demographic questions related to most recent partner(s) include: race/ethnicity, age, partner relationship type, partner serostatus, one-time vs repeat partner, and exchange vs nonexchange partner. HIV disclosure questions include: knowing partner(s) serostatus before or after having sex, asking partner(s) status, telling partner(s) one's serostatus, who disclosed their serostatus first (participant or partner), how they learned about the partner(s) serostatus (eg, asking, telling, online profile)

Secondary Outcome Measures

Secondary outcomes assessed at each time point include self-reported adherence to HIV medications, viral load, and CD4 count. Syndemic factors, or co-occurring epidemics, thought to be related to HIV transmission risk will also be assessed at various survey time points, including drug and alcohol use [45,46], depressive and anxiety symptoms [47-49], condom use and HIV disclosure self-efficacy [50], sexual compulsivity [51], HIV stigma, and interpersonal violence [52-54]. Process measures are used to track participants' interest in, acceptability of, and verification of video viewing by having men complete brief postvideo online surveys. These surveys are designed to assess participants' likes and dislikes as well as to elicit critical thinking about the video as it pertains to study outcomes [19,55].

Sample Size

Based on the prevalence of behaviors in our previous studies, we calculated true proportions and sample sizes using chi-square tests for this two-arm design. We estimated that by enrolling approximately 750 men per group and retaining 75% at 12-month follow-up, we would have 80% power at a 5% alpha level to detect a minimum reduction of 8% in the number of serodiscordant CAS partners between the intervention and attention control arms.

Intervention Content

Video messages are an effective way to deliver HIV prevention to GBMSM [19,56-58]. The first of our three theoretically grounded HIV prevention videos (from the HIV Big Deal project) tackling issues of CAS, HIV disclosure, and testing was rigorously evaluated among HIV-negative, HIV-positive, and untested GBMSM recruited online [19]. In our single-session video pilot for 971 GBMSM, we found significant reductions in CAS in the most recent encounter (9% decrease) and significant increases in HIV disclosure at 3-month follow-up (13% increase) compared to baseline [19]. In our subsequent online, single-session RCT for 3092 GBMSM that used videos from the HIV Big Deal project, we found significant reductions in CAS among men in the video study arm at 60-day follow-up (8% decrease) compared to baseline; HIV-positive men in the video study arm reduced their CAS (14% decrease), including with HIV-negative or status unknown partners, at 60-day follow-up (13% decrease) compared to baseline. Men living with HIV were also significantly more likely than men who were HIV-negative or untested to complete follow-up (57% vs 51%, P=.002) [18].

Theoretical Framework for the Intervention Videos

Employing a dramatic video series grounded in social learning and social cognitive theories [59,60], the Sex Positive![+] study engages learners through storytelling and promotes critical thinking on issues of HIV disclosure to sex partners, medication adherence and viral suppression, and serodiscordant CAS. In collaboration with a local production team, including a scriptwriter, producer, and director, we produced *Just a Guy*, a 6-episode video series that follows the story of "Guy," an openly gay man living with HIV in Brooklyn, NY. The video series is based, in part, on the HIV Big Deal project described previously, which was launched online in 2008 [61]. According to social learning theory, individuals learn through the observation of others' attitudes, behaviors, and the outcomes of those behaviors [59]. Videos developed for the intervention described in this paper include elements of social learning and attitude change theories, both of which informed the instructional design and delivery of our pilot online video intervention [19] and online feasibility trial of GBMSM [12]. More specifically, the intervention relies on three critical design dimensions including the medium, the degree of realism, and modeling (Table 2).

Table 2. Survey instrument summary of theoretical constructs assessed at baseline and at 3-, 6-, 9-, and 12-month follow-ups.

Construct, topic, and lead questions	Response options
Construct: self-efficacy	
Topic: disclosure to sex partners	
Lead question: How confident are you that you could tell a potential sex partner your HIV status...	Not at all confident, not very confident, somewhat confident, very confident, extremely confident
...in your online or mobile phone app dating profile?	
...in an email?	
...in a text message?	
...over the phone?	
...in person?	
Topic: safer sex [91]	
Lead question: Now think about future sexual encounters with HIV-negative or unknown HIV status male partners. How confident are you that you could have anal sex with a condom...	Not at all confident, not very confident, somewhat confident, very confident, extremely confident, prefer not to answer
When you feel depressed?	
When you think that your partner does not want to use condoms?	
When you are drunk or high on drugs?	
When you are really sexually aroused?	
Construct: self-regulatory skills	
Topic: sexual compulsivity [92]	
Lead question: Below are statements about sex that you may agree or disagree with.	Not at all like me, slightly like me, mainly like me, very much like me, prefer not to answer
My sexual appetite has gotten in the way of my relationships.	
My sexual thoughts and behaviors are causing problems in my life.	
My desires to have sex have disrupted my daily life.	
I sometimes fail to meet my commitments and responsibilities because of my sexual behaviors.	
I sometimes get so horny I could lose control.	
I find myself thinking about sex while at work.	
I feel that sexual thoughts and feelings are stronger than I am.	
I have to struggle to control my sexual thoughts and behavior.	
I think about sex more than I would like to.	
It has been difficult for me to find sex partners who desire having sex as much as I want to.	
Construct: outcome expectancies	
Topic: condoms and anal sex (adapted from Bimbi et al [93])	
Lead question: Below is a list of statements that you may agree or disagree with.	Strongly agree, somewhat agree, neutral, somewhat disagree, strongly disagree, prefer not to answer
I am more likely to use a condom with men who are HIV-negative or of unknown status.	
I am more likely to have anal insertive sex (top) without a condom while drinking or high.	
I am more likely to have anal receptive sex (bottom) without a condom while drinking or high.	
I am less likely to have anal sex with men who are HIV-negative or of unknown status.	
Construct: perceived responsibility	
Topic: personal and partner responsibility for preventing HIV transmission [94]	
Lead question: Below is a list of statements that you may agree or disagree with.	Strongly agree, somewhat agree, neutral, somewhat disagree, strongly disagree, prefer not to answer

Construct, topic, and lead questions	Response options
It is very important for me to use condoms to protect my sex partners from HIV.	
HIV-positive gay men have a responsibility to keep other gay men from becoming positive.	
When HIV-positive and HIV-negative men have sex with each other, they have an equal responsibility for being safe.	
HIV-positive gay men have a special obligation to have safe sex with men who are negative or do not know their HIV status.	
I feel responsible for protecting my partners from HIV.	
If my partner is HIV-negative, he should not put the responsibility on me for safer sex.	
If men who are HIV-negative want to have risky sex, it is their choice to do so.	
It should be the responsibility of someone who is HIV-negative—not someone who is positive—to make sure their sex is safe.	
I feel it is my partner's responsibility to protect himself from HIV if he is negative.	
It is my responsibility to protect others from getting HIV.	

Increasingly, eHealth HIV behavioral interventions are incorporating digital media, ranging from brief, untailored video interventions to complex computer-tailored multimedia interventions that target individual behaviors [62,63]. Online video-based interventions are an appealing and effective medium to deliver HIV prevention content to GBMSM [56,57]. Furthermore, video has greater potential to engage learners than conventional text or graphics in Web-based or print materials [64-66].

Storytelling, often more effective than exposition, is characterized by realism. From the perspectives of social learning and social cognitive theories [67], and attitude change theories [68], plausible "stories like mine" and "characters like me" are critical factors for engagement [69,70]. A Community Advisory Group, assembled for the Sex Positive![+] study, recommended that the videos feature an HIV-positive main character who overcomes a "victim" status and develops a sense of empowerment that positively impacts his personal relationships and physical health.

Social learning and cognitive theories emphasize the role of outcome expectancies regarding HIV disclosure and condom use self-efficacy and modeling of self-regulatory skills [59,60,71-73]. The tenets of social learning and social cognitive theories are embedded in the content, dialog, and nonverbal cues of the intervention videos, with the goal of preventing risk behavior before it happens. This intervention aims to reduce sexual risk behaviors by modeling HIV disclosure and discussions about safer sex. For example, in *Just a Guy*, the viewer learns through a nonverbal cue that Guy and Matt—a potential love interest—used a condom for anal sex the night before as Matt places the condom wrapper on his forehead on waking up. In this scene, Matt learns that Guy is HIV-positive and the two have a heated discussion about HIV disclosure responsibility. The video does not attempt to answer the question of personal responsibility or assert any one behavioral prescription, but rather encourages the viewer to think critically and discuss the issue with their sex partners.

Attention Control Videos

The two study arms are designed to be equal in the number of sessions, video length, study duration, and interest level. All videos are available for free viewing on the Sex Positive![+] study website, although men can view only videos that are assigned to their study arm. The control arm receives 10 healthy living videos that cover a range of topics including nutrition, physical exercise, smoking, and sleep quality. Attention control videos were selected from video-sharing websites and voted on by members of the research team.

Video Boosters

Because the effects of most preventive interventions tend to gradually wane over time, the inclusion of follow-up booster sessions can support prior skills learned to sustain an intervention impact [74]. Based on our team's experience with intervention effects attenuating at 6 months [75], participants in the intervention arm will receive four video boosters after they complete the 6-month assessment survey. We edited *Ask Me, Tell Me* [76], the fourth video installment of our HIV Big Deal series, into three booster episodes (each episode is approximately 3 minutes in length). This particular prevention video from the HIV Big Deal series was selected for its emphasis on the importance of discussing one's history of sexually transmitted infections (STIs) with sex partners and reducing episodes of CAS with serodiscordant partners. The final booster video focuses on the issue of social support for persons living with HIV and was selected from a video-sharing website. Participants in the attention control arm receive four additional healthy living videos after they complete the 6-month assessment survey.

Intervention Activities

Overview

Participants in the intervention and attention control arms complete assessments at baseline and at 3-, 6-, 9-, and 12-month time points. To reduce the chance of instrument reactivity, we provide detailed online survey assessments at baseline and 12-month follow-up and brief assessments at 3-, 6-, and 9-month follow-ups. Participants will receive a text message and/or email

with a survey link when it is time for them to complete a follow-up survey or watch a video. The dissemination of intervention and attention control videos occurs between the baseline and 3-month assessments, spaced 1 week apart. Following the 6-month assessment, participants in both arms receive four video boosters, spaced 1 week apart. The intervention and attention control videos are only available to study participants via a secure URL and men cannot forward video links to anyone, thus preventing potential cross-contamination between arms. All intervention activities occur online and are optimized for mobile performance.

Administrative Platform

For complex online interventions, developing a user-friendly administrative platform for the deployment and monitoring of data collection and intervention activities is critical. The online administrative platform enables study staff to screen potential participants, obtain consent, register, randomize participants into one of two study arms (intervention or attention control), monitor recruitment and retention, and flag suspicious cases. The administrative platform can be programmed to produce reports on participants, such as who completed certain study activities, who needs to be sent incentives, who needs to receive retention calls, and so forth. In addition, the study dashboard that participants see when they log in provides information on what study activities they have completed or need to complete, their personal information (eg, name, address, phone number) that can be updated, their communication preferences (eg, receiving texts or calls), and how much in Amazon.com incentives they have earned. The dashboard can also host hyperlinks to provide health information (eg, nutrition and HIV, ART adherence) and track which links participants click on.

Eligibility, Screening, and Consent

Men who click on a study banner, email, or online classified advertisement are directed to a brief, secure screener survey housed on the online administrative platform. Those who are determined to be eligible for study inclusion are directed to the study landing page and registration platform, which describes the study and provides a consent form for intervention activities. Men who are determined to be ineligible are provided with a message indicating that they are not eligible, thanking them for their time, and directing them to HIV prevention and other health resources, including an invitation to join a participant registry for future study opportunities.

Registration, Verification, and Randomization

After consent, participants are guided through online study registration, including the creation of a log-in username and password and collection and automated verification of their email address and mobile phone number. Then, they are automatically randomized into the intervention or attention control arm [77] through a stratified block randomization (by race/ethnicity and age), which will balance groups within a 5% range [77,78]. On accessing their study account, men are instructed to complete the baseline survey, which is hosted on a secure server on Survey Gizmo that is compliant with the Health Insurance Portability and Accountability Act. Men remain in their original assignment group (intention to treat) and are sent text message and email notifications for each of their intervention activities even if they discontinue participation.

Remuneration

Participants can receive up to a total of US $115 in Amazon.com gift cards (distributed electronically and via direct mail). Figure 1 provides the incentive schedule for Sex Positive![+].

Figure 1. Study incentive structure.

Study Retention

Historically, online research has had lower retention rates than offline research because there are fewer social constraints compared to in-person interviewing [79]. However, recent advances in retention protocols and technology have greatly improved researchers' ability to retain participants in HIV prevention trials, with 90% retention at 6 months and 82% retention at 12 months [80,81]. To ensure minimal attrition, Sex Positive![+] conducts multiple sessions, offers video boosters to maintain study interest, provides incentives for each study activity, sends reminder emails and text messages for videos and follow-up assessments, and uses the online administrative platform to create daily lists of nonresponsive participants for the retention coordinator to contact.

Protection Against Fraud

An advantage of online research is data validity for sensitive information. Indeed, a growing number of studies indicate higher reporting of sexual risk and substance-using behaviors with computer-based surveys compared to mail, phone, and in-person surveys [82-84]. However, compared to the gold standard of in-person interviewing, a limitation of online research—as with mail and phone surveys—is the challenge of verifying a participant's identity [85]. Based on recommendations made during an open session of our Data and Safety Monitoring Board, as well as a meeting of Internet experts about the issue

of online fraud in research studies [86], the Sex Positive![+] study implements several protections aimed at reducing the likelihood of fraud. Specifically, (1) contact information is verified during registration using multiple methods; (2) duplicate detection (of Internet Protocol [IP] address and mailing address) software is used to detect instances of participants attempting to create multiple study profiles; (3) mobile phone numbers are investigated to determine whether they are voice over IP (VoIP) numbers—an individual can obtain multiple VoIP numbers on the Internet, typically for no charge, that can be routed to the individual's mobile device (eg, this helps a potential participant to sign up numerous times with unique phone numbers); (4) proxy IP addresses and invalid mailing addresses are flagged for further scrutiny by the research team; (5) trap questions are used in the baseline survey to flag cases with inconsistent data—"I am HIV-negative"—or careless responses (eg, straightlining); (6) study staff conduct weekly analyses of new screener data to identify individuals (by IP address) who make multiple attempts to join the study; (7) compensation is kept sufficiently low to reduce the chances of participating solely to gain incentive payments; and (8) to ensure participant authenticity, the final study incentive is mailed to a verified physical address.

Analysis

Primary analyses for intervention efficacy will examine whether participants in the intervention arm report fewer CAS acts with serodiscordant partners, a higher percentage of anal sex acts with condoms, fewer sexual partners, and more disclosure of HIV status with partners compared to participants in the attention control arm. Dose-response analyses will allow us to examine whether a certain number of intervention videos—"doses"—are necessary to effect study goals.

Even with a robust retention plan, incentives, and survey programming that requires responses, missing data are inevitable because participants can "refuse" survey items or drop out of the study. For this study, data from the online screener will verify that blocked randomization produced equivalent groups and will also be used to assess possible sample attrition bias. Although there are many ways to handle missing data, our experience suggests that maximum likelihood estimation is the best approach, using the appropriate algorithm for estimation purposes.

We will also conduct analyses to assess the savings in averted HIV-related lifetime treatment costs, the total number of quality-adjusted life years (QALYs) saved by preventing a single HIV infection, and the cost of developing and implementing the Sex Positive![+]study. In general terms, after the 12-month follow-up we will analyze up to three partner-by-partner sexual encounters, for biological male partners only, as well as global number of condomless anal or vaginal sex partners (ie, biological male and female partners, transidentified females, and transidentified males) at each of the four follow-up assessment time points. This will provide an estimate of the number of secondary infections expected among the participant's serodiscordant sex partners. The main analysis will assume that study participants with an undetectable viral load at a particular time point are noninfectious. Although a separate estimate will be calculated for each participant at each of the four follow-up time points, the sum of these time point findings will estimate the total number of secondary infections expected among the participant's sex partners during the entire study period. We will then calculate the total number of estimated infections prevented by the intervention arm versus the control by measuring the difference in the mean number of expected secondary infections for all men in the intervention and control arms over the 12-month period. Based on the total number of prevented infections, we will calculate the corresponding savings in averted HIV-related lifetime treatment costs as well as the total number of QALYs saved by preventing a single HIV infection. Finally, we will calculate the net cost of the intervention, the cost per infection prevented, and the net cost per QALY saved (ie, the cost-utility ratio) [87]. The intervention can be considered "cost saving" if the net cost is negative and "cost-effective" if the cost-utility ratio is less than US $100,000 per QALY saved [88].

Results

Participant recruitment began in June 2015 and ended in December 2015.

Discussion

Those eHealth interventions, such as Sex Positive![+], that allow participation through multiple Internet-based mediums (ie, computer and mobile access) have the potential to reach and engage a broader population of GBMSM with HIV. More specifically, this type of online intervention can reach men living with HIV who are outside of HIV epicenters, who may be beyond the reach of traditional prevention services, and are poorly represented in research. Furthermore, the online administrative platform and videos will be accessible to a much larger population at a relatively low cost following completion and evaluation of the study. For populations with limited Internet access, the intervention can be adapted for use in HIV clinics and community-based organizations via private kiosks, laptops or tablets, or in small group settings. Thus, this self-administered, online video-based intervention can be implemented in various settings at minimal cost.

Limitations

This study protocol has several limitations that deserve mention. All men were recruited online, through social networking and gay-oriented sexual networking websites and mobile phone apps. As such, the findings may not be generalizable to HIV-positive GBMSM who do not own a mobile phone or have Internet access, access these types of websites or mobile phone apps, to men who do not identify as gay, to individuals exposed to a study banner or email but choose not to click on it, or to men who do not identify as black, white, or Hispanic/Latino. Study content is only available in English, which limits its reach to participants. There is a need to translate content into Spanish because it is the second most-spoken language in the United States and represents a subpopulation of GBMSM with high rates of HIV [4,89]. Lastly, a potential limitation is that participants self-report their health outcomes, specifically viral

load. However, a recent validation study of 639 individuals with HIV from an ongoing prospective study in New York found that participant recall of viral load agreed with the Department of Health's registry data 85% of the time [90].

Conclusion

In conclusion, the Sex Positive![+] study addresses the lack of interventions designed for GBMSM living with HIV. This protocol describes the underlying theoretical framework and measures, study design, recruitment challenges, and antifraud measures. If efficacious, it will have a significant impact on reducing HIV transmission risk in a disproportionately affected population. Although this eHealth intervention is being implemented with virally unsuppressed men or men who struggle with ART adherence, it can be adapted for delivery in other settings and with other populations.

Acknowledgments

This research was supported by a grant from the National Institute of Mental Health (R01 MH100973, PI: Hirshfield).

Authors' Contributions

SH, MJD, JTP, CG, RG, RS, PSS, and MAC planned aspects of the trial and wrote the manuscript. STH, IA, MJD, ISY worked on trial implementation and collaborated on the writing of the manuscript. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

References

1. Centers for Disease Control and Prevention. 2014. HIV Surveillance Report, 2012 URL: http://www.cdc.gov/hiv/library/reports/surveillance/2012/surveillance_Report_vol_24.html [accessed 2016-05-26] [WebCite Cache ID 6hnLSs37s]
2. Kilmarx PH, Mermin J. Prevention with people with HIV in the United States: the nexus of HIV prevention and treatment. J Acquir Immune Defic Syndr 2012 Jul 1;60(3):219-220. [doi: 10.1097/QAI.0b013e3182531ba2] [Medline: 22433845]
3. Centers for Disease Control and Prevention. 2015. Compendium of evidence-based interventions and best practices for HIV prevention URL: http://www.cdc.gov/hiv/prevention/research/compendium/index.html [accessed 2016-05-26] [WebCite Cache ID 6hnNihPFD]
4. Singh S, Bradley H, Hu X, Skarbinski J, Hall HI, Lansky A, Centers for Disease Control and Prevention (CDC). Men living with diagnosed HIV who have sex with men: progress along the continuum of HIV care--United States, 2010. MMWR Morb Mortal Wkly Rep 2014 Sep 26;63(38):829-833 [FREE Full text] [Medline: 25254559]
5. Hall HI, Holtgrave DR, Tang T, Rhodes P. HIV transmission in the United States: considerations of viral load, risk behavior, and health disparities. AIDS Behav 2013 Jun;17(5):1632-1636. [doi: 10.1007/s10461-013-0426-z] [Medline: 23456577]
6. Centers for Disease Control and Prevention. HIV Surveillance Report: Diagnoses of HIV Infection in the United States and Dependent Areas, 2014. 2015 Nov. URL: http://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-report-us.pdf [accessed 2016-05-26] [WebCite Cache ID 6hnPaovjX]
7. Gant Z, Bradley H, Hu X, Skarbinski J, Hall HI, Lansky A, Centers for Disease Control and Prevention (CDC). Hispanics or Latinos living with diagnosed HIV: progress along the continuum of HIV care - United States, 2010. MMWR Morb Mortal Wkly Rep 2014 Oct 10;63(40):886-890 [FREE Full text] [Medline: 25299604]
8. Whiteside YO, Cohen SM, Bradley H, Skarbinski J, Hall HI, Lansky A, Centers for Disease Control and Prevention. Progress along the continuum of HIV care among blacks with diagnosed HIV- United States, 2010. MMWR Morb Mortal Wkly Rep 2014 Feb 7;63(5):85-89 [FREE Full text] [Medline: 24500286]
9. The White House Office of National AIDS Policy. National HIV/AIDS Strategy for the United States: Updated to 2020. 2015 Jul. URL: https://www.aids.gov/federal-resources/national-hiv-aids-strategy/nhas-update.pdf [accessed 2016-05-26] [WebCite Cache ID 6hnQ9woDe]
10. Beymer MR, Weiss RE, Bolan RK, Rudy ET, Bourque LB, Rodriguez JP, et al. Sex on demand: geosocial networking phone apps and risk of sexually transmitted infections among a cross-sectional sample of men who have sex with men in Los Angeles County. Sex Transm Infect 2014 Nov;90(7):567-572 [FREE Full text] [doi: 10.1136/sextrans-2013-051494] [Medline: 24926041]
11. Rendina HJ, Jimenez RH, Grov C, Ventuneac A, Parsons JT. Patterns of lifetime and recent HIV testing among men who have sex with men in New York City who use Grindr. AIDS Behav 2014 Jan;18(1):41-49 [FREE Full text] [doi: 10.1007/s10461-013-0573-2] [Medline: 23925515]
12. Chiasson MA, Parsons JT, Tesoriero JM, Carballo-Dieguez A, Hirshfield S, Remien RH. HIV behavioral research online. J Urban Health 2006 Jan;83(1):73-85 [FREE Full text] [doi: 10.1007/s11524-005-9008-3] [Medline: 16736356]

13. Rosser BR, Oakes JM, Horvath KJ, Konstan JA, Danilenko GP, Peterson JL. HIV sexual risk behavior by men who use the Internet to seek sex with men: results of the Men's INTernet Sex Study-II (MINTS-II). AIDS Behav 2009 Jun;13(3):488-498 [FREE Full text] [doi: 10.1007/s10461-009-9524-3] [Medline: 19205866]
14. Wolitski RJ, Gómez CA, Parsons JT. Effects of a peer-led behavioral intervention to reduce HIV transmission and promote serostatus disclosure among HIV-seropositive gay and bisexual men. AIDS 2005 Apr;19 Suppl 1:S99-S109. [Medline: 15838199]
15. Grov C, Breslow AS, Newcomb ME, Rosenberger JG, Bauermeister JA. Gay and bisexual men's use of the Internet: research from the 1990s through 2013. J Sex Res 2014;51(4):390-409 [FREE Full text] [doi: 10.1080/00224499.2013.871626] [Medline: 24754360]
16. Duggan M. Pew Research Center. 2013 Sep 19. Cell phone activities 2013 URL: http://www.pewinternet.org/2013/09/19/cell-phone-activities-2013/ [accessed 2016-05-26] [WebCite Cache ID 6hnQJ2jk9]
17. Grov C, Ventuneac A, Rendina HJ, Jimenez RH, Parsons JT. Perceived importance of five different health issues for gay and bisexual men: implications for new directions in health education and prevention. Am J Mens Health 2013 Jul;7(4):274-284 [FREE Full text] [doi: 10.1177/1557988312463419] [Medline: 23093075]
18. Hirshfield S, Chiasson MA, Joseph H, Scheinmann R, Johnson WD, Remien RH, et al. An online randomized controlled trial evaluating HIV prevention digital media interventions for men who have sex with men. PLoS One 2012;7(10):e46252 [FREE Full text] [doi: 10.1371/journal.pone.0046252] [Medline: 23071551]
19. Chiasson MA, Shaw FS, Humberstone M, Hirshfield S, Hartel D. Increased HIV disclosure three months after an online video intervention for men who have sex with men (MSM). AIDS Care 2009 Sep;21(9):1081-1089. [doi: 10.1080/09540120902730013] [Medline: 20024766]
20. Rosser BR, Horvath KJ, Hatfield LA, Peterson JL, Jacoby S, Stately A. Predictors of HIV disclosure to secondary partners and sexual risk behavior among a high-risk sample of HIV-positive MSM: results from six epicenters in the US. AIDS Care 2008 Sep;20(8):925-930 [FREE Full text] [doi: 10.1080/09540120701767265] [Medline: 18777221]
21. US Census Bureau. The Black Alone or in Combination Population in the United States: 2012. Washington, DC: Government Printing Office; 2012. URL: http://www.census.gov/population/race/data/ppl-bc12.html [accessed 2016-05-26] [WebCite Cache ID 6hnRIMrmb]
22. Sullivan PS, Khosropour CM, Luisi N, Amsden M, Coggia T, Wingood GM, et al. Bias in online recruitment and retention of racial and ethnic minority men who have sex with men. J Med Internet Res 2011;13(2):e38 [FREE Full text] [doi: 10.2196/jmir.1797] [Medline: 21571632]
23. Hooper S, Rosser BR, Horvath KJ, Oakes JM, Danilenko G, Men's INTernet Sex II (MINTS-II) Team. An online needs assessment of a virtual community: what men who use the internet to seek sex with men want in Internet-based HIV prevention. AIDS Behav 2008 Nov;12(6):867-875 [FREE Full text] [doi: 10.1007/s10461-008-9373-5] [Medline: 18401701]
24. Bauermeister JA, Pingel ES, Jadwin-Cakmak L, Harper GW, Horvath K, Weiss G, et al. Acceptability and preliminary efficacy of a tailored online HIV/STI testing intervention for young men who have sex with men: the Get Connected! Program. AIDS Behav 2015 Feb 1. [doi: 10.1007/s10461-015-1009-y] [Medline: 25638038]
25. Sun CJ, Stowers J, Miller C, Bachmann LH, Rhodes SD. Acceptability and feasibility of using established geosocial and sexual networking mobile applications to promote HIV and STD testing among men who have sex with men. AIDS Behav 2015 Mar;19(3):543-552. [doi: 10.1007/s10461-014-0942-5] [Medline: 25381563]
26. Card JJ, Kuhn T, Solomon J, Benner TA, Wingood GM, DiClemente RJ. Translating an effective group-based HIV prevention program to a program delivered primarily by a computer: methods and outcomes. AIDS Educ Prev 2011 Apr;23(2):159-174. [doi: 10.1521/aeap.2011.23.2.159] [Medline: 21517664]
27. Lewis MA, Uhrig JD, Bann CM, Harris JL, Furberg RD, Coomes C, et al. Tailored text messaging intervention for HIV adherence: a proof-of-concept study. Health Psychol 2013 Mar;32(3):248-253. [doi: 10.1037/a0028109] [Medline: 22545972]
28. Simoni JM, Kutner BA, Horvath KJ. Opportunities and challenges of digital technology for HIV treatment and prevention. Curr HIV/AIDS Rep 2015 Sep 28. [doi: 10.1007/s11904-015-0289-1] [Medline: 26412082]
29. Pellowski JA, Kalichman SC. Recent advances (2011-2012) in technology-delivered interventions for people living with HIV. Curr HIV/AIDS Rep 2012 Dec;9(4):326-334 [FREE Full text] [doi: 10.1007/s11904-012-0133-9] [Medline: 22922945]
30. Horvath KJ, Oakes JM, Rosser BR, Danilenko G, Vezina H, Amico KR, et al. Feasibility, acceptability and preliminary efficacy of an online peer-to-peer social support ART adherence intervention. AIDS Behav 2013 Jul;17(6):2031-2044 [FREE Full text] [doi: 10.1007/s10461-013-0469-1] [Medline: 23553347]
31. Hightow-Weidman LB, Muessig KE, Bauermeister J, Zhang C, LeGrand S. Youth, technology, and HIV: recent advances and future directions. Curr HIV/AIDS Rep 2015 Dec;12(4):500-515. [doi: 10.1007/s11904-015-0280-x] [Medline: 26385582]
32. Gamage DG, Sidat M, Read T, Cummings R, Bradshaw CS, Howley K, et al. Evaluation of Health Map: a patient-centred web-based service for supporting HIV-infected patients. Sex Health 2011 Jun;8(2):194-198. [doi: 10.1071/SH10072] [Medline: 21592433]
33. Harris LT, Lehavot K, Huh D, Yard S, Andrasik MP, Dunbar PJ, et al. Two-way text messaging for health behavior change among human immunodeficiency virus-positive individuals. Telemed J E Health 2010 Dec;16(10):1024-1029 [FREE Full text] [doi: 10.1089/tmj.2010.0050] [Medline: 21087122]

34. Bachmann LH, Grimley DM, Gao H, Aban I, Chen H, Raper JL, et al. Impact of a computer-assisted, provider-delivered intervention on sexual risk behaviors in HIV-positive men who have sex with men (MSM) in a primary care setting. AIDS Educ Prev 2013 Apr;25(2):87-101. [doi: 10.1521/aeap.2013.25.2.87] [Medline: 23514077]
35. Miranda J, Côté J, Godin G, Blais M, Otis J, Guéhéneuc YG, et al. An internet-based intervention (Condom-Him) to increase condom use among HIV-positive men who have sex with men: protocol for a randomized controlled trial. JMIR Res Protoc 2013;2(2):e39 [FREE Full text] [doi: 10.2196/resprot.2723] [Medline: 24132072]
36. Marseille E, Shade SB, Myers J, Morin S. The cost-effectiveness of HIV prevention interventions for HIV-infected patients seen in clinical settings. J Acquir Immune Defic Syndr 2011 Mar 1;56(3):e87-e94. [doi: 10.1097/QAI.0b013e318204123e] [Medline: 21317579]
37. Lee MB, Leibowitz A, Rotheram-Borus MJ. Cost-effectiveness of a behavioral intervention for seropositive youth. AIDS Educ Prev 2005 Apr;17(2):105-118. [doi: 10.1521/aeap.17.3.105.62906] [Medline: 15899749]
38. Cohen DA, Wu S, Farley TA. Comparing the cost-effectiveness of HIV prevention interventions. J Acquir Immune Defic Syndr 2004 Nov 1;37(3):1404-1414. [Medline: 15483470]
39. Claborn KR, Fernandez A, Wray T, Ramsey S. Computer-based HIV adherence promotion interventions: a systematic review: Translation Behavioral Medicine. Transl Behav Med 2015 Sep;5(3):294-306 [FREE Full text] [doi: 10.1007/s13142-015-0317-0] [Medline: 26327935]
40. Muessig KE, Nekkanti M, Bauermeister J, Bull S, Hightow-Weidman LB. A systematic review of recent smartphone, internet and Web 2.0 interventions to address the HIV continuum of care. Curr HIV/AIDS Rep 2015 Jan 28. [doi: 10.1007/s11904-014-0239-3] [Medline: 25626718]
41. Hirshfield S, Grov C, Parsons JT, Anderson I, Chiasson MA. Social media use and HIV transmission risk behavior among ethnically diverse HIV-positive gay men: results of an online study in three U.S. states. Arch Sex Behav 2015 Oct;44(7):1969-1978. [doi: 10.1007/s10508-015-0513-5] [Medline: 26179596]
42. Crepaz N, Lyles CM, Wolitski RJ, Passin WF, Rama SM, Herbst JH, HIV/AIDS Prevention Research Synthesis (PRS) Team. Do prevention interventions reduce HIV risk behaviours among people living with HIV? A meta-analytic review of controlled trials. AIDS 2006 Jan 9;20(2):143-157. [doi: 10.1097/01.aids.0000196166.48518.a0] [Medline: 16511407]
43. US Department of Health and Human Services, Office for Human Research Protections. 2009 Jan 15. 45 CFR 46: Protection of human subjects: documentation of informed consent URL: http://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/ [accessed 2016-05-26] [WebCite Cache ID 6hnZapICt]
44. Mayer KH, Wang L, Koblin B, Mao C, Mannheimer S, Magnus M. An evolving concentrated epidemic: comparison of newly diagnosed, previously diagnosed and HIV-uninfected black men who have sex with men in 6 US cities. 2012 Presented at: International AIDS Conference; July 22-27, 2012; Washington, DC.
45. Velasquez MM, von Sternberg K, Johnson DH, Green C, Carbonari JP, Parsons JT. Reducing sexual risk behaviors and alcohol use among HIV-positive men who have sex with men: a randomized clinical trial. J Consult Clin Psychol 2009 Aug;77(4):657-667 [FREE Full text] [doi: 10.1037/a0015519] [Medline: 19634959]
46. Hirshfield S, Remien RH, Chiasson MA. Crystal methamphetamine use among men who have sex with men: results from two national online studies. J Gay Lesbian Psychotherapy 2006 Aug 14;10(3-4):85-93. [doi: 10.1300/J236v10n03_08]
47. Salomon EA, Mimiaga MJ, Husnik MJ, Welles SL, Manseau MW, Montenegro AB, et al. Depressive symptoms, utilization of mental health care, substance use and sexual risk among young men who have sex with men in EXPLORE: implications for age-specific interventions. AIDS Behav 2009 Aug;13(4):811-821 [FREE Full text] [doi: 10.1007/s10461-008-9439-4] [Medline: 18709453]
48. Rabkin JG. HIV and depression: 2008 review and update. Curr HIV/AIDS Rep 2008 Nov;5(4):163-171. [Medline: 18838056]
49. Leserman J. Role of depression, stress, and trauma in HIV disease progression. Psychosom Med 2008 Jun;70(5):539-545. [doi: 10.1097/PSY.0b013e3181777a5f] [Medline: 18519880]
50. Parsons JT, Huszti HC, Crudder SO, Rich L, Mendoza J. Maintenance of safer sexual behaviours: evaluation of a theory-based intervention for HIV seropositive men with haemophilia and their female partners. Haemophilia 2000 May;6(3):181-190. [Medline: 10792477]
51. Grov C, Parsons JT, Bimbi DS. Sexual compulsivity and sexual risk in gay and bisexual men. Arch Sex Behav 2010 Aug;39(4):940-949 [FREE Full text] [doi: 10.1007/s10508-009-9483-9] [Medline: 19308715]
52. Benoit E, Downing MJJ. Childhood sexual experiences among substance-using non-gay identified Black men who have sex with men and women. Child Abuse Negl 2013 Sep;37(9):679-690 [FREE Full text] [doi: 10.1016/j.chiabu.2013.04.007] [Medline: 23768936]
53. Mimiaga MJ, Noonan E, Donnell D, Safren SA, Koenen KC, Gortmaker S, et al. Childhood sexual abuse is highly associated with HIV risk-taking behavior and infection among MSM in the EXPLORE Study. J Acquir Immune Defic Syndr 2009 Jul 1;51(3):340-348 [FREE Full text] [doi: 10.1097/QAI.0b013e3181a24b38] [Medline: 19367173]
54. Welles SL, Baker AC, Miner MH, Brennan DJ, Jacoby S, Rosser BR. History of childhood sexual abuse and unsafe anal intercourse in a 6-city study of HIV-positive men who have sex with men. Am J Public Health 2009 Jun;99(6):1079-1086 [FREE Full text] [doi: 10.2105/AJPH.2007.133280] [Medline: 19372529]
55. Tarnowski KJ, Simonian SJ. Assessing treatment acceptance: the Abbreviated Acceptability Rating Profile. J Behav Ther Exp Psychiatry 1992 Jun;23(2):101-106. [Medline: 1460097]

56. Chiasson MA, Hirshfield S, Rietmeijer CA. HIV prevention and care in the digital age. J Acquir Immune Defic Syndr 2010 Dec;55 Suppl 2:S94-S97. [doi: 10.1097/QAI.0b013e3181fcb878] [Medline: 21406996]
57. Blas MM, Alva IE, Carcamo CP, Cabello R, Goodreau SM, Kimball AM, et al. Effect of an online video-based intervention to increase HIV testing in men who have sex with men in Peru. PLoS One 2010;5(5):e10448 [FREE Full text] [doi: 10.1371/journal.pone.0010448] [Medline: 20454667]
58. Rosser BR, Hatfield LA, Miner MH, Ghiselli ME, Lee BR, Welles SL, Positive Connections Team. Effects of a behavioral intervention to reduce serodiscordant unsafe sex among HIV positive men who have sex with men: the Positive Connections randomized controlled trial study. J Behav Med 2010 Apr;33(2):147-158 [FREE Full text] [doi: 10.1007/s10865-009-9244-1] [Medline: 20101454]
59. Bandura A. Social Learning Theory. Englewood Cliffs, NJ: Prentice Hall; 1977.
60. Bandura A. Social Foundations of Thought and Action: A Social Cognitive Theory. Englewood Cliffs, NJ: Prentice-Hall; 1986.
61. HIV Big Deal. 2011. URL: http://www.hivbigdeal.org/ [accessed 2016-05-26] [WebCite Cache ID 6hnjJ2fit]
62. Guse K, Levine D, Martins S, Lira A, Gaarde J, Westmorland W, et al. Interventions using new digital media to improve adolescent sexual health: a systematic review. J Adolesc Health 2012 Dec;51(6):535-543. [doi: 10.1016/j.jadohealth.2012.03.014] [Medline: 23174462]
63. Noar SM, Black HG, Pierce LB. Efficacy of computer technology-based HIV prevention interventions: a meta-analysis. AIDS 2009 Jan 2;23(1):107-115. [doi: 10.1097/QAD.0b013e32831c5500] [Medline: 19050392]
64. Collins A. Design issues for learning environments. In: Vosniadou S, De Corte E, Glaser R, Mandl H, editors. International Perspectives on the Design of Technology-Supported Learning Environments. Mahwah, NJ: L Erlbaum Associates; 1996:347-362.
65. Bransford J, Sherwood R, Hasselbring T, Kinzer C, Williams S. Anchored instruction: why we need it and how technology can help. In: Nix D, Spiro R, editors. Cognition, Education, and Multimedia: Exploring Ideas in High Technology. Hillsdale, NJ: L Erlbaum Associates; 1990:115-141.
66. Jonassen D, Howland J, Moore J, Marra R. Learning to Solve Problems with Technology: A Constructivist Perspective. 2nd Ed. Upper Saddle River, NJ: Merrill Prentice-Hall; 2003.
67. Resnick LB. The 1987 presidential address: learning in school and out. Educ Researcher 1987 Dec 01;16(9):13-54. [doi: 10.3102/0013189X016009013]
68. Allport G. Attitudes. In: Murchison C, editor. Handbook of Social Psychology. Worchester: Clark University Press; 1935:798-844.
69. Jonassen DH, Hernandez-Serrano J. Case-based reasoning and instructional design: using stories to support problem solving. Educ Technol Res Dev 2002 Jun;50(2):65-77. [doi: 10.1007/BF02504994]
70. Chiasson MA, Shuchat-Shaw F, Humberstone M. The Morning After. New York: The Steinhardt School of Education, New York University & Medical and Health Research Association; 2005. URL: http://www.hivbigdeal.org/ [accessed 2016-05-26] [WebCite Cache ID 6hnsNROGq]
71. Bandura A. Psychological Modeling: Conflicting Theories. New York: Chicago Liber-Atherton; 1974:1-64.
72. Piaget J. Mechanisms of Perception. London: Rutledge & Kegan Paul; 1969.
73. Schank R, Berman T. The pervasive role of stories in knowledge and action. In: Green M, Strange JJ, Brock TC, editors. Narrative Impact: Social and Cognitive Foundations. Mahway, NJ: Lawrence Erlbaum Associates; 2002:287-313.
74. Wu Y, Stanton BF, Galbraith J, Kaljee L, Cottrell L, Li X, et al. Sustaining and broadening intervention impact: a longitudinal randomized trial of 3 adolescent risk reduction approaches. Pediatrics 2003 Jan;111(1):e32-e38. [Medline: 12509592]
75. Parsons JT, Golub SA, Rosof E, Holder C. Motivational interviewing and cognitive-behavioral intervention to improve HIV medication adherence among hazardous drinkers: a randomized controlled trial. J Acquir Immune Defic Syndr 2007 Dec 1;46(4):443-450 [FREE Full text] [Medline: 18077833]
76. Ahlberg T. HIV Big Deal. 2011. Ask me tell me URL: http://www.hivbigdeal.org/ [accessed 2016-05-26] [WebCite Cache ID 6hnvYts2O]
77. Kernan WN, Viscoli CM, Makuch RW, Brass LM, Horwitz RI. Stratified randomization for clinical trials. J Clin Epidemiol 1999 Jan;52(1):19-26. [Medline: 9973070]
78. Friedman L, Furberg C, DeMets D. Fundamentals of Clinical Trials. 3rd Ed. St Louis: Mosby-Year Book, Inc; 1996.
79. Birnbaum MH. Human research and data collection via the internet. Annu Rev Psychol 2004;55:803-832. [doi: 10.1146/annurev.psych.55.090902.141601] [Medline: 14744235]
80. Khosropour CM. Retention and HIV testing of MSM enrolled in a 12-month online study. 2011 Presented at: Sex Tech Conference; April 1,2011; San Francisco, CA.
81. Rosser BR, Oakes JM, Konstan J, Hooper S, Horvath KJ, Danilenko GP, et al. Reducing HIV risk behavior of men who have sex with men through persuasive computing: results of the Men's INTernet Study-II. AIDS 2010 Aug 24;24(13):2099-2107 [FREE Full text] [doi: 10.1097/QAD.0b013e32833c4ac7] [Medline: 20601853]
82. Link MW, Mokdad AH. Alternative modes for health surveillance surveys: an experiment with web, mail, and telephone. Epidemiology 2005 Sep;16(5):701-704. [Medline: 16135951]

83. Perlis TE, Des Jarlais DC, Friedman SR, Arasteh K, Turner CF. Audio-computerized self-interviewing versus face-to-face interviewing for research data collection at drug abuse treatment programs. Addiction 2004 Jul;99(7):885-896. [doi: 10.1111/j.1360-0443.2004.00740.x] [Medline: 15200584]
84. Elford J, Bolding G, Davis M, Sherr L, Hart G. Web-based behavioral surveillance among men who have sex with men: a comparison of online and offline samples in London, UK. J Acquir Immune Defic Syndr 2004 Apr 1;35(4):421-426. [Medline: 15097159]
85. Grey JA, Konstan J, Iantaffi A, Wilkerson JM, Galos D, Rosser BR. An updated protocol to detect invalid entries in an online survey of men who have sex with men (MSM): how do valid and invalid submissions compare? AIDS Behav 2015 Oct;19(10):1928-1937. [doi: 10.1007/s10461-015-1033-y] [Medline: 25805443]
86. Teitcher JE, Bockting WO, Bauermeister JA, Hoefer CJ, Miner MH, Klitzman RL. Detecting, preventing, and responding to “fraudsters” in internet research: ethics and tradeoffs. J Law Med Ethics 2015;43(1):116-133 [FREE Full text] [doi: 10.1111/jlme.12200] [Medline: 25846043]
87. Pinkerton SD, Holtgrave DR. A method for evaluating the economic efficiency of HIV behavioral risk reduction interventions. AIDS Behav 1998;2(3):189-201.
88. Braithwaite RS, Meltzer DO, King JTJ, Leslie D, Roberts MS. What does the value of modern medicine say about the $50,000 per quality-adjusted life-year decision rule? Med Care 2008 Apr;46(4):349-356. [doi: 10.1097/MLR.0b013e31815c31a7] [Medline: 18362813]
89. Ryan C. Language Use in the United States: American Community Survey. Washington, DC: US Census Bureau; 2013. URL: https://www.census.gov/prod/2013pubs/acs-22.pdf [accessed 2016-05-26] [WebCite Cache ID 6hnvvObuL]
90. Messeri P, McAllister-Hollod L, Irvine M. Validating self-reported HIV test results using surveillance registry data. CHAIN Report 2012-8 2013.
91. Parsons JT, Halkitis PN, Bimbi D, Borkowski T. Perceptions of the benefits and costs associated with condom use and unprotected sex among late adolescent college students. J Adolesc 2000 Aug;23(4):377-391. [doi: 10.1006/jado.2000.0326] [Medline: 10936012]
92. Kalichman SC, Rompa D. Sexual Sensation Seeking and Sexual Compulsivity Scales: reliability, validity, and predicting HIV risk behavior. J Pers Assess 1995 Dec;65(3):586-601. [doi: 10.1207/s15327752jpa6503_16] [Medline: 8609589]
93. Bimbi DS, Nanin JE, Parsons JT, Vicioso KJ, Missildine W, Frost DM. Assessing gay and bisexual men's outcome expectancies for sexual risk under the influence of alcohol and drugs. Subst Use Misuse 2006;41(5):643-652. [doi: 10.1080/10826080500411080] [Medline: 16603452]
94. Wolitski RJ, Flores SA, O'Leary A, Bimbi DS, Gómez CA. Beliefs about personal and partner responsibility among HIV-seropositive men who have sex with men: measurement and association with transmission risk behavior. AIDS Behav 2007 Sep;11(5):676-686. [doi: 10.1007/s10461-006-9183-6] [Medline: 17103125]

Abbreviations

ART: antiretroviral therapy
CAS: condomless anal sex
GBMSM: gay, bisexual, and other men who have sex with men
GPS: Global Positioning System
HIV: human immunodeficiency virus
IP: Internet Protocol
QALY: quality-adjusted life years
RCT: randomized controlled trial
STI: sexually transmitted infection
VoIP: voice over Internet Protocol

Edited by G Eysenbach; submitted 22.01.16; peer-reviewed by R W, L Kuhns; comments to author 18.02.16; revised version received 26.03.16; accepted 28.03.16; published 17.06.16.

Please cite as:
Hirshfield S, Downing Jr MJ, Parsons JT, Grov C, Gordon RJ, Houang ST, Scheinmann R, Sullivan PS, Yoon IS, Anderson I, Chiasson MA
Developing a Video-Based eHealth Intervention for HIV-Positive Gay, Bisexual, and Other Men Who Have Sex with Men: Study Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2016;5(2):e125
URL: http://www.researchprotocols.org/2016/2/e125/
doi:10.2196/resprot.5554
PMID:27315764

Protocol

Novel Use of Hydroxyurea in an African Region With Malaria: Protocol for a Randomized Controlled Clinical Trial

Juliana N Anyanwu[1], MD; Olatundun Williams[2], MD; Casey L Sautter[1], BS, MS; Phillip Kasirye[3], MB BcH; Heather Hume[4], MD; Robert O Opoka[3], MB ChB; Teresa Latham[5], MA; Christopher Ndugwa[3], MB ChB; Russell E Ware[5], MD PhD; Chandy C John[6], MD, MS

[1]University of Minnesota, Minneapolis, MN, United States

[2]Northwestern University, Chicago, IL, United States

[3]Makerere University, Kampala, Uganda

[4]University of Montreal, Montreal, QC, Canada

[5]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States

[6]Indiana University School of Medicine, Indianapolis, IN, United States

Corresponding Author:
Chandy C John, MD, MS
Indiana University School of Medicine
1044 W. Walnut St, R4 402D
Indianapolis, IN, 46202
United States
Phone: 1 3172748940
Fax: 1 3172748944
Email: chjohn@iu.edu

Abstract

Background: Sickle cell anemia (SCA), one of most prevalent monogenic diseases worldwide, is caused by a glutamic acid to valine substitution on the beta globin protein of hemoglobin, which leads to hemolytic anemia. Hydroxyurea, the only disease-modifying therapy approved by the Food and Drug Administration for SCA, has proven to be a viable therapeutic option for SCA patients in resource-rich settings, given clinical improvements experienced while taking the medication and its once-daily oral dosing. Significant studies have demonstrated its safety and clinical efficacy among children and adults in developed countries. In Sub-Saharan Africa, however, the risk of malaria, hematologic toxicities, and safety of hydroxyurea in children with SCA living in malaria-endemic areas are unknown.

Objectives: Study objectives include determining the incidence of malaria in SCA patients taking hydroxyurea versus placebo; establishing the frequency of hematologic toxicities and adverse events (AEs) in children with SCA treated with hydroxyurea versus placebo; and defining the relationships between hydroxyurea treatment and fetal hemoglobin, soluble intracellular adhesion molecule-1, and nitric oxide levels, and between levels of these factors and risk of subsequent malaria.

Methods: Novel use Of Hydroxyurea in an African Region with Malaria (NOHARM, NCT01976416) is a prospective, randomized, placebo-controlled, double-blinded phase III trial to compare risk of malaria with oral hydroxyurea versus placebo. Children will be recruited from the Mulago Hospital Sickle Cell Clinic in Kampala, Uganda.

Results: Two hundred Ugandan children aged between 1.00 and 3.99 years with confirmed SCA will be randomized into treatment groups by order of entry in the study, based on a predetermined blinded randomization list. The primary outcome of the trial is malaria incidence in the 2 study groups, defined as episodes of clinical malaria occurring over the 1-year randomized study treatment period.

Conclusion: NOHARM will be the first prospective randomized, placebo-controlled clinical trial investigating the use of hydroxyurea for children with SCA in a malaria-endemic region within Africa. The results of this trial have the potential to significantly advance understanding of how to safely and effectively use hydroxyurea in children with SCA in malaria-endemic areas.

Trial Registration: Clinicaltrials.gov NCT01976416; https://clinicaltrials.gov/ct2/show/NCT01976416 (Archived by WebCite at http://www.webcitation.org/6hmoilZnp)

(JMIR Res Protoc 2016;5(2):e110) doi:10.2196/resprot.5599

KEYWORDS

sickle cell anemia; hydroxyurea; malaria

Introduction

Background and Rationale

Sickle cell anemia (SCA) is a genetic blood disorder where sickling of red blood cells, due to a genetic alteration in hemoglobin, leads to chronic hemolysis, organ damage, vaso-occlusive events, and other potentially life-threatening complications [1]. It is acquired in an autosomal recessive fashion and is most prevalent in Africa, where over 230,000 babies with SCA are born annually [2]. Without any identification by newborn screening or early interventions, many of these children will die [3,4] from acute anemia or infection, especially bacterial sepsis or malaria, and many before the age of 5 years. Because SCA is an important cause of under-5 mortality, the World Health Organization (WHO) has urged African nations to make its recognition and management a priority [5,6].

Despite being the most prevalent genetic disease in the African region, disease prevention and management for SCA are inadequate [5]. With the high prevalence and morbidity of SCA in Sub-Saharan Africa, there is need for improved access to diagnostic and therapeutic options. Stem cell transplant and blood transfusions are effective therapeutic considerations in high-income countries but often not feasible in low-income countries owing to limited availability and greater risks within these settings [7]. In many developed countries, interventions such as prophylactic penicillin, pneumococcal immunizations, newborn screening programs, and the availability of hydroxyurea have significantly decreased SCA-associated morbidity and mortality, thereby leading to improved survival into adulthood.

Hydroxyurea, an inducer of fetal hemoglobin (HbF), saw its first clinical application for SCA in 1984. The drug has been shown to dramatically reduce vascular crises, hospitalizations, and the need for transfusions among SCA patients. It is inexpensive, can be given with once-daily dosing, and has been shown to be safe and effective from the age of 9 months to adulthood [8,9]. Thus, it has been proposed as the standard of care for children in the United States with SCA [9].

At the time of this paper's publication, however, hydroxyurea is not the standard of care in Sub-Saharan Africa for SCA, as the safety of the drug in a malaria-endemic region is not known. Studies have shown that children with SCA have higher mortality rates from malaria than children with either sickle cell trait (hemoglobin AS, HbAS) or children with normal hemoglobin. Children with HbAS are strongly protected from severe malaria [10], and this is thought to be the main reason why the hemoglobin S gene has been retained through selection in African populations living in malaria-endemic areas. Children with SCA appear to have a similar or lower risk of uncomplicated and severe malaria as children without SCA but have a much higher rate of death when hospitalized with malaria [11]. The reasons for the increased risk are not fully elucidated but likely relate to worsened anemia and/or sepsis from the gram-negative bacteremia that often occurs with severe malaria [12]. Thus, prevention of malaria is critical in children with SCA because severe malaria disproportionately leads to death in these children.

Many of the factors relating to vaso-occlusive crises and other complications in SCA are important in the pathogenesis of severe malaria. Factors associated with severe malaria that may be affected by hydroxyurea in children with SCA include intracellular adhesion molecule-1 (ICAM-1) [13,14], vascular cellular adhesion molecule-1 (VCAM-1) [15,16], von Willebrand factor (VWF) [17], tumor necrosis factor-alpha (TNF-α) [18], and nitric oxide (NO) [19]. All these factors, except NO, are elevated in severe malaria, and all are potentially involved in the pathogenesis of severe malaria. For example, elevated ICAM-1 expression in animal models of severe malaria leads to increased parasite adhesion and worsened clinical malaria [20], and our group and others have shown that children with severe malaria have elevated VWF levels, suggesting that endothelial activation in severe malaria may be associated with more severe disease [21]. Studies have found that TNF-α is elevated in children with severe malaria [22] and increased in children who die of malaria [22]. Animal studies suggest that TNF-α is directly involved in pathogenesis of severe malaria and is not simply a marker of disease severity [23]. In contrast, NO appears to be an important factor in protection against severe malaria in human [24] and animal [25,26] studies, through mechanisms including vasodilation and direct toxicity against the parasite.

Hydroxyurea is thought to prevent vaso-occlusive crises and pain episodes in children with SCA in part through generation of NO [19,27,28]. Through this mechanism, hydroxyurea could actually lead to protection from malaria. Similarly, HbF has been shown to inhibit *Plasmodium falciparum* growth *in vitro* [29] and is thought to be responsible for much of the protection from clinical malaria seen in children aged <3 months in malaria-endemic areas [30], and hydroxyurea typically increases (in older children) or slows the decrease (in children aged <18 months) of HbF levels. Both these changes should lead to *decreased* risk of malaria in children taking hydroxyurea. However, the effect of hydroxyurea on markers of endothelial activation is less clear. Early studies found that hydroxyurea raised concentrations of ICAM-1 in an *in vitro* model of SCA [13], raising concern that this could lead to an increased risk of parasite binding in children with SCA and therefore to increased sequestration and complications (including death) from malaria. However, one study in humans showed that hydroxyurea decreased levels of soluble ICAM-1 (sICAM-1) [15], and another study showed no change in sICAM-1[16]. A subsequent animal study did not show increased ICAM-1 expression or worse outcome with hydroxyurea treatment of animals with animal model SCA [14], but the animal models used a

Plasmodium species other than *P. falciparum*, which may interact differently with ICAM-1 than *P. falciparum*. *In vitro* studies suggest that hydroxyurea decreases VWF incorporation into the endothelial cell extracellular matrix [17], but human studies show no change in VWF levels with hydroxyurea treatment [16]. Early studies of hydroxyurea in rats demonstrated that it increased TNF-α levels [31], but one human study of individuals with SCA receiving hydroxyurea treatment showed a decrease in TNF-α levels [18], and another showed no difference in TNF-α levels [32]. A recent review of malaria in children with sickle cell disease nicely outlined other ways in which hydroxyurea might combat malaria, including direct antiparasitic activity at high concentrations, and improvement in splenic function [33], but it is unclear whether these effects or an increase in ICAM-1 or TNF-α, which may increase risk of malaria severity, will be seen in children with SCA in Sub-Saharan Africa.

The hematologic toxicities of hydroxyurea, particularly neutropenia, are additional important safety concerns for children with SCA in malaria-endemic areas of Sub-Saharan Africa. The recently completed BABY-HUG study reported hematologic toxicities with hydroxyurea treatment that included severe neutropenia (5%), severe anemia (1%), and thrombocytopenia (11%), although similar toxicities were also noted in the placebo-treated arm [8]. Malaria can decrease bone marrow erythropoietic response and lower platelet count, so, the side effects of anemia and thrombocytopenia from hydroxyurea treatment could be greater in children repeatedly exposed to malaria than in children in North America or Europe who lack malaria exposure. Neutropenia in children in Sub-Saharan Africa may also place them at higher risk of severe bacterial infection than neutropenia in children in North America or Europe because of the much higher baseline rates of bacterial infection in African children, which could then lead to invasive and severe bacterial infection.

In summary, some changes associated with hydroxyurea treatment (increased NO and HbF and improved splenic function) would be expected to protect against malaria, but the data on hydroxyurea-related endothelial changes thought to be important in severe malaria pathogenesis (eg, ICAM-1, VWF, TNF-α) are less clear, with some studies suggesting that these factors might be increased with hydroxyurea and others suggesting no difference or even a decrease. The frequency, severity, and consequences of the hematologic toxicities of hydroxyurea in children with SCA in malaria-endemic areas are also unknown. Thus, a prospective clinical trial to determine definitively whether hydroxyurea poses special risks to children with SCA in malarial regions is warranted.

Study Objectives and Hypotheses

The objectives of the study are:

1. To determine the incidence of malaria in children with SCA treated with hydroxyurea versus placebo: The working hypothesis of this aim is that incidence of malaria is not greater in children with SCA treated with hydroxyurea in comparison to those treated with placebo. We will test this hypothesis by comparing malaria incidence over a 1-year period in children with SCA in the hydroxyurea versus placebo treatment groups.

2. To establish the frequency of hematologic toxicities and AEs in children with SCA treated with hydroxyurea versus placebo: The working hypothesis of this aim is that children with SCA treated with hydroxyurea will have more medication-related hematologic toxicities, such as neutropenia, but no increase in SCA-related AEs (eg, pain crises, hospitalizations, requirement of blood transfusion) compared with children treated with placebo. We will test this hypothesis by comparing hematologic toxicities and AEs in children with SCA in the hydroxyurea versus placebo treatment groups.

3. To define the relationship between hydroxyurea treatment and HbF, sICAM-1, and NO levels and between levels of these factors and risk of subsequent malaria. The working hypotheses of this aim are that: (1) hydroxyurea will increase HbF and plasma NO levels and decrease plasma sICAM-1 levels and (2) HbF and plasma NO levels will inversely correlate, and plasma sICAM-1 levels will positively correlate, with subsequent malaria incidence. We will test this hypothesis by testing the associations between (1) hydroxyurea and change in levels of HbF, sICAM-1, and NO at 2-, 4-, and 12-month follow-up and (2) change in levels of HbF, sICAM-1, and NO at 2 and 4 months and risk of subsequent malaria.

Trial Design

We are conducting a prospective, randomized, placebo-controlled, double-blinded phase III trial to compare oral hydroxyurea with placebo among Ugandan children with SCA. The trial opened to accrual in September 2014, and we estimate that the 2-year follow-up will be completed in December 2017.

Methods

Study Setting

Study participants will be recruited from the Mulago Hospital Sickle Cell Clinic (MHSCC) in Kampala, Uganda. The MHSCC is the first and largest specialized clinic for the treatment of SCA in Uganda. The clinic was established by Professor Christopher Ndugwa in 1968, and since its inception, over 11,000 SCA patients have been registered at the MHSCC. Currently, approximately 3,500 patients are actively treated at this clinic, about 20% of whom are aged younger than 4 years. Kampala is an area of mesoendemic malaria transmission, but the outpatient and inpatient malaria burden is still high. Malaria is the primary diagnosis in more than 2,500 children admitted annually to Mulago Hospital and more than 20,000 children seen as outpatients at Mulago Hospital.

Eligibility Criteria

Children were recruited for the Novel use Of Hydroxyurea in an African Region with Malaria (NOHARM) study through the MHSCC Database of active patients, using the following criteria:

Inclusion Criteria

1. Pediatric patients with documented SCA (hemoglobin SS supported by hemoglobin electrophoresis or by peripheral blood smear showing sickled red blood cells).

2. Age range of 1.00-3.99 years, inclusive, at the time of enrollment.

3. Weight at least 5.0 kg at the time of enrollment.

4. Willingness to comply with all study-related treatments, evaluations, and follow-up.

Children who meet the aforementioned criteria, but who are acutely ill at the time of recruitment will be asked to return to clinic at a later date to establish baseline laboratory values and ensure that they do not meet any of the following exclusion criteria:

Exclusion Criteria

1. Active use of hydroxyurea on a regular basis.

2. Known chronic medical condition (eg, HIV, malignancy, active clinical tuberculosis).

3. Severe malnutrition determined by impaired growth parameters as defined by WHO (weight for length and height < −3 z-scores below the median WHO growth standards).

4. Preexisting severe hematologic toxicity: Hb <4.0 gm/dL, Hb <6.0 gm/dL with absolute reticulocyte count (ARC) <100 × 10^9/L, ARC <80 × 10^9/L with Hb <7.0 gm/dL, platelets <80 × 10^9/L, and absolute neutrophil count (ANC) <1.0 × 10^9/L.

5. Alanine aminotransferase or creatinine >2× the upper limit of normal for age.

6. Blood transfusion within 30 days before enrollment.

Interventions

Medical evaluation and treatment for standard clinical issues will be performed as per the MHSCC guidelines. Control and treatment groups will receive the same standard care and will complete evaluations in the same time frame. Standard preventive measures provided in the MHSCC for children with SCA include the following: (1) folic acid (1 mg of PO) daily; (2) penicillin prophylaxis (250 mg PO) daily for all children aged younger than 5 years; (3) sulfadoxine-pyrimethamine prophylaxis, once monthly; and (4) anthelmintic treatment every 6 months. All children in the study will also receive an insecticide-treated bednet (ITN) because of the documented benefits of ITNs in population-based studies of malaria [34].

Eligibility screening and Baseline Evaluations will occur together at month 0. Study treatment initiation will also occur at month 0 or within 1 to 3 days of being found eligible for randomization. Study treatment will commence at 20 ± 2.5 mg/kg of PO daily (for all participants except those weighing 6.0-8.0 kg, in whom the dose will be closer to 20 ± 5mg/kg), with appropriate adjustments as needed for hematologic toxicities as outlined in the following section. The appropriate dose will be achieved using a combination of 100 mg and 1000 mg (4 × 250 mg scored) tablets.

Dose Initiation Plan for Study Months 0 to 12

Using the participant's weight at month 0, the daily dose will be calculated using available tablet sizes and a goal of 20 ± 2.5 mg/kg/day using dosing tables based on the participant's weight. At each interval visit, laboratory studies will be used to assess treatment toxicity, typically anemia or neutropenia, but possibly also reticulocytopenia or thrombocytopenia. The daily dose will be held or lowered based on protocol treatment toxicity guidelines. Medication adherence will be assessed at each visit, and attempts will be made to collect treatment compliance data.

Rationale for Placebo-Controlled Treatment

Due to the concerns about potentially increasing the risk of severe malaria with the use of hydroxyurea, a placebo-controlled randomized clinical trial is the only way the issue of hydroxyurea safety in this patient population can be resolved. The risk of death from malaria makes it imperative that the effects of hydroxyurea on malaria be studied in Ugandan children with SCA who are at risk of malaria. The study design was discussed and refined with local academic leaders before submission and approval by the Makerere School of Medicine Research Ethics Committee and the other institutional review boards (IRBs) listed in the following *Ethical Considerations* section.

Outcomes

Specific Aim 1

Primary Outcome

The primary outcome of the NOHARM trial is malaria incidence, defined as episodes of clinical malaria occurring over the 1-year randomized study treatment period. Clinical malaria is defined as a history of fever or presence of measured fever (axillary temperature ≥37.5°C) in a child with a blood smear positive for *Plasmodium* species on microscopy. All parents or guardians are asked to bring their children to the MHSCC for any illness, and we anticipate compliance to be high because free evaluation and care by study personnel are available at the clinic. Children will be evaluated for malaria by a study clinician, and microscopy will be done by study personnel trained in malaria microscopy. All blood smears will be read independently by 2 readers, and any reading with a discrepancy between the 2 readers will have a third reading done to establish final diagnosis.

Secondary Outcomes

To assess incidence of malaria by additional criteria that may add specificity (at the cost of some sensitivity), we will add the following definitions as secondary outcomes. These definitions will include all children with the primary definition but with the added criteria of the following: (1) *P. falciparum* parasitemia >1000 parasites/μL; (2) measured axillary temperature ≥37.5°C; (3) *P. falciparum* parasitemia >1000 parasites/μL and measured axillary temperature ≥37.5°C; and (4) malaria requiring hospital admission. The following covariates will be assessed: (1) local council area or village (location of household where child lives), as a surrogate for malaria exposure. Malaria exposure in Kampala is heterogeneous. Randomization should effectively place children from different areas of exposure risk evenly in the 2 treatment groups, but we will assess this; (2) socioeconomic status (SES). We have developed a simple tool for evaluation of SES of the families of children in our malaria studies. SES is often related to malaria exposure; (3) age and gender.

Specific Aim 2

Primary Outcomes

The primary outcomes include: (1) composite outcome: one or more of the SCA-related AEs summarized in Table 1 (modified from the BABY-HUG trial) and (2) any hematologic toxicity noted in the *Dose Toxicity* section.

Table 1. Definitions of sickle cell anemia-related adverse events.

Adverse event	Definition
Pain event	Pain in the arms or legs, back, abdomen, chest, or head with no other explanation, lasting at least 2 hours, that brings child to clinic for evaluation and requires nonsteroidal anti-inflammatory or narcotic analgesics
Dactylitis	Pain and tenderness, with or without swelling, limited to the hands and feet
Acute chest syndrome	Clinical syndrome characterized by new pulmonary infiltrate and at least 3 of: chest pain, axillary temperature greater than 37.5°C, tachypnea, wheezing, or cough
Splenic sequestration	Increase in palpable spleen size by 2 cm or more below the costal margin from the last examination, accompanied by a decrease in hemoglobin of 2 g/dL or more or 20% or more from steady state values
Requirement of blood transfusion	Reason for transfusion will be recorded

Secondary Outcomes

The secondary outcomes include: (1) individual AEs, including painful events and (2) toxicities for hemoglobin, reticulocytes, neutrophils, or platelets. The following covariates will be assessed: age; gender; and weight and height for age, weight for height (nutrition).

Specific Aim 3

Primary Outcomes

The primary outcome will be change in percent HbF and plasma concentration of sICAM-1 and NO.

Secondary Outcomes

The secondary outcome will be change in concentration of plasma VCAM, VWF, and TNF. HbF levels and initial hemoglobin S testing will be performed by capillary electrophoresis (Sebia MINICAP) in the Uganda Cancer Institute laboratory. sICAM-1 and soluble VCAM-1 will be assessed by ELISA (R&D Systems), VWF activity by ELISA (Corgenix), and TNF-α by cytometric bead assay (EMD-Millipore). All these tests will be done in the University of Minnesota or University of California—San Francisco or Makerere University laboratory in Kampala, Uganda. NO levels will be measured by fluorometric assay of total plasma nitrate and nitrite (EMD-Millipore). NO levels will be tested at the Indiana University because a fluorometric assay reader is not available on the Makerere campus.

Participant Timeline

Subjects will have clinic visits and laboratory assessments at specific time points as detailed in Multimedia Appendix 1).

Sample Size Calculation

We aimed to randomize 200 children with SCA into study arms (100 in each treatment arm). Twelve months of age was chosen as the minimum age based on published experience from the phase III infant hydroxyurea (BABY HUG) clinical trial [8]. An upper age limit of 4 years was chosen because older children have less common and less severe malarial events. Sample size calculations were completed for each specific aim as follows:

For Specific Aim 1, the detectable difference in malaria incidence depends on incidence in the control group. Few relevant data are available for children with SCA in Uganda, so, we present a range of detectable differences corresponding to a range of 0.3 to 1.3 malaria incidents per child in a year in the control group (based on data from an ongoing study of malaria in Kampala that involves assessment of malaria incidence in community children—lowest estimated incidence—and children with severe malaria—highest estimated incidence). With 100 children per group, these control-group rates imply 90% power to detect between 59% and 34% difference between groups, respectively in malaria incidence (This assumes a 2-sided test, alpha=0.05, and variance or mean=1.7 as in the ongoing study mentioned previously.)

For Specific Aim 2, the outcome of greatest interest for this aim is the occurrence of 1 or more AEs. We estimate that approximately 50% of control-group children will have 1 or more of the AEs summarized in Table 1, most frequently a pain event. The decision to treat 100 children per group provides 90% power to detect a difference from a rate of 73% in the hydroxyurea group (80% power for a rate of 70%). For the hematologic measures, we do not have estimates of the fraction of children who will reach the dose-limiting toxicities or the incidence of such events. Comparing the hydroxyurea and placebo groups according to average values of ANC or Hb, we have 90% power to detect a difference between groups of 0.46 standard deviations (ie, describing variation between children in the same group, hydroxyurea or placebo).

For Specific Aim 3, to test the association of study treatment with each marker, we have 80% power to detect a difference between groups of 0.40 standard deviations in the marker (this is conservative and is based on having a single follow-up marker measurement per child instead of the 3 we will have). To analyze the association between markers and malaria episodes, the detectable difference in rate of malaria episodes depends on the rate of episodes per child. For a low rate of 0.3 episodes per child in 10 months, we have 80% power to detect a rate ratio of 2.1 for a 1-standard-deviation change in the marker; for a high rate of 1.2 episodes per child, the detectable rate ratio is 1.5.

Recruitment and Enrollment

Families of recruited subjects will be informed of study procedures and the expected follow-up schedule. Subjects will be enrolled by the study nurse or medical officer based on meeting inclusion criteria, not meeting exclusion criteria, and being able to maintain the follow-up schedule. Subjects will be enrolled after written informed consent has been obtained from the parent or guardian, according to the guidelines of the main IRB and the local ethics committees (Multimedia Appendix 2, 3 and 4). Given the burden of traveling to the clinic each month, remuneration per visit will be provided to families to help defray the costs of travel and lost wages.

Randomization and Blinding

Block randomization will be used and will occur via the OnCore Electronic Data Capture system. OnCore is a software system widely used in many clinical research centers across the United States and internationally. The data coordinating center (DCC) will have uploaded randomization "block files" into the system so that participants can be randomized into the study.

Study participants will be randomized by the DCC staff into treatment groups by order of entry in the study, based on the predetermined blinded randomization list. The child's study identification number will be recorded, and treatment group may only be determined by comparing the child's study identification number to the blinded list, which only the DCC staff will have access to until the study is completed or stopping rules are reached and unblinding is required. The study pharmacist will have identical appearing hydroxyurea or placebo tablets and will provide the appropriate medication to the child. Dosage adjustment will be done according to the aforementioned guidelines so that if lower counts occur on placebo, placebo dose will also be lowered. Neither study participants nor their care providers, investigators, study personnel treating the participants, study coordinators, and outcomes assessors will know which arm a child is in. Laboratory values for scheduled visits are entered in the database and provided to the clinicians taking care of the study participant only if the laboratory value is a critical value.

Data Management

Before site activation, the study investigators will ensure that adequate clinical, laboratory, pharmacy, data management facilities, and operations are in place. In addition, adequate training in all aspects of the trial, including electronic data entry, will be conducted. Research staff will undergo retraining as needed to ensure sound practices are maintained.

OnCore is Web based and password protected. The DCC has been using it for clinical trials management since 2009. Security privileges will be assigned in OnCore based on team roles and duties, within the context of the protocol. OnCore allows for validation of electronic case report forms, which allows data to be locked once they are verified.

Data from this study will be reviewed in real time by the study team members. Source documents will be reviewed, and data entries will be confirmed. Inconsistencies will be examined with the data manager, and corrective actions will be taken as needed. In regard to subject confidentiality, coded numbers will be used for identification of participant records and laboratory specimen. Clinical information will not be released by the NOHARM Medical Coordinating Center (MCC) or DCC without written permission from the subject, parent, or guardian, except as necessary for monitoring. Clinical information can be shared by the site investigators and staff for patient care reasons, for example, local consultations. The final trial dataset will be kept by the DCC, and no one outside the DCC, including the Principal Investigator, will have access to the randomization information or to the full trial dataset until the end of the randomized trial, unless findings in interim analysis lead the data safety and monitoring board (DSMB) to request study un-blinding. The DCC and MCC have a written agreement clarifying these roles.

Efforts for participant retention in the trial will be encouraged through the regular contact via visits for refill of hydroxyurea or placebo and provision of ongoing clinical care for the duration of the study. Outcome data will be recorded for those who withdraw from the study up to the time of withdrawal.

Analysis

For *Specific Aim 1*, we will compare the hydroxyurea versus placebo groups according to total malaria incidence (inpatient and outpatient) over the 12-month treatment period, using an intention-to-treat analysis. The comparison will use negative binomial regression with adjustment for age (a known predictor of outcome), gender (if associated with outcome), local council area or village, and SES. This choice is based on analysis of preliminary data indicating significant overdispersion compared with Poisson-distributed counts. Secondary outcomes will be tested using similar methods. We will record whether a child was admitted for malaria, and the complication that led to admission, but the final number of episodes of malaria recorded as the primary outcome will be all episodes, whether treated as outpatient or requiring admission. Episodes requiring admission will be assessed in secondary analysis (see Secondary Outcomes, in the previous section).

Specific Aim 2 is to establish the frequency of hematologic toxicities and AEs in children with SCA treated with hydroxyurea versus placebo. The working hypothesis is that children with SCA treated with hydroxyurea will have more medication-related hematologic toxicities, such as neutropenia, but no increase in SCA-related AEs (eg, pain crises, hospitalizations, requirement of blood transfusion) than children treated with placebo. We will test this hypothesis by comparing hematologic toxicities and AEs in children with SCA in the hydroxyurea versus placebo treatment groups. The frequency and incidence of each of the SCA-related hematologic toxicities listed in "Dose Toxicities" will be compared between the hydroxyurea and placebo groups using the chi-square test and negative binomial regression, respectively. Fractions of children having 1 or more AEs will be compared between hydroxyurea and placebo groups using chi-square tests, and incidence of all AEs per child will be compared between groups using negative binomial regression (because of overdispersion, as noted under Specific Aim 1). Secondary analysis will assess incidence and frequency of individual AEs.

Specific Aim 3 is to define the relationship between hydroxyurea treatment and HbF, sICAM-1, and NO levels and between levels of these factors and risk of subsequent malaria. The working hypotheses of this aim are that (1) hydroxyurea will increase HbF and plasma NO levels and decrease plasma sICAM-1 levels and (2) HbF and plasma NO levels will inversely correlate, and plasma sICAM-1 levels will positively correlate, with subsequent malaria incidence. We will test this hypothesis by testing the association between (1) hydroxyurea and change in levels of HbF, sICAM-1, and NO at 2-, 4-, and 12-month follow-up and (2) change in levels of HbF, sICAM-1, and NO at 2 and 4 months and risk of subsequent malaria.

The hypothesized causal pathway is hydroxyurea → marker changes → increased malaria risk. To assess the first step in the causal pathway, the hydroxyurea and control groups will be compared according to change in and absolute level of HbF, sICAM-1, and NO levels. Markers will be analyzed separately; for each marker, the analysis will use a mixed linear model with child as the random effect and with fixed effects being group (hydroxyurea versus control) and visit (2, 4, and 12 months), possibly after transforming the marker, so, its distribution is more symmetric. Analysis for the second step in this pathway, association between change in or absolute level of HbF, sICAM-1, and NO levels and malaria risk, will use negative binomial regression as in Specific Aim 1. Each marker will be analyzed separately, and then, all 3 will be analyzed simultaneously. The predictors will be change in child's 2-month and 4-month marker measurements, and the outcome will be the child's counts of malaria episodes in the 10-month period between 2 and 12 months of follow-up, with adjustment for age, gender, local council area or village, and SES. For these analyses, hydroxyurea and placebo groups will be analyzed separately. Analysis of secondary predictors will be done analogously.

All analyses will be done as randomized analyses. Missing data will be recorded as missing and will not be used in analysis.

Duration of Study Participation

The primary study end point will be evaluated after 12 months of study treatment (hydroxyurea or placebo). After these 12 months, children will enter a follow-up phase, during which they can receive an additional 12 months of open-label hydroxyurea treatment (through the full period of study follow-up) if they or their parents wish to do so, after consultation with local physicians at the MHSCC, and a clear explanation of the potential benefits and problems of treatment with hydroxyurea. We are working with the Ministry of Health to see if hydroxyurea can be subsidized, if it is safe and effective, so that children can continue to receive it after the trial is completed. Parents or guardians who are concerned that their child suffered harm from study participation are encouraged to talk to study personnel, who will review the issue with the ethics review committee and determine whether compensation is required.

Monitoring

Hydroxyurea is the only disease-modifying therapy that is approved by the Food and Drug Administration (FDA) for SCA [35,36]. Approval was based on a landmark randomized trial, by Charache et al, which showed decreased episodes of acute chest syndrome, painful crises, blood transfusions, and hospitalizations among adults with SCA [37]. Hydroxyurea is not yet approved by the FDA for pediatric SCA patients. However, various studies of children with SCA have demonstrated its clinical and laboratory efficacy, in addition to its safety [8,38,39].

Hematologic toxicities and occasional dose adjustments are expected with hydroxyurea therapy. Laboratory toxicities from hydroxyurea will manifest primarily as reversible and transient myelosuppression, especially of granulocytes [40]. Careful monitoring of complete blood counts will be performed at 2 weeks and then at 1, 2, 3, 4, 6, 8, 10, and 12 months after initiation of study treatment. If a hematologic toxicity occurs (eg, the ANC falls $<1.0 \times 10^9$/L), study treatment will be held and weekly blood counts performed. If the hematologic toxicity resolves within 2 weeks, the daily dose will resume at 20 ± 2.5 mg/kg/day. If the toxicity persists for 2 weeks or occurs twice within a 3-month period, the study treatment dose will be reduced by 5 mg/kg/day to 15 ± 2.5 mg/kg/day.

A similar algorithm will be used for platelet toxicity, defined as $<80 \times 10^9$/L. For anemia, the thresholds will be any of the following: if the Hb concentration falls to <4.0 g/dL; or Hb <6.0 g/dL with the ARC $<100 \times 10^9$/L; or Hb <7.0 g/dL with the ARC $<80 \times 10^9$/L, study treatment should be withheld until weekly counts document recovery. If the toxicity resolves within 2 weeks, the daily dose will resume at 20 ± 2.5 mg/kg/day. If the toxicity persists for 2 weeks or occurs twice within a 3-month period, the study treatment dose will be reduced by 5 mg/kg/day to 15 ± 2.5 mg/kg/day. Study treatment will also be held during acute hepatic or renal toxicity (eg, ALT >2× the upper limit of normal for age, creatinine more than doubled from the baseline value, and >1.0 mg/dL).

An independent DSMB will supervise the trial. The DSMB will consist of a group of experienced investigators and a lay advocate. Among these individuals, there will be expertise in international pediatric hematology clinical research and specifically malaria and the use of hydroxyurea in SCA, as well as representation in biostatistics, ethics, clinical research, and patient advocacy.

In our trial, we expect AEs to occur, but we expect that children with SCA treated with hydroxyurea will have more medication-related hematologic toxicities, but no increase in SCA-related AEs. After obtaining written consent from study participants, all AEs and serious adverse events (SAE) will be collected and reported to the MCC and the DCC using the correct data collection forms. The Common Terminology Criteria for Adverse Events version 4.0, available since 2009, will be used for AE reporting. All AEs are categorized by organ system and graded by severity. SAE reporting will occur in a timely manner to the DSMB and to the ethical boards that approved this study. All SAEs will be followed until resolution or stabilization.

Periodic review of data will occur with the external DSMB, and the NOHARM study will be discontinued if at any time the

DSMB or study team feels that it is in the best interests of the study subjects. Because NOHARM is a phase III trial in a potentially vulnerable patient population, it is important that an independent group have access to the feasibility, safety, and efficacy data. Review by the DSMB will be critical to ensure that the subjects are protected from harm, while also ensuring that the study integrity is not compromised.

Interim Analysis

Interim analyses will occur when 50, 100, and 150 participants have completed 1 year of follow-up (ie, the first analysis will occur when there are 25 children in each treatment arm, the next when there are 50 children in each treatment arm, and so forth). Clear stopping rules, presentation of data to the DSMB, and regular meetings of the DSMB will ensure that the NOHARM trial does indeed protect its study participants from harm, by determining whether differences in severe malaria or death rates between the 2 treatment arms are large enough to demonstrate superiority of one treatment arm over the other. Stopping rules will be created to evaluate: (1) excess risk of severe malaria (malaria requiring admission) and (2) the excess risk of death (the primary unexpected AE) in one treatment arm versus the other. The DSMB will review the protocol, including stopping rules, and decide on a schedule of meetings.

Each of the 2 harm outcomes listed previously will be monitored using a stopping rule based on the Lan–DeMets alpha-spending function approach. For each outcome, the total alpha (type I error risk) will be 0.025, so that the total chance of a false-positive finding (combining the 2 outcomes) is the usual 0.05. The stopping rule will be 2 sided. Different choices of the alpha-spending function make different allocations of the type I error risk between earlier and later interim analyses. The best-known spending function, the O'Brien–Fleming boundaries, is conservative in the sense of requiring a very small *P* value at early interim analyses (ie, require a very large difference between groups). Other spending functions (eg, power family or Hwang-Shih-DeCani, H-S-D, family) require somewhat smaller differences between groups at early interim analyses compared with O'Brien–Fleming, at the price of requiring somewhat larger differences in later interim analyses. These other spending functions can also provide slightly greater statistical power. Table 2 summarizes the *P* values required to stop at the 3 planned interim analyses (labeled as Analysis 1, 2, and 3) and the final analysis (labeled as Analysis 4), for some candidate spending functions. These are also the risk of a type I (false positive) error at each analysis, if in fact, the groups do not differ in the chance of an AE (For any spending function, the 4 *P* values add to .025, the overall type I error risk.) See Table 2 for *P* values required to stop at each interim analysis.

Table 2. *P* values required to stop at each interim analysis[a].

Analysis	O'Brien Fleming	Pfam Φ=3	H-S-D γ=-3
1	<.001	<.001	.001
2	<.001	.003	.003
3	.007	.007	.007
4	.02	.01	.01

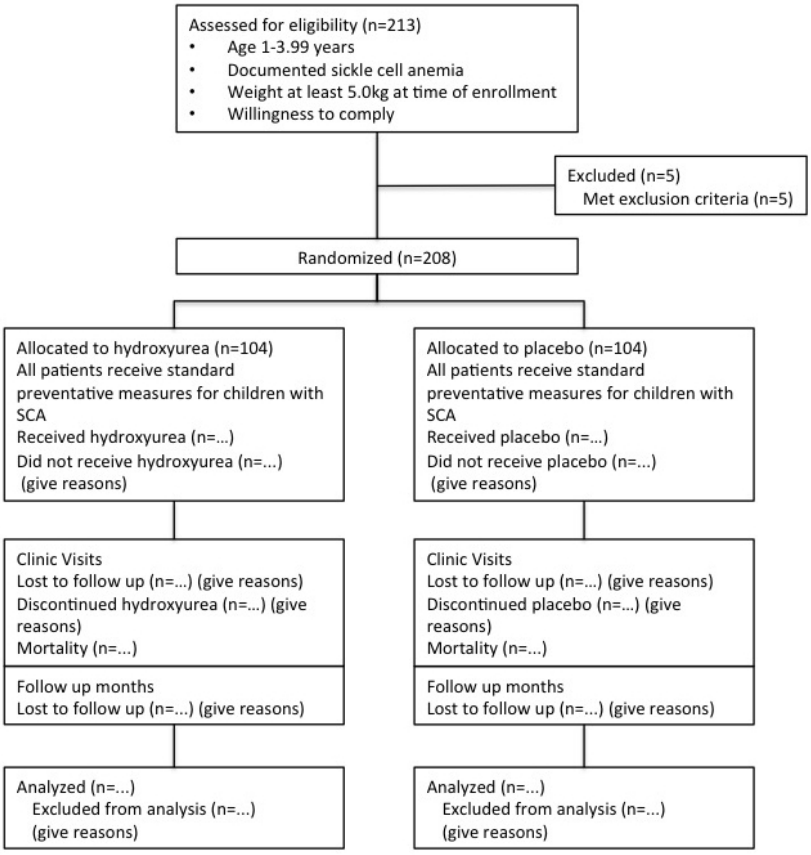
[a]The power family of spending functions has an adjustable constant $\Phi > 0$; $\Phi=0$ results in equal *P* values at all interim analyses, increasing Φ gives higher *P* values for later analyses. The H-S-D family has an adjustable constant $\gamma \neq 0$; $\gamma=-4$ gives approximately the O'Brien–Fleming spending function, whereas $\gamma=1$ results in approximately equal *P* values at all interim analyses.

To maximize the power for early detection of excess risk without unduly sacrificing power at the final analysis (Analysis 4), we prefer the H-S-D spending function with $\gamma=-3$.

Progress to Date

The NOHARM trial enrolled its first participants in September 2014, and enrollment was completed in November 2015. A total of 213 consented participants were enrolled, of which 208 were randomized into the blinded study treatment phase (months 0-12, Figure 1). As of March 28, 2016, 90 participants have completed the blinded treatment phase of the study, and monthly visits are currently ongoing. Data validation efforts are focused on the first cohort of participants to complete the blinded treatment, to ensure timely data analysis. The blinded study phase is scheduled to be completed in November 2016.

Figure 1. Participant flow diagram for the NOHARM study.



Ethical Considerations

The NOHARM study received ethical approval from Makerere University School of Medicine Research and Ethics Committee (SOMREC; Kampala, Uganda; approval #2014-006), the Mulago Hospital Research and Ethics Committee (approval #528), the University of Minnesota Institutional Review Board (approval # 1310M44703), Indiana University Institutional Review Board (Bloomington, IN, USA; approval #1412985992), Cincinnati Children's Hospital Medical Center (approval #2014-1409), the Uganda National Council on Science and Technology (approval #HS 1553), and the Uganda National Drug Authority. In the event of the need for protocol amendments, such changes will be discussed with all investigators on the trial, and once agreed on, a protocol amendment form or a change in protocol request will be made to the appropriate IRB or ethics committees.

Informed consent is obtained after discussion between at least 1 parent or guardian of a prospective study participant and trained study team personnel. Every consent discussion will include: purpose of the study, study procedures (including enrollment, screening, randomization, treatment, monitoring, and follow-up), and potential benefits or risks of hydroxyurea. An additional consent for sharing and storing blood samples is also obtained. All discussions and informed consent processes will be completed in either English or Luganda, at an education-appropriate level.

Dissemination

When the open-label phase is completed and the study analysis done, we will provide a forum for all interested study participants to review the study findings. We will review them in clear, nontechnical terms in the local language and leave time for questions and ongoing discussion after the session. The final study findings will be published in a peer-reviewed publication and presented at 1 or more national or international meetings, including meetings in Uganda. We will use standard International Committee of Medical Journal Editors criteria for authorship. Through this publication, the public will have access to the study protocol. Participant level data will be maintained in our database until fully analyzed. If permitted by the study IRBs, we will eventually make participant-level data available to researchers on request in a deidentified dataset.

Results

As noted in the *Progress to Date* subsection of the *Methods* section, as of March 28, 2016, 90 participants have completed the blinded treatment phase of the study, and all study participants are expected to have completed the blinded treatment phase of the study by November 2016. We anticipate analysis of results for the blinded phase to be completed by early to mid-2017. The open-label phase of the study will be completed in November 2017, and we are working with the Ministry of Health and other partners to see how children in the study can continue hydroxyurea if it proves to be safe and effective (Multimedia Appendix 5).

Discussion

Hydroxyurea as a once-daily oral medication has been shown to be safe, well tolerated, and easy to administer. Pivotal trials, such as the Phase III BABY HUG trial, have shown the clinical benefits of hydroxyurea in very young children [8]. In addition, hydroxyurea is associated with decreased medical care costs. A recent study in pediatrics by Wang et al looked at the children from the BABY HUG trial and estimated the cost of medical care for those taking hydroxyurea versus those taking placebo and found that the total yearly cost for children on hydroxyurea was estimated at $11 072, which was 21% less than the placebo group, whose annual costs averaged $13 962 [41]. If hydroxyurea is safe and effective for children with SCA in Uganda, advocacy for subsidization of the cost will be explored. Hydroxyurea is available in Uganda and is used in some private clinics for children with SCA, but the drug is not yet registered by the National Drug Authority, and there is no formal Ministry of Health approval for this indication, so, it is not routinely provided to children in the MHSCC. In addition, if this study shows that hydroxyurea is beneficial, clinicians at the MHSCC will have received training and gained valuable experience that will enable them to assume the provision of care and monitoring of children with SCA who are receiving hydroxyurea.

Conducting a trial in a resource-limited setting poses some challenges in regard to ethical considerations and informed consent processes. However, the challenges faced with regard to participant or guardian understanding of clinical trials are not unique to Sub-Saharan Africa [42,43]. Multiple papers discuss ethical considerations of doing trials in Sub-Saharan Africa, highlighting issues such as differences in health care systems, limited access to care, quality of informed consent, educational disparities, and knowledge of research, as factors that could make participants vulnerable to exploitation [44-47].

Concerns about the misunderstandings parents may have with collecting blood samples and the use of samples for future research are also an important consideration for our trial. Studies in resource-limited countries highlight some of the misgivings participants have in relation to blood [48-50], ranging from the volume of blood being taken from an already sick child to concerns that the blood will be sold and used in witchcraft [51,52].

The vulnerability of our study population, which is well documented in the literature, adds another dimension to the trial [53-55]. In addition, the phenomenon of therapeutic misconception, where research participants fail to differentiate the consequences of research participation from ordinary treatment, is also well described in the literature, and is another challenge, especially in our cross-cultural setting [56-58].

For this trial, we received local ethics approval from the SOMREC, at Makerere University College of Health Sciences before trial commencement (in addition to approval from multiple other institutions listed in the *Ethical Considerations* section). A culturally sensitive, language-appropriate informed consent has been developed and aligns with the format recommended by the SOMREC. Aside from the ethical challenges, ensuring adequate laboratory infrastructure has been essential, especially with the frequency of blood draws in our study. Qualified laboratory staff performed blood draws, and topical anesthetics were used to minimize discomfort related to these procedures.

One limitation of this trial pertains to our ability to assess the primary end point, namely, the effects of 12 months of hydroxyurea versus placebo treatment on malaria incidence. We will provide ITNs and standard malaria prophylaxis to all NOHARM study children, which should lower the incidence of malarial infections, and thus could potentially impact our primary end point. Prevalence data obtained for sample size calculations were collected from populations in which children did receive ITNs; however, these populations may live in areas with higher malaria incidence because some children in those neighborhoods developed severe malaria. If malaria incidence in the study population is low, we may have power to detect only very large differences in malaria incidence between the treatment and placebo groups. In this circumstance, valuable data will still be gained about safety, incidence of neutropenia and infections other than malaria, and effectiveness against vascular crises and other complications of SCA. We will be able to provide estimates of the differences in malaria incidence, but these estimates will have wide confidence intervals, so, further study in areas of higher malaria transmission may be required to determine more precisely the risk of malaria and severe malaria with hydroxyurea treatment in SCA.

Other potential limitations pertain to randomization and blinding. Ideally, persons treating study participants would be separate from the trial, so that changes in laboratory values will not lead study personnel to guess the study arm in which the child is enrolled. In this study, to minimize the potential confusion of having multiple physicians and nurses involved in evaluation and care of the child, we instead instituted a system where laboratory results for all scheduled visits came to the data manager, and the clinicians taking care of the child saw laboratory values only if they were critical values. Thus, most laboratory values were not seen by clinical study personnel and made it unlikely that they would or could accurately guess the study arm for most study children.

In summary, the NOHARM trial is a randomized controlled clinical trial of hydroxyurea for children with SCA in a malaria-endemic region. If the study demonstrates a clear benefit of hydroxyurea with no increased malaria risk or AEs in children with SCA, these critical data could lead to transformation of treatment practices for SCA across Africa.

Trial Status

The trial is currently ongoing. Children are currently in either the randomized treatment phase or open-label treatment phase of follow-up.

Acknowledgments

Dr Anyanwu is a Fogarty/NIH fellow 2014-2015, supported by the NIH Research Training grant # R25 TW009345 funded by the Fogarty International Center. CLS was supported by a Doris Duke International Clinical Research Fellowship.

Study funding was provided by the Doris Duke Charitable Foundation. The Foundation has no role in the design of the study, data collection, analysis, or manuscript submission. Study treatments are provided free of charge by Addmedica Pharmaceuticals, in the form of hydroxyurea (hydroxycarbamide, Siklos®) formulations. Addmedica has the ability to review draft publications approximately 30 days before submission but will not have access to the primary data, authority to edit the results, or influence any presentations or publications. Additional support for the trial includes John Boesing and Justin McAdams from the DCC and Dr Patrick McGann who serves as Medical Monitor.

Authors' Contributions

JNA and CLS wrote the manuscript and worked on the NOHARM trial as a Fogarty/NIH Global Health Fellow and Doris Duke International Clinical Research Fellow, respectively. OW wrote the original research protocol and was involved in study logistics and obtaining ethical approval. PK was involved in study design and obtaining ethical clearance from Ugandan research and ethics committees. HH was involved in study design and logistical planning. ROO participated in study design, logistics, and ethical approval. TL participated in study logistics. CN worked on study design, logistical planning, and helping to obtain ethical approval from Ugandan research and ethics committees. REW was involved in study design, manuscript drafting, and logistics. CCJ was involved in study design, manuscript drafting, logistics, and ethical approval of the study. All authors were involved in review of the protocol and read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Participant timeline.

[PDF File (Adobe PDF File), 27KB - resprot_v5i2e110_app1.pdf]

Multimedia Appendix 2

Informed consent materials.

[PDF File (Adobe PDF File), 71KB - resprot_v5i2e110_app2.pdf]

Multimedia Appendix 3

Makerere School of Medicine Research Ethics Committee Comments and investigator replies.

[PDF File (Adobe PDF File), 41KB - resprot_v5i2e110_app3.pdf]

Multimedia Appendix 4

University of Minnesota IRB peer review comments and investigator responses.

[PDF File (Adobe PDF File), 32KB - resprot_v5i2e110_app4.pdf]

Multimedia Appendix 5

Spirit Checklist.

[PDF File (Adobe PDF File), 61KB - resprot_v5i2e110_app5.pdf]

References

1. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet 2010 Dec 11;376(9757):2018-2031. [doi: 10.1016/S0140-6736(10)61029-X] [Medline: 21131035]
2. Piel FB, Patil AP, Howes RE, Nyangiri OA, Gething PW, Dewi M, et al. Global epidemiology of sickle haemoglobin in neonates: a contemporary geostatistical model-based map and population estimates. Lancet 2013 Jan 12;381(9861):142-151 [FREE Full text] [doi: 10.1016/S0140-6736(12)61229-X] [Medline: 23103089]
3. Grosse SD, Odame I, Atrash HK, Amendah DD, Piel FB, Williams TN. Sickle cell disease in Africa: a neglected cause of early childhood mortality. Am J Prev Med 2011 Dec;41(6 Suppl 4):S398-S405 [FREE Full text] [doi: 10.1016/j.amepre.2011.09.013] [Medline: 22099364]

4. Weatherall DJ, Clegg JB. Inherited haemoglobin disorders: an increasing global health problem. Bull World Health Organ 2001;79(8):704-712 [FREE Full text] [Medline: 11545326]
5. World Health Organization: Regional Office for Africa. Sickle-cell disease: A strategy for the WHO African Region. June 2010 Jan 01:2010.
6. We Can End Poverty. 2016. Millenium Development Goals and Beyond 2015 URL: http://www.un.org/millenniumgoals/childhealth.shtml [WebCite Cache ID 6hnI2Y5yV]
7. McGann PT, Ware RE. Hydroxyurea for sickle cell anemia: what have we learned and what questions still remain? Curr Opin Hematol 2011 May;18(3):158-165 [FREE Full text] [doi: 10.1097/MOH.0b013e32834521dd] [Medline: 21372708]
8. Wang WC, Ware RE, Miller ST, Iyer RV, Casella JF, Minniti CP, et al. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). Lancet 2011 May 14;377(9778):1663-1672 [FREE Full text] [doi: 10.1016/S0140-6736(11)60355-3] [Medline: 21571150]
9. McGann PT, Ware RE. Hydroxyurea therapy for sickle cell anemia. Expert Opin Drug Saf 2015;14(11):1749-1758. [doi: 10.1517/14740338.2015.1088827] [Medline: 26366626]
10. Allison AC. Protection afforded by sickle-cell trait against subtertian malareal infection. Br Med J 1954 Feb 6;1(4857):290-294 [FREE Full text] [Medline: 13115700]
11. McAuley CF, Webb C, Makani J, Macharia A, Uyoga S, Opi DH, Scott John Anthony G, et al. High mortality from Plasmodium falciparum malaria in children living with sickle cell anemia on the coast of Kenya. Blood 2010 Sep 9;116(10):1663-1668 [FREE Full text] [doi: 10.1182/blood-2010-01-265249] [Medline: 20530796]
12. Williams TN, Uyoga S, Macharia A, Ndila C, McAuley CF, Opi DH, Scott J Anthony G. Bacteraemia in Kenyan children with sickle-cell anaemia: a retrospective cohort and case-control study. Lancet 2009 Oct 17;374(9698):1364-1370 [FREE Full text] [doi: 10.1016/S0140-6736(09)61374-X] [Medline: 19747721]
13. Brun M, Bourdoulous S, Couraud PO, Elion J, Krishnamoorthy R, Lapoumeroulie C. Hydroxyurea downregulates endothelin-1 gene expression and upregulates ICAM-1 gene expression in cultured human endothelial cells. Pharmacogenomics J 2003;3(4):215-226. [doi: 10.1038/sj.tpj.6500176] [Medline: 12931135]
14. Pino P, Taoufiq Z, Brun M, Tefit M, Franetich JF, Ciceron L, et al. Effects of hydroxyurea on malaria, parasite growth and adhesion in experimental models. Parasite Immunol 2006 Dec;28(12):675-680. [doi: 10.1111/j.1365-3024.2006.00907.x] [Medline: 17096647]
15. Conran N, Fattori A, Saad Sara T O, Costa FF. Increased levels of soluble ICAM-1 in the plasma of sickle cell patients are reversed by hydroxyurea. Am J Hematol 2004 Aug;76(4):343-347 [FREE Full text] [doi: 10.1002/ajh.20129] [Medline: 15282666]
16. Saleh AW, Duits AJ, Gerbers A, de VC, Hillen HF. Cytokines and soluble adhesion molecules in sickle cell anemia patients during hydroxyurea therapy. Acta Haematol 1998;100(1):26-31. [Medline: 9691143]
17. Laurance S, Lansiaux P, Pellay F, Hauchecorne M, Benecke A, Elion J, et al. Differential modulation of adhesion molecule expression by hydroxycarbamide in human endothelial cells from the micro- and macrocirculation: potential implications in sickle cell disease vasoocclusive events. Haematologica 2011 Apr;96(4):534-542 [FREE Full text] [doi: 10.3324/haematol.2010.026740] [Medline: 21228039]
18. Keikhaei B, Mohseni AR, Norouzirad R, Alinejadi M, Ghanbari S, Shiravi F, et al. Altered levels of pro-inflammatory cytokines in sickle cell disease patients during vaso-occlusive crises and the steady state condition. Eur Cytokine Netw 2013 Mar;24(1):45-52. [doi: 10.1684/ecn.2013.0328] [Medline: 23608554]
19. Gladwin MT, Shelhamer JH, Ognibene FP, Pease-Fye ME, Nichols JS, Link B, et al. Nitric oxide donor properties of hydroxyurea in patients with sickle cell disease. Br J Haematol 2002 Feb;116(2):436-444. [Medline: 11841449]
20. Ma N, Hunt NH, Madigan MC, Chan-Ling T. Correlation between enhanced vascular permeability, up-regulation of cellular adhesion molecules and monocyte adhesion to the endothelium in the retina during the development of fatal murine cerebral malaria. Am J Pathol 1996 Nov;149(5):1745-1762 [FREE Full text] [Medline: 8909263]
21. Park GS, Ireland KF, Opoka RO, John CC. Evidence of Endothelial Activation in Asymptomatic Plasmodium falciparum Parasitemia and Effect of Blood Group on Levels of von Willebrand Factor in Malaria. J Pediatric Infect Dis Soc 2012 Mar;1(1):16-25 [FREE Full text] [doi: 10.1093/jpids/pis010] [Medline: 23687570]
22. Grau GE, Taylor TE, Molyneux ME, Wirima JJ, Vassalli P, Hommel M, et al. Tumor necrosis factor and disease severity in children with falciparum malaria. N Engl J Med 1989 Jun 15;320(24):1586-1591. [doi: 10.1056/NEJM198906153202404] [Medline: 2657427]
23. Medana IM, Hunt NH, Chaudhri G. Tumor necrosis factor-alpha expression in the brain during fatal murine cerebral malaria: evidence for production by microglia and astrocytes. Am J Pathol 1997 Apr;150(4):1473-1486 [FREE Full text] [Medline: 9095002]
24. Anstey NM, Weinberg JB, Hassanali MY, Mwaikambo ED, Manyenga D, Misukonis MA, et al. Nitric oxide in Tanzanian children with malaria: inverse relationship between malaria severity and nitric oxide production/nitric oxide synthase type 2 expression. J Exp Med 1996 Aug 1;184(2):557-567 [FREE Full text] [Medline: 8760809]
25. Cabrales P, Zanini GM, Meays D, Frangos JA, Carvalho Leonardo J M. Nitric oxide protection against murine cerebral malaria is associated with improved cerebral microcirculatory physiology. J Infect Dis 2011 May 15;203(10):1454-1463 [FREE Full text] [doi: 10.1093/infdis/jir058] [Medline: 21415018]

26. Serghides L, Kim H, Lu Z, Kain DC, Miller C, Francis RC, et al. Inhaled nitric oxide reduces endothelial activation and parasite accumulation in the brain, and enhances survival in experimental cerebral malaria. PLoS One 2011;6(11):e27714 [FREE Full text] [doi: 10.1371/journal.pone.0027714] [Medline: 22110737]
27. Canalli AA, Franco-Penteado CF, Saad Sara T O, Conran N, Costa FF. Increased adhesive properties of neutrophils in sickle cell disease may be reversed by pharmacological nitric oxide donation. Haematologica 2008 Apr;93(4):605-609 [FREE Full text] [doi: 10.3324/haematol.12119] [Medline: 18326523]
28. Cokic VP, Smith RD, Beleslin-Cokic BB, Njoroge JM, Miller JL, Gladwin MT, et al. Hydroxyurea induces fetal hemoglobin by the nitric oxide-dependent activation of soluble guanylyl cyclase. J Clin Invest 2003 Jan;111(2):231-239 [FREE Full text] [doi: 10.1172/JCI16672] [Medline: 12531879]
29. Pasvol G, Weatherall DJ, Wilson RJ, Smith DH, Gilles HM. Fetal haemoglobin and malaria. Lancet 1976 Jun 12;1(7972):1269-1272. [Medline: 73695]
30. Amaratunga C, Lopera-Mesa TM, Brittain NJ, Cholera R, Arie T, Fujioka H, et al. A role for fetal hemoglobin and maternal immune IgG in infant resistance to Plasmodium falciparum malaria. PLoS One 2011;6(4):e14798 [FREE Full text] [doi: 10.1371/journal.pone.0014798] [Medline: 21532754]
31. Navarra P, Grohmann U, Nocentini G, Tringali G, Puccetti P, Riccardi C, et al. Hydroxyurea induces the gene expression and synthesis of proinflammatory cytokines in vivo. J Pharmacol Exp Ther 1997 Jan;280(1):477-482 [FREE Full text] [Medline: 8996231]
32. Tavakkoli F, Nahavandi M, Wyche MQ, Perlin E. Plasma levels of TNF-alpha in sickle cell patients receiving hydroxyurea. Hematology 2004 Feb;9(1):61-64. [doi: 10.1080/10245330320000158869] [Medline: 14965870]
33. Aneni EC, Hamer DH, Gill CJ. Systematic review of current and emerging strategies for reducing morbidity from malaria in sickle cell disease. Trop Med Int Health 2013 Mar;18(3):313-327 [FREE Full text] [doi: 10.1111/tmi.12056] [Medline: 23320577]
34. Giardina F, Kasasa S, Sié A, Utzinger J, Tanner M, Vounatsou P. Effects of vector-control interventions on changes in risk of malaria parasitaemia in sub-Saharan Africa: a spatial and temporal analysis. Lancet Glob Health 2014 Oct;2(10):e601-e615 [FREE Full text] [doi: 10.1016/S2214-109X(14)70300-6] [Medline: 25304636]
35. Segal J, Strouse J, Beach C, Haywood C, Witkop C, Park H, et al. AHRQ. 2016. Hydroxyurea for the Treatment of Sickle Cell Disease URL: http://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/evidence-based-reports/hydscd-evidence-report.pdf [accessed 2016-05-16] [WebCite Cache ID 6hXsNyJ93]
36. Green NS, Barral S. Emerging science of hydroxyurea therapy for pediatric sickle cell disease. Pediatr Res 2014 Jan;75(1-2):196-204 [FREE Full text] [doi: 10.1038/pr.2013.227] [Medline: 24252885]
37. Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. N Engl J Med 1995 May 18;332(20):1317-1322. [doi: 10.1056/NEJM199505183322001] [Medline: 7715639]
38. Kinney TR, Helms RW, O'Branski EE, Ohene-Frempong K, Wang W, Daeschner C, et al. Safety of hydroxyurea in children with sickle cell anemia: results of the HUG-KIDS study, a phase I/II trial. Pediatric Hydroxyurea Group. Blood 1999 Sep 1;94(5):1550-1554 [FREE Full text] [Medline: 10477679]
39. Thornburg CD, Dixon N, Burgett S, Mortier NA, Schultz WH, Zimmerman SA, et al. A pilot study of hydroxyurea to prevent chronic organ damage in young children with sickle cell anemia. Pediatr Blood Cancer 2009 May;52(5):609-615. [doi: 10.1002/pbc.21738] [Medline: 19061213]
40. Wong TE, Brandow AM, Lim W, Lottenberg R. Update on the use of hydroxyurea therapy in sickle cell disease. Blood 2014 Dec 18;124(26):3850-7; quiz 4004 [FREE Full text] [doi: 10.1182/blood-2014-08-435768] [Medline: 25287707]
41. Wang WC, Oyeku SO, Luo Z, Boulet SL, Miller ST, Casella JF, et al. Hydroxyurea is associated with lower costs of care of young children with sickle cell anemia. Pediatrics 2013 Oct;132(4):677-683 [FREE Full text] [doi: 10.1542/peds.2013-0333] [Medline: 23999955]
42. Lynöe N, Sandlund M, Dahlqvist G, Jacobsson L. Informed consent: study of quality of information given to participants in a clinical trial. BMJ 1991 Sep 14;303(6803):610-613 [FREE Full text] [Medline: 1932901]
43. Joffe S, Cook EF, Cleary PD, Clark JW, Weeks JC. Quality of informed consent in cancer clinical trials: a cross-sectional survey. Lancet 2001 Nov 24;358(9295):1772-1777. [doi: 10.1016/S0140-6736(01)06805-2] [Medline: 11734235]
44. Glickman SW, McHutchison JG, Peterson ED, Cairns CB, Harrington RA, Califf RM, et al. Ethical and scientific implications of the globalization of clinical research. N Engl J Med 2009 Feb 19;360(8):816-823. [doi: 10.1056/NEJMsb0803929] [Medline: 19228627]
45. Kiguba R, Kutyabami P, Kiwuwa S, Katabira E, Sewankambo NK. Assessing the quality of informed consent in a resource-limited setting: a cross-sectional study. BMC Med Ethics 2012;13:21 [FREE Full text] [doi: 10.1186/1472-6939-13-21] [Medline: 22906301]
46. Joubert G, Steinberg H, van der Ryst Elna, Chikobvu P. Consent for participation in the Bloemfontein vitamin A trial: how informed and voluntary? Am J Public Health 2003 Apr;93(4):582-584. [Medline: 12660201]
47. Pace C, Talisuna A, Wendler D, Maiso F, Wabwire-Mangen F, Bakyaita N, et al. Quality of parental consent in a Ugandan malaria study. Am J Public Health 2005 Jul;95(7):1184-1189. [doi: 10.2105/AJPH.2004.053082] [Medline: 15933235]

48. Moodley K, Sibanda N, February K, Rossouw T. “It's my blood”: ethical complexities in the use, storage and export of biological samples: perspectives from South African research participants. BMC Med Ethics 2014;15:4 [FREE Full text] [doi: 10.1186/1472-6939-15-4] [Medline: 24447822]
49. Tindana P, Molyneux CS, Bull S, Parker M. Ethical issues in the export, storage and reuse of human biological samples in biomedical research: perspectives of key stakeholders in Ghana and Kenya. BMC Med Ethics 2014;15:76 [FREE Full text] [doi: 10.1186/1472-6939-15-76] [Medline: 25326753]
50. Wendler D, Pace C, Talisuna AO, Maiso F, Grady C, Emanuel E. Research on stored biological samples: the views of Ugandans. IRB 2005;27(2):1-5. [Medline: 15948324]
51. Molyneux CS, Peshu N, Marsh K. Understanding of informed consent in a low-income setting: three case studies from the Kenyan Coast. Soc Sci Med 2004 Dec;59(12):2547-2559. [doi: 10.1016/j.socscimed.2004.03.037] [Medline: 15474208]
52. Geissler PW, Pool R. Editorial: Popular concerns about medical research projects in sub-Saharan Africa--a critical voice in debates about medical research ethics. Trop Med Int Health 2006 Jul;11(7):975-982 [FREE Full text] [doi: 10.1111/j.1365-3156.2006.01682.x] [Medline: 16827698]
53. Bwakura-Dangarembizi M, Musesengwa R, Nathoo KJ, Takaidza P, Mhute T, Vhembo T. Ethical and legal constraints to children's participation in research in Zimbabwe: experiences from the multicenter pediatric HIV ARROW trial. BMC Med Ethics 2012;13:17 [FREE Full text] [doi: 10.1186/1472-6939-13-17] [Medline: 22818109]
54. Kuthning M, Hundt F. Aspects of vulnerable patients and informed consent in clinical trials. Ger Med Sci 2013;11:Doc03 [FREE Full text] [doi: 10.3205/000171] [Medline: 23346043]
55. Hoberman A, Shaikh N, Bhatnagar S, Haralam MA, Kearney DH, Colborn DK, et al. Factors that influence parental decisions to participate in clinical research: consenters vs nonconsenters. JAMA Pediatr 2013 Jun;167(6):561-566 [FREE Full text] [doi: 10.1001/jamapediatrics.2013.1050] [Medline: 23546617]
56. Jansen LA. Mindsets, informed consent, and research. Hastings Cent Rep 2014;44(1):25-32 [FREE Full text] [doi: 10.1002/hast.237] [Medline: 24375292]
57. Kim Scott Y H, Schrock L, Wilson RM, Frank SA, Holloway RG, Kieburtz K, de Vries Raymond G. An approach to evaluating the therapeutic misconception. IRB 2009;31(5):7-14 [FREE Full text] [Medline: 19873836]
58. Henderson GE, Churchill LR, Davis AM, Easter MM, Grady C, Joffe S, King Nancy M P, et al. Clinical trials and medical care: defining the therapeutic misconception. PLoS Med 2007 Nov 27;4(11):e324 [FREE Full text] [doi: 10.1371/journal.pmed.0040324] [Medline: 18044980]

Abbreviations

AE: adverse event
ALT: alanine aminotransferase
ANC: absolute neutrophil count
ARC: absolute reticulocyte count
CTCAE: Common Terminology Criteria for Adverse Events
DCC: data coordinating center
DSMB: Data Safety and Monitoring Board
FDA: Food and Drug Administration
Hb: hemoglobin
HbAS: hemoglobin AS
HbF: fetal hemoglobin
ICAM-1: intracellular adhesion molecule-1
IRB: institutional review board
ITN: insecticide-treated bednet
MCC: Medical Coordinating Center
MHSCC: Mulago Hospital Sickle Cell Clinic
NO: nitric oxide
NOHARM: Novel use Of Hydroxyurea in an African Region with Malaria
SAE: severe adverse event
SCA: sickle cell anemia
SES: socioeconomic status
sICAM-1: soluble intracellular adhesion molecule-1
SOMREC: School of Medicine Research and Ethics Committee
TNF: tumor necrosis factor
VCAM: vascular cell adhesion molecule
VWF: von Willebrand factor
WHO: World Health Organization

Edited by G Eysenbach; submitted 03.02.16; peer-reviewed by L Luchtman-Jones, L Smart; comments to author 02.03.16; accepted 03.04.16; published 23.06.16.

Please cite as:
Anyanwu JN, Williams O, Sautter CL, Kasirye P, Hume H, Opoka RO, Latham T, Ndugwa C, Ware RE, John CC
Novel Use of Hydroxyurea in an African Region With Malaria: Protocol for a Randomized Controlled Clinical Trial
JMIR Res Protoc 2016;5(2):e110
URL: http://www.researchprotocols.org/2016/2/e110/
doi:10.2196/resprot.5599
PMID:27339303

Protocol

Telemonitoring and Protocolized Case Management for Hypertensive Community-Dwelling Seniors With Diabetes: Protocol of the TECHNOMED Randomized Controlled Trial

Raj Padwal[1], MD MSc; Finlay Aleck McAlister[1], MD MSc; Peter William Wood[1], MSc; Pierre Boulanger[2], PhD; Miriam Fradette[1], BScPharm; Scott Klarenbach[1], MD MSc; Alun L Edwards[3], MD; Jayna M Holroyd-Leduc[3], MD; Kannayiram Alagiakrishnan[1], MD, MPH; Doreen Rabi[3], MD MSc; Sumit Ranjan Majumdar[1], MD MPH

[1]Department of Medicine, University of Alberta, Edmonton, AB, Canada

[2]Department of Computing Science, University of Alberta, Edmonton, AB, Canada

[3]Department of Medicine, University of Calgary, Calgary, AB, Canada

Corresponding Author:
Raj Padwal, MD MSc
Department of Medicine
University of Alberta
5-134A Clinical Sciences Bldg
11350 83 Ave
Edmonton, AB, T6G2G3
Canada
Phone: 1 7804923686
Fax: 1 7804927711
Email: rpadwal@ualberta.ca

Abstract

Background: Diabetes and hypertension are devastating, deadly, and costly conditions that are very common in seniors. Controlling hypertension in seniors with diabetes dramatically reduces hypertension-related complications. However, blood pressure (BP) must be lowered carefully because seniors are also susceptible to low BP and attendant harms. Achieving "optimal BP control" (ie, avoiding both undertreatment and overtreatment) is the ultimate therapeutic goal in such patients. Regular BP monitoring is required to achieve this goal. BP monitoring at home is cheap, convenient, widely used, and guideline endorsed. However, major barriers prevent proper use. These may be overcome through use of BP telemonitoring—the secure teletransmission of BP readings to a health portal, where BP data are summarized for provider and patient use, with or without protocolized case management.

Objective: To examine the incremental effectiveness, safety, cost-effectiveness, usability, and acceptability of home BP telemonitoring, used with or without protocolized case management, compared with "enhanced usual care" in community-dwelling seniors with diabetes and hypertension.

Methods: A 300-patient, 3-arm, pragmatic randomized controlled trial with blinded outcome ascertainment will be performed in seniors with diabetes and hypertension living independently in seniors' residences in greater Edmonton. Consenting patients will be randomized to usual care, home BP telemonitoring alone, or home BP telemonitoring plus protocolized pharmacist case management. Usual care subjects will receive a home BP monitor but neither they nor their providers will have access to teletransmitted data. In both telemonitored arms, providers will receive telemonitored BP data summaries. In the case management arm, pharmacist case managers will be responsible for reviewing teletransmitted data and initiating guideline-concordant and protocolized changes in BP management.

Results: Outcomes will be ascertained at 6 and 12 months. Within-study-arm change scores will be calculated and compared between study arms. These include: (1) clinical outcomes: proportion of subjects with a mean 24-hour ambulatory systolic BP in the optimal range (110-129 mmHg in patients 65-79 years and 110-139 mmHg in those ≥80 years: primary outcome); additional ambulatory and home BP outcomes; A1c and lipid profile; medications, cognition, health care use, cardiovascular events, and mortality. (2) Safety outcomes: number of serious episodes of hypotension, syncope, falls, and electrolyte disturbances (requiring third party assistance or medical attention). (3) Humanistic outcomes: quality of life, satisfaction, and medication adherence. (4) Economic outcomes: incremental costs, incremental cost-utility, and cost per mmHg change in BP of telemonitoring ± case

management compared with usual care (health payor and societal perspectives). (5) Intervention usability and acceptability to patients and providers.

Conclusion: The potential benefits of telemonitoring remain largely unstudied and unproven in seniors. This trial will comprehensively assess the impact of home BP telemonitoring across a range of outcomes. Results will inform the value of implementing home-based telemonitoring within supportive living residences in Canada.

Trial Registration: Clinicaltrials.gov NCT02721667; https://clinicaltrials.gov/ct2/show/NCT02721667 (Archived by Webcite at http://www.webcitation.org/6i8tB20Mc)

(JMIR Res Protoc 2016;5(2):e107) doi:10.2196/resprot.5775

KEYWORDS

blood pressure; hypertension; seniors; telemonitoring; randomized controlled trial; case management

Introduction

Impact of Hypertension in Seniors With Diabetes

Diabetes is present in more than 20% of seniors (defined herein as age ≥ 65 years) and often leads to devastating complications and premature death. Hypertension affects over 80% of seniors with diabetes and is widely viewed as the most important cause of cardiovascular complications and death in these patients. Despite its critical importance to health, hypertension remains undertreated and uncontrolled in approximately 40% of seniors with diabetes [1].

Aggressive blood pressure (BP) reduction substantially reduces mortality, cardiovascular events, and microvascular complications in all patients with diabetes [2]. Seniors are at particularly high risk for hypertension-related complications and derive greater treatment benefit than younger patients (ie, greater absolute risk reduction) [3,4]. Achieving BP control in high-risk patients, including those with diabetes, is cost saving (which is rare, as few medical interventions save money over the long term) [5]. Contemporary Canadian guidelines recommend a treatment target BP ≤130 mmHg for these individuals; however, 52% of Canadian seniors with diabetes do not achieve this target [1,6]. Treatment consists of health behavior modification (low sodium diet, optimizing weight, exercise) and antihypertensive drugs [6]. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are first-line agents, dihydropyridine calcium channel blockers second line, and thiazide diuretics third line [6,7]. Of note, most patients with diabetes and hypertension will need multiple medications to achieve adequate BP control [8].

Treatment of Hypertension in Seniors With Diabetes: A Complex Care Challenge

The need for aggressive BP control in seniors with diabetes must be balanced against the very real risk of serious treatment-related complications. Seniors, especially those who have cognitive impairment or who are frail, very old, or institutionalized, are more likely to experience treatment-related complications. These include hypotension, postural dizziness, syncope, falls, and metabolic side effects (including high/low potassium, sodium, and to a lesser extent, elevated glucose levels) [9-12]. Autonomic dysfunction and postural hypotension, more common in older individuals and in those with diabetes, may limit uptitration of antihypertensive drugs even if sitting BP levels are above target [10]. Dose reduction or drug discontinuation may be warranted in many patients to avoid inappropriate polypharmacy, adverse effects (plus additional drug treatments that are used to treat these adverse effects), need for laboratory monitoring, and costs.

Antihypertensive dose reduction or drug discontinuation is clearly warranted when serious adverse effects manifest. However, in asymptomatic patients with low BP, no obvious trigger is present to signal the need for dosage reduction. Furthermore, no widely accepted threshold definition for low BP exists at which dose reduction/discontinuation is mandated. In our opinion, systolic BP (SBP) levels <110 mmHg may confer increased risk for hypotension (and <100 mmHg clearly increase risk) [13].

Importantly, there is no randomized trial evidence that clinical benefits occur from reducing BP to <110 mmHg in seniors with diabetes [9]. For this reason and because it is critically important to avoid drug-related adverse effects (which are quite common [11]), reducing therapy when SBP is below 110 mmHg seems warranted unless a compelling nonhypertension-related indication for an antihypertensive agent is present. The extent to which dosage reductions are made in asymptomatic seniors in real-world clinical practice is unclear. We speculate that dosage adjustments are rarely made either because patients are not monitored frequently (thus, the low BP is not detected) or because a low BP fails to trigger an appropriate dose correction (because providers are primarily trained to focus on high not low readings). This might change if monitoring and a protocol that triggered appropriate dosage modification were implemented.

BP management in seniors with diabetes is further complicated by current guidelines that permit higher SBP treatment targets (<150 mmHg versus the usual <130 mmHg) in patients aged ≥80 years [6,14]. The intent of these guidelines is to allow practitioners to use more lenient targets in seniors who are frail or who, based on clinical opinion, may not tolerate lower BP levels. These guidelines allow us to define an upper limit to the BP therapeutic range for most seniors, above which more aggressive antihypertensive therapy to lower BP should be considered.

Types of BP Monitoring

To ensure that BP levels are neither too high nor too low, accurate BP monitoring is required. Serial office BP measurements are currently used to monitor the vast majority

of Canadians with hypertension. Unfortunately, office readings are inaccurate frequently because recommended measurement techniques are not followed or equipment is not regularly calibrated [15]. Furthermore, in seniors, office measurements are falsely high (white coat effect) in 15%-20% of cases and falsely low (masked effect) in 10%-15% of cases [16]. An additional disadvantage of office measurements is that patients are required to attend clinical appointments, a barrier for seniors who don't drive or who have mobility or financial limitations. Office measurements, therefore, may be infrequent, and this limits the ability to make timely therapeutic adjustments to address low or high BP.

Because of these limitations of office BP monitoring, contemporary guidelines strongly endorse use of out-of-office measurement [6]. Out-of-office measurement has additional advantage over office BP in that it allows multiple temporally separated readings to be performed. This provides a more accurate assessment of true BP because BP is a continuous parameter that changes every second of the day. Out-of-office measurement is currently performed by measuring 24-hour ambulatory BP monitoring (ABPM) or home BP monitoring. ABPM is widely regarded as the gold-standard measurement method [6,17], but is not widely available, not widely reimbursed, and often not well tolerated (because frequent measurements are needed and sleep disturbance may occur). Home BP measurement is thus much more commonly used for follow-up BP measurement [6]. Nearly 50% of hypertensive Canadians own a home monitor [18]. Home measurement has additional advantages, it increases treatment adherence and patient activation (by encouraging BP self-monitoring) [19-21], and when used alone, modestly reduces SBP (by 1.3 mmHg [95% CI 0.3-2.2] in a meta-analysis of 17 studies) [22].

Methods of Performing Home BP Measurement

Measuring a home BP series is the recommended method of performing home BP measurement [6]. A home BP series is composed of duplicate readings in the morning and evening (ie, 4 per day) daily for 7 days [6]. Readings taken on the first day are discarded and the latter 6 days (24 measurements) are averaged. If BP levels are at target, the home BP series is repeated quarterly. If BP levels are uncontrolled, therapeutic adjustments are made and the home BP series repeated in 4 weeks.

Home readings can be used in 1 of 3 major ways: (1) by the patient alone (who bears responsibility for giving the readings to their provider); (2) via telemonitoring, in which readings are automatically summarized and sent to the care provider; and (3) through telemonitoring plus protocolized case management, in which the summarized readings are reviewed by a case manager authorized to adjust treatments. BP telemonitoring ± case management is not being used in Canada because data on effectiveness and feasibility in this country are limited, the required technological infrastructure is not available, and a provider reimbursement plan does not exist.

Although contemporary guidelines strongly endorse home BP measurement, describe how to self-measure BP and outline how to perform a home BP series, more needs to be done to ensure correct uptake in clinical practice [6]. A major drawback is the onus is placed on the patient to measure, record, and present the home readings to their care provider though, this patient alone method has the advantage of requiring no additional resources and is the predominant method used in Canada. However, patients often forget to record their measurements, do not follow the recommended protocol (timing, frequency, and number of measurements), and/or self-select readings for presentation to their physician [23,24]. Recent data indicate that less than one-third of patients report ≥80% of measurements to their physician [25]. Important physician-related barriers to proper use of home BP measurement also exist. Physicians often do not calculate the mean BP (treatment adjustments are based on the mean), do not scan and upload hand-written BPs into their Electronic Medical Record (thus, no permanent record is available), and/or do not act on out-of-target readings ("therapeutic inertia") [23,24].

Home BP telemonitoring is a second method that, through process automation and protocols, can potentially overcome some of the aforementioned barriers [25,26]. BP telemonitoring consists of electronically and securely transmitting remotely collected BP measurements in real time to a central electronic health care portal. Data can be summarized for use by patients and providers, this includes calculation of BP means and graphing temporal trends in BP. Mean BPs that are too high or low can be flagged for action, whereas those in the normal range provide evidence for optimal control. Telemonitoring may eliminate the need for in-person clinic visits, and contributes to health care delivery efficiency and making better use of provider time. A recent meta-analysis of 23 randomized controlled trial (RCTs; 7037 patients) reported that home BP telemonitoring reduced BP by 5/3 mmHg compared with usual care (P<.0001 for both SBP and diastolic BP) [27]. This is a clinically important reduction, a 5-mmHg reduction in BP in high-risk patients (including diabetes) reduces cardiovascular events by 15% [28] and, in patients with diabetes, reduces stroke by 13% [29].

The third method of implementing home BP monitoring is to combine telemonitoring with case management. Case managers, usually nurses or pharmacists, work collaboratively with patients and physicians to optimize health behaviors, monitor risk factors, implement therapeutic adjustments, encourage adherence, and coordinate follow-up care [30-32]. Case management is well established and is currently used in contemporary clinical practice (our Pharmacare industry partner specializes in providing pharmacist case management services to seniors living in apartments, lodges, and assisted living facilities). Case management works best when the case managers have prescribing authority and use algorithms or protocols to make guideline-concordant therapeutic initiations and adjustments [30,33,34]. This can potentially overcome therapeutic inertia. BP improvements are greater when interventions have combined case management with telemonitoring [27]. Thus, it is essential to study case management because it may be needed in conjunction with telemonitoring to maximize the effectiveness of the latter.

Reasons Why Home BP Telemonitoring is not Currently Used in Canada

Collaboration between health care providers, decision makers, and device makers/technology companies is limited. This collaboration is required to make telemonitoring feasible. Historically, such collaborations have been rare, primarily because of lack of dialogue and interaction among potential partners.

Canadian data are very limited. A 1-year study in 110 hypertensive patients with diabetes (age ≥30 years; mean age 63 years) home BP telemonitoring and automated cellphone text messages that instructed patients to seek follow-up care was compared with usual care [35]. BP was reduced by 7.1/2.3 mmHg (P<.005) in the telemonitoring arm, and there was a 20% increase in the proportion of patients with controlled BP (51% versus 31%; P<.05). To our knowledge, this is the only published Canadian study of relevance. Patients did not receive treatment recommendations, seniors were not specifically studied, cost-effectiveness was not assessed, usability or acceptability not reported, and case management was not used. For these reasons, another trial is warranted to build on this important foundational work.

Costs have, historically, been a major barrier. This is primarily because of uncertainty over who will pay for teletransmission, health portal development, and portal maintenance. However, home BP monitors are now inexpensive and widely used, cellphone or Internet use is very high (enabling convenient, secure electronic data transmission), payment solely for teletransmission is not necessary (ie, as long as an existing data plan is present, the extra data usage for intermittent BP teletransmission is minimal), and established companies exist that specialize in health data transmission and health portal creation and maintenance. Thus, because of these technological advancements, fewer barriers remain. Importantly, BP control in high-risk populations (including diabetes) is cost saving [5]; therefore, health care payors funding or subsidizing this expenditure can expect initial costs to be offset by substantial downstream savings. In the United States, health care payors can spend an additional $600-1250 USD per patient per year controlling BP in high-risk patients yet still remain cost-neutral, this is a huge “safety margin” that supports the potential for telemonitoring to be cost-effective (because total costs are likely to be under these thresholds). Because previous studies have demonstrated mixed results in terms of BP telemonitoring cost-effectiveness [27,36], it is important to create a system that minimizes costs, maximizes cost-effectiveness, and leverages expenditures already borne by the individual for other reasons (ie, mobile phones, set top boxes, and data plans) to promote health care system sustainability.

Need for user training had been nearly prohibitive. This has largely been eliminated through technological advancements and major advances in user-friendliness. Systems require little additional action (other than BP self-measurement) because BP teletransmission can be automated once the reading is taken.

Summary of Rationale for a Tech-Based Canadian Study in High-Risk Seniors

To summarize, hypertension is very common in seniors with diabetes and substantially increases morbidity, mortality, and health costs. Controlling BP markedly reduces complications and can be cost saving. However, BP reduction is not the only goal, in some cases (white coat effect, low BP), drug dosage reductions are appropriate. BP management in seniors with diabetes is complicated by the need to balance cardiovascular risk reduction against the risk of adverse effects and polypharmacy. Age-appropriate BP thresholds and targets in the very elderly (age ≥ 80 years) must also be considered. Effective BP management is further hindered by the near ubiquitous dependence on inconvenient, infrequently performed and inaccurate office BPs to titrate therapy. Home BP readings should be used instead, but the optimal implementation method in terms of effectiveness, acceptability, and costs remains unclear. Measuring and reporting home BP could be left up to the patient, automated using telemonitoring, or automated and protocolized using telemonitoring and case management.

Although over 20 published trials reported clinically important BP reductions using home BP telemonitoring and case management, data in seniors are lacking, and it is important to confirm feasibility, effectiveness, safety, usability, and acceptability in this population in Canada. Importantly, prior studies have focused on reducing high BP only; in seniors, avoiding low BP and polypharmacy are equally important. Telemonitoring has initial (BP device) and ongoing (teletransmission and health portal maintenance) costs. Case management costs must also be considered. These costs ought to be offset by cost reductions achieved through avoidance of hypertension-related complications, drug-related adverse events, and reduced drug use. If done the way we propose, telemonitoring has the potential to be highly cost effective in these high-risk patients. However, a formal economic analysis is needed before widespread implementation can be justified.

Objectives

This Telemonitoring and Protocolized Case Management for Hypertensive Community-Dwelling Seniors With Diabetes (TECHNOMED) trial is designed to (1) assess the “real world” effectiveness and safety of home BP telemonitoring alone or in combination with protocolized pharmacist case management in seniors with diabetes and hypertension when compared with “enhanced” usual care; (2) evaluate the usability and acceptability of home BP telemonitoring; and (3) examine the cost-effectiveness of home BP telemonitoring alone and home BP telemonitoring plus protocolized case management.

In aggregate, these objectives will assess the impact on a comprehensive range of outcomes important to patients, providers, decision makers, industry partners, and funders.

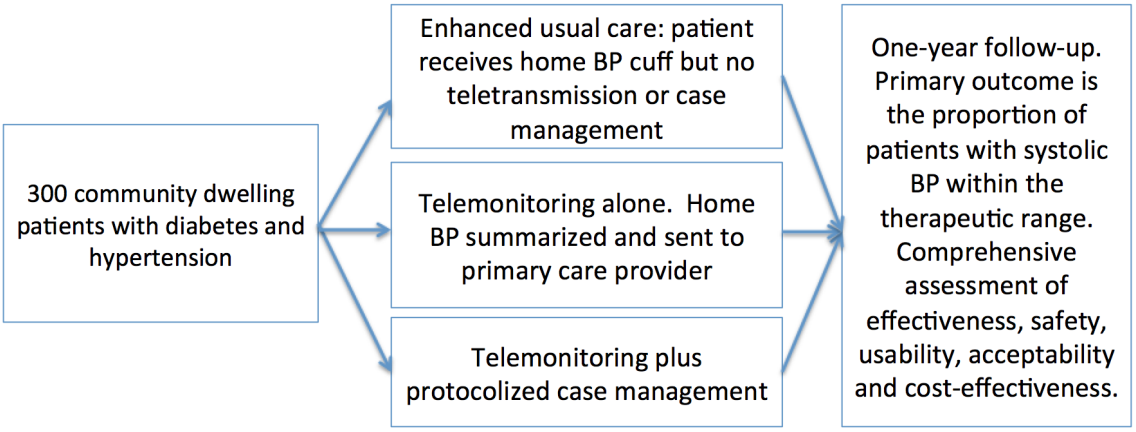
Methods

Study Design

In this 1-year pragmatic, prospective randomized open label trial with blinded ascertainment of end points, 300 patients will be randomly assigned (1:1:1) to one of 3 study arms (Figure 1):

(1) enhanced usual care (in which participants will be given a home monitor but BP teletransmission will not be accessible and case management not available to them); (2) home BP telemonitoring alone; and (3) home BP telemonitoring plus protocolized case management.

Figure 1. Study design.



Randomization

Computer-generated randomization will be performed centrally and independently by the EPICORE center (www.epicore.ualberta.ca) to ensure allocation concealment from all research personnel. Randomization will be stratified by baseline SBP (<140 mmHg versus ≥140 mmHg). Although clinic staff and pharmacist case managers cannot be blinded to allocation status, all outcome assessments will be performed by research assistants working independently from regular clinic staff and the pharmacist case managers.

Recruitment

Consecutive, consenting seniors (aged ≥65 years) will be recruited from seniors independent living or supportive living residences in greater Edmonton.

Inclusion Criteria (All Criteria Must Be Met)

These include: (1) age ≥65 years with a documented diagnosis of diabetes and hypertension, and (2) adequate English fluency, both verbal and written.

Exclusion Criteria (Any 1 Sufficient to Exclude)

These include: (1) SBP level >220 mmHg or diastolic BP level >110 mmHg on screening BP measurement (WatchBP [Microlife Corp., Widnau, Switzerland]); (2) heart failure; (3) severe cognitive impairment, defined as a score of ≥5 on the Short Portable Mental Status Questionnaire [37]; (4) severe depression (Patient Health Questionnaire [PHQ-8] ≥15) [38]; (5) foreshortened life expectancy (<1 years); (6) participation in a concurrent cardiovascular trial; and (7) currently receiving case management services for cardiovascular risk factor control.

Telemonitoring Intervention

The telemonitoring system will be built in collaboration with TeleMED (www.telemeddiagnostic.com). TeleMED, a Canadian company specializing in the electronic management of noninvasive diagnostic test data, will provide their services in-kind. All patients will receive a validated electronic upper arm oscillometric BP device (A&D Ltd. UA-651BLE; San Jose, CA) and a set top box that will enable wireless transmission of BP readings. This equipment will remain in their residence for the duration of the study. All patients will be shown how to view their BP readings on their device. Pushing a single button activates the device and initiates a BP measurement, which is autotransmitted to the set top box via a Bluetooth low-energy connection. Once set top box receives the data, it encodes the data to prevent “sniffing” by a third party. Without any further action required by the patient, the data are sent to a dedicated research server. The server decodes the data and encrypts it using the Advanced Encryption Standard with 256-bit key and inserts the encrypted data into the database. The research server is physically located at the University of Alberta in a secure facility accessible only to authorized personnel. The data are then securely pushed to TeleMED, where it is summarized in a web portal for provider use.

Patients will be instructed to perform all measurements according to recommended techniques for home BP measurement (Table 1). Four measurements will be taken daily for 1 week. If BP is uncontrolled (high or low), this 1-week of measurements will be done each month until BP is in the therapeutic range. Once controlled, the 1-week protocol will be repeated every 3 months, as recommended by contemporary guidelines [6]. Teletransmitted BP readings will be summarized within the health portal and an overall weekly mean will be calculated (first-day measurements will be discarded and the subsequent 24 measurements taken over the next 6 days will be averaged) [6]. This mean will be used for clinical management decisions. Temporal trends will be plotted to graphically summarize the data for provider use.

Table 1. Blood pressure measurement.

Method	Details
24-hour ambulatory BP[a]monitoring	BP readings will be taken every 15 minutes during the daytime and every 30 minutes at night with a Spacelabs 90227 device. Twenty-one readings during the daytime and 7 during nighttime will be required for a successful study [39]. Otherwise, a repeat study will be necessary. Patients will be given a diary to record the times that they retire to and arise from bed. Day and night intervals will be defined according to these patient-reported times and used to determine the daytime and nighttime BP averages. Timing of drug administration will also be recorded. Patients will also be instructed to go about their daily activity but refrain from exercising for the duration of the monitoring period and to stand still with their arm at their side when the monitor cuff is inflating.
Home BP measurement	Two measurements 1 minute apart will be taken in the morning between 0800 and 1000 and 2 measurements will be taken in the evening between 1800 and 2200 taken using the A&D home device. This will be done on 7 consecutive days for 1 week. If BP is uncontrolled (high or low), this 1-week measurement protocol will be repeated each month until BP is within the therapeutic range. Once controlled, the 1-week protocol will be repeated every 3 months.
Automated office BP	Three reading average in both arms taken while seated plus 1 supine reading and 1 standing reading taken at 1 min and 3 min using the WatchBP device.

[a]BP: blood pressure

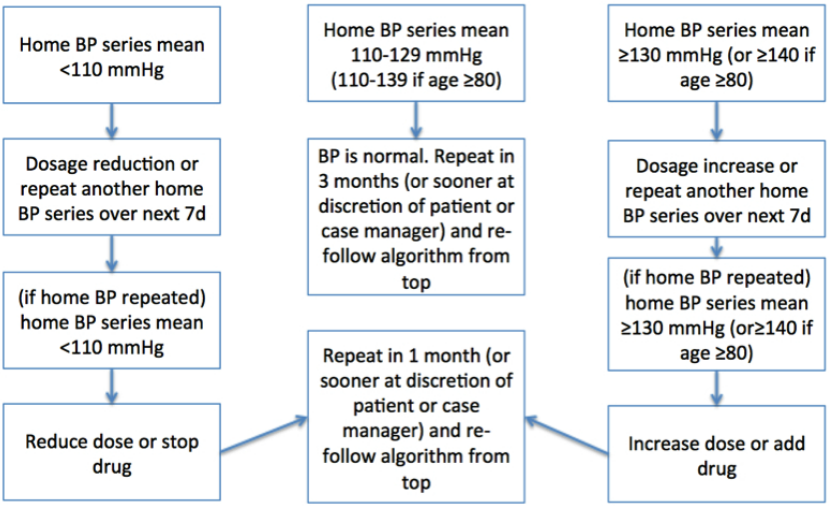
BP teletransmission will occur in all study arms but will be used differently in each:

- Enhanced usual care: Home BP readings will be teletransmitted for data collection purposes but neither patients nor providers will have access to the teletransmitted readings. High BP levels that trigger safety alerts to research personnel are the only exception, patients and their primary care providers will be made aware of these (see safety end points below). This is nevertheless considered "enhanced" usual care because patients receive a home BP monitor, are taught how to measure home BP, and are encouraged to take BP readings to appointments with their providers. In addition, they will be reminded to perform a home BP series each quarter for study outcome purposes, which will encourage self-monitoring. This reflects contemporary Canadian recommendations [6]. A summary of the Canadian hypertension guidelines will also be faxed to each primary care provider at the time of patient enrolment [6]. Recognizing that it takes years for guideline adoption to occur, we suspect that many patients in this arm will be managed solely using office BP measurements despite the potential availability of patient-reported (but not teletransmitted) home BP readings.
- Telemonitoring alone: Home BP series mean, trends, and individual readings will be faxed to the primary care provider with a 1-page summary of Canadian guidelines for BP thresholds, targets, and treatments [6].
- Telemonitoring plus protocolized case management: Patients in this arm will each be assigned a pharmacist case manager who holds full prescribing privileges and who will (1) administer health behavior modification counselling, teach BP self-monitoring, and monitor medication adherence; (2) review telemonitored health portal BP summaries and make protocolized therapeutic adjustments if appropriate (Figure 2); (3) fax a summary of these adjustments to the participant's primary care provider (to make them aware of treatment changes); and (4) facilitate communication between patients and providers.

Pharmacare (www.mypharmacare.ca), an Alberta company specializing in pharmaceutical service delivery, will provide pharmacist case managers as an in-kind contribution to the study. Pharmacare case managers hold full drug prescribing licences, enabling them to independently initiate and titrate drugs. To ensure full guideline concordant standardization of the intervention, case managers will undergo a training session with a group of clinical experts from the University of Alberta Hypertension Clinic (who also serve on the executive of Hypertension Canada) on home BP monitoring and hypertension guidelines before study initiation.

Medication regimen adjustments will be performed according to a guideline-concordant protocol [6]. Drugs will be added in the following order: angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, dihydropyridine calcium channel blocker, thiazide diuretic, beta-blocker, spironolactone, doxazosin, clonidine, and hydralazine. Drugs will be reduced or stopped in reverse order. When initiating new agents, the longest-acting agents in each class will be used.

Figure 2. Case manager protocol for antihypertensive drug titration.



Data Collection Including End Points

Unless otherwise indicated, data will be collected at baseline, 6 and 12 months after randomization. Study personnel will collect data using standardized case report forms. Home BP series data will then be sent to secure servers housed within the Department of MedIT, Faculty of Medicine and Dentistry, University of Alberta and then forwarded to the Web portal.

Baseline data collection will include(1) demographics and health behaviours: age, sex, race, marital status, smoking, and alcohol intake; (2) past medical history: atrial fibrillation, dyslipidemia, coronary artery disease, stroke or transient ischemic attack, peripheral vascular disease, chronic kidney disease (glomerular filtration rate ≤60 mL/min and/or proteinuria), syncope, bradyarrhythmias, pacemaker, and history of hyponatremia, hyperkalemia, or hypokalemia; (3) past diabetes-related information: duration of disease, presence of retinopathy, neuropathy, nephropathy, amputation, symptomatic hypoglycemia, and use of insulin; (4) medication history including antihypertensive drugs: name, type, dosage, and frequency. This will be based on self-report and then will be cross-indexed with the patient's pharmacy medication record; (5) anthropomorphic indices: height, weight, body mass index, and waist circumference; (6) upper mid arm circumference (to determine proper cuff size): measured using a tape measure half way between the acromion and the olecranon with the arm at heart level; (7) 24-hr ambulatory BP, home BP series, and pulse rate: BP will be measured according to recommended techniques (Table 2) using validated devices [40]. Three screening BP measurements will be taken while seated in each arm at baseline with the validated WatchBP office automated device to determine if exclusion criteria are present [41]. Lying and standing BP at 1 and 3 minutes will also be taken. A 24-hr ambulatory BP and mean 24-hour heart rate will be measured using the validated Spacelabs 90227 monitor (Snoqualmie, Wash) [42]. A home BP series taken with the UA-651BLE oscillometric home device (A&D Ltd., San Jose, CA) will be performed as outlined (Table 2). (8) Laboratory investigations will include serum sodium, potassium and creatinine; glycated hemoglobin (A1c); lipids (total cholesterol, high-density or HDL cholesterol, low-density or LDL cholesterol, triglycerides), urinary albumin or creatinine ratio and electrocardiogram; (9) Montreal Cognitive Assessment Scale **:**validated cognitive assessment instrument [43]; (10) Clinical Frailty Score: a validated 9-point instrument, with frailty defined as a score of 5 or more [44]; (11) health care use in past year includes physician visits, emergency department use, and hospitalizations ascertained through patient self-report and by linking to provincial administrative data sources and the provincial electronic health record; (12) quality of life and utility measurement: assessed using the EQ-5D [45]; (13) depression/anxiety measured using the Patient Health Questionnaire (PHQ-8) for depression [38] and the Generalized Anxiety Disorder Scale (GAD-2) for anxiety [46] These end points are being evaluated to ensure that increased monitoring does not lead to greater depression or anxiety via adoption of the "sick role" [35]; and (14) satisfaction with medical care: assessed similar to other studies that we have conducted [47-49] using the validated Patient Satisfaction Questionnaire (PSQ) [50], scored on a 5-point Likert Scale.

Table 2. Costing data for economic analysis.

Identification	Measurement	Valuation	Comments
Program Development			
Health care professional time (physician, nurse, pharmacist)	Estimated hours for each health care professional to create care algorithm (algorithm start-up costs); Estimated hours for staff training to administer care algorithm (training costs)	Alberta Health Services wage rates, Alberta Health Care Insurance Plan/Alternate Funding Plan	Cost per patient estimated by plausible number of patients in program/managed per staff
IT infrastructure	Equipment required to setup BP[a]telemonitoring and hours of IT support will be estimated from local experience and TeleMED input.	Wage rates. Price lists of IT equipment from manufacturer.	Costs apportioned over # of patients monitored in region over 5 years (estimated lifespan of equipment).
Program Delivery			
Equipment	Number of home BP cuffs (standard and telemonitoring)	List price	Includes expected lifetime/repair costs and replacement.
Internet/data	Mobile phone device/data plan used for telemonitoring (tested in sensitivity analysis).	Local cost of lowest priced suitable service	Included in sensitivity analysis, may be paid by health provider or patient (societal perspective)
Medication use	Type, dose, frequency, and duration of use.	Alberta Blue Cross	
Health care professional time (pharmacist)	Estimated hours for staff to administer care algorithm (ongoing costs)	Alberta Health Services wage rates, Alberta Health Care Insurance Plan/lternate Funding Plan	Cost per patient estimated by plausible number of patients in program/managed per staff
Staff costs/infrastructure	IT support/telemedicine portal/fax costs	TeleMED	Costs apportioned over # of patients monitored in region over 5 years.
Utilization			
Physician visits	Number of primary care or hypertension specialist visits over 12 months (patient reported).	Alberta Health Ambulatory Care Case Costing (utilizing National Ambulatory Care Reporting System)	Telemonitoring ± case management may reduce need for physician visits for BP management, scenarios tested in SA.
Emergency department visits	Number of emergency room visits over 12 months attributable to BP or complications of treatment	Alberta Schedule of Benefits	Study may be underpowered to detect emergency department visits. Safety end points will be examined and likely resource use for each safety end point will be estimated.
Hospitalizations	Number of hospitalizations over 12 months attributable to BP or complications of treatment	Alberta Health administrative data	
Societal costs	Patient and caregiver time costs for physician visits, emergency department visits, out of pocket medication costs. May also include data/mobile phone costs (explored in sensitivity analysis).	Standard Alberta wage rates (human capital approach)	Explored using a societal perspective.

[a]BP: blood pressure

The 6- and 12-month follow-up data (measured as described previously) will be (1) clinical end points and patient-centered outcomes (as described previously): 24-hr ABPM, automated BP (seated, lying, and standing as described previously), telemonitored home BP, heart rate, medications, anthropomorphics, cardiovascular risk factors and markers (A1c, lipids, smoking, urinary albumin), cognition, frailty score, health care use (physician visits, emergency department visits and hospitalizations ascertained through self-report and via linked administrative health care data), quality of life and utilities, satisfaction with medical care, and depression and anxiety. (2) safety end points includes the frequency of (a) nonmechanical falls, syncope, hypotension requiring third-party assistance or medical attention and (b) electrolyte disturbances (hypokalemia [<3.3 mmol/L], hyperkalemia [>5.0 mmol/L], and hyponatremia [<130 mmol/L]. In addition, potentially life-threatening adverse effects will trigger an immediate alert causing the study team to notify the Data and Safety Monitoring Board, which will act independent of the study team to contact the patient and arrange appropriate nonstudy medical follow-up. Triggers for DSMB follow-up will include a BP ≥220/110 mmHg or a SBP <70 mmHg; potassium level ≤2.7 or ≥5.5 mmol/L; sodium level

≤126 or ≥152 mmol/L; or a PHQ-8 score ≥15, indicating severe depression. (3) User acceptability: will consist primarily of qualitative data collection. In addition, two 10-point Likert scales evaluating usability and acceptability will be collected. (4) Costing data: costing will adhere to the three-step microcosting technique of identification, measurement, and valuation of relevant health care and non–health care resources [51,52] and are outlined below and in Table 2. Resource use by category, including program start-up costs and on-going costs for each study arm, will be tabulated. In a 10% random sample of patients, time-motion studies related to the case manager will be conducted. The cost per patient will be calculated, and where any uncertainty in resource use or costs exists, plausible ranges of resource use will be determined and tested in sensitivity analysis. Resource use and cost data will be used to determine the overall and per-patient total costs, and incremental costs of interventions (telemonitoring ± case management) compared with usual care will be calculated [51,52].

Analytic Plan for Major Outcomes

Aim 1: Effectiveness of Telemonitoring ± Protocolized Case Management

All primary analyses will be conducted according to the intention-to-treat principle. The primary outcome is the 1-year change in proportion of patients with overall 24-hour SBP in the optimal range (SBP is used because it is a stronger predictor of risk and because diastolic BP is rarely elevated in seniors [10]). We will use 24-hour ABPM because it is the gold-standard measurement method and the best validated clinical trial BP end point [40]. The 24-hr ABPM therapeutic range will be 110-129 mmHg in patients aged 65-79 years and 110-139 mmHg in those ≥ 80 years. Justification for the upper thresholds chosen is based on current guidelines that specify an overall 24-hour ABPM of ≥130 mmHg as high in all patients, including those with diabetes [6]. In patients ≥80 years, we will allow the option of a higher 24-hour target of <140 mmHg (ambulatory BP threshold definitions of normal versus high are lower than office BP thresholds; therefore, this threshold is analogous to the Canadian guideline concordant <150 mmHg office BP target that is allowed in older frailer patients [6]).

Major secondary outcomes will include the change in mean 24-hour SBP and diastolic BP (overall, daytime, and nighttime). Home BP and the automated BP measurements taken at each study visit will be examined similarly. Additional major outcomes will include postural BP changes and changes in A1c, lipids, anthropomorphic indices, quality of life, depression/anxiety, satisfaction with medical care, resource utilization, and the safety end points described previously.

Data Analysis

First, variables will be examined descriptively and graphically, including assessments of temporal trends and tests of normality. Second, the 6-month and 1-year mean change from baseline in each outcome will be calculated and compared between study arms (each intervention arm to the control arm, then between intervention arms) using chi-square tests for dichotomous outcomes and unpaired *t*-tests for continuous outcomes. Third, multivariable predictors of the 1-year change in a given outcome will be identified using appropriately constructed and calibrated logistic regression models for dichotomous outcomes (including the primary outcome) or linear regression models for continuous ones. Initial models will adjust for age, sex, SBP, and residential site (eg, Greater Edmonton Foundation versus Rosedale). Examples of additional covariates that may be examined include sociodemographic variables, comorbidities, baseline medications, primary care physician, and tests of potential interaction.

Sample Size Considerations

The study will be adequately powered to detect a clinically important 20% absolute difference in the primary outcome between each intervention arm and usual care and similar 20% difference between the 2 intervention arms (20% has been previously identified by a consensus of Canadian experts as the required minimum clinically important difference for any new hypertension [or any other cardiometabolic] intervention directed at patients with diabetes [53]). Based on pilot data collected in 60 seniors residing in supportive living at two Edmonton sites, only 18% were within the therapeutic range at baseline. Assuming 5% improvement with usual care (related to secular or temporal trends and trial participation or Hawthorne type effects), 20% further improvement with telemonitoring, and a further 20% improvement with telemonitoring + case management, a 2-tailed alpha of 0.05, power of 0.80, the required sample size will be ~80 patients per arm or 240 total. Accounting for ≈20% attrition over 1 year, 100 patients per arm or 300 patients total will be recruited.

Aim 2: Usability and Acceptability of Telemonitoring

Assessment of usability and acceptability is critical for all technology-enhanced care interventions because unanticipated and undesired effects can commonly occur after implementation [54-56]. End-user input into system design and operation is needed throughout the evaluation process; otherwise, interventions risk being ineffective, unusable, or unsafe [54,55]. Usability testing involves assessment of the human-computer interaction and, specifically, issues related to use, interface, design, and function are examined [57,58]. System evaluation is performed iteratively and includes assessment then redesign and retesting.

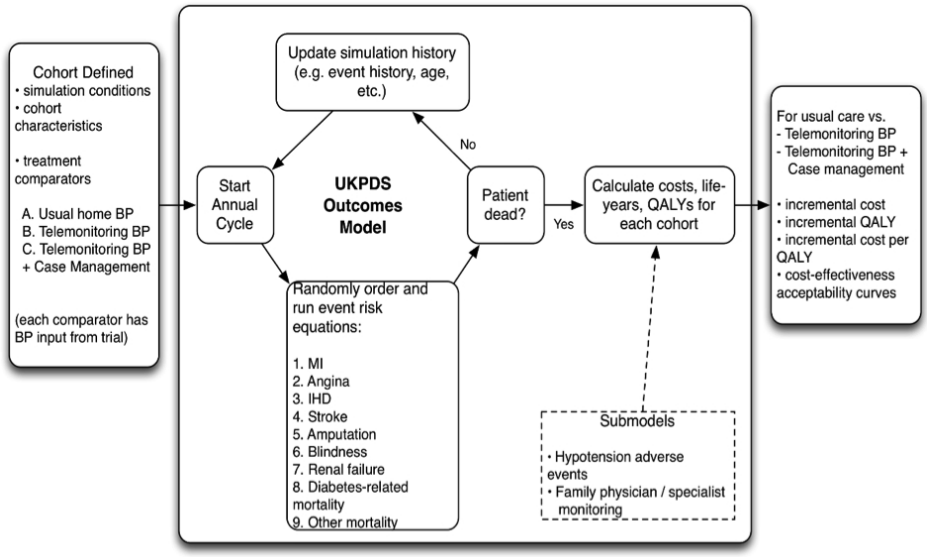
Usability and acceptability testing (device, data transmission, health portal) will be performed using well-accepted frameworks [57,59-61]. The evaluation will focus on functional goals (features, format, and interface), usability needs (outcome impact goals, end users' requirements, and information needs), and end-users' perceptions of the facilitators and barriers to use. End users that will be considered will include random samples of seniors with hypertension, family members who are primary caregivers, pharmacist case managers, and primary care physicians. We will perform usability and acceptability testing of the refined telemonitoring intervention at the beginning of the study and during the study. The evaluation will use standard mixed methods approach, with focus groups of all stakeholders, semistructured indepth interviews with think aloud and talk back with patients, and repeated surveys regarding the technology itself [54,55,57,58,60,62,63].

Aim 3: Cost-Effectiveness of Telemonitoring ± Case Management

Outcomes

The total and incremental cost for each intervention compared to usual care will be calculated (Table 2 and Figure 3), and the cost per decrement in SBP (cost-effectiveness model A), and incremental cost/QALY gained (cost-utility model B), will be determined.

Figure 3. Overview of economic model.



Methods

A validated economic model (used by the research team in prior work examining interventions in type 2 diabetes [64,65]) will be modified and used to compare both telemonitoring alone and telemonitoring + case management versus usual care (Figure 3), adhering to recommended best practices for conduct of economic evaluation [51,66]. The patient population simulated will have characteristics of the patients studied (seniors with diabetes and hypertension). The model will be informed by primary data from the RCT, including detailed costing data (Table 2), utility scores (EQ-5D), and BP changes for each treatment strategy. A 1-year time horizon and a public health care payer perspective will be used for model A, where the surrogate of change in BP will be examined (cost per mm of reduction in SBP). No discounting of costs and benefits will be performed in the reference case (given the short time frame). We will also perform a cost-utility analysis (model B) linking the validated surrogate of BP reduction at 1 year to longer term health outcomes (including probability of developing heart disease, stroke, kidney failure, blindness) [67,68], and associated increased risk of death, decrement in quality of life, and increased health care costs with these events. The model will also incorporate other study end points including avoidance of low BP and reductions in adverse effects that result in health or resource use (short-term reduction in quality of life, physician, or emergency room visits), and other health care utilization that may be impacted by treatment strategy (cost of BP drugs, clinic visits to monitor and manage BP, and hospitalizations to treat adverse effects).

We have previously used the United Kingdom Prospective Diabetes Study (UKPDS) outcomes model to examine the cost-effectiveness of interventions in patients with type 2 diabetes [64,65]. Advantages of this model include robust validation [69], ability to specify characteristics of the patient population, and previous adaptation of the model to represent the Canadian context for resource use, costs, and quality of life [64,65]. Uncertainty and variability will be explored through sensitivity analysis, including one-way and probabilistic sensitivity analysis including cost-effectiveness acceptability curves, where a range of willingness to pay thresholds are examined. Sensitivity analysis considering a range of estimates obtained from the RCT (for example, 95% CI in BP differences) as well as other plausible ranges of parameters will be performed. These include assignment of some costs to either patient or health care payer (device, set top box, data plan, health portal access fee) or a range of costs of delivering telemonitoring ± case management for varying economies of scale.

Subgroup Analyses and Substudies

Analyses of interest include examination of the effect of telemonitoring in subjects aged 80 years or greater as well as substudies on vascular stiffness, orthostatic changes, and novel BP measurement methods. In addition, passive, long-term follow-up using linked administrative data are planned to ascertain effects on cardiovascular morbidity and mortality.

Ethics, Funding, and Registration

All subjects will provide written informed consent. The TECHNOMED trial protocol has been approved by the University of Alberta Research Ethics Board (PRO00051624), and the trial has received peer reviewed funding from the Canadian Institutes of Health Research (grant #EH2-143571) and Alberta Innovates Health Solutions (grant #201900506). The trial has been formally registered at clinicaltrials.gov (NCT02721667).

Discussion

In summary, the TECHNOMED trial is a pragmatic randomized control trial that will comprehensively study, in the Canadian context, home BP telemonitoring in seniors. It will compare 3 different methods of implementing home BP measurement and examine a broad range of outcomes important to patients, providers, caregivers, and policy makers.

Home BP telemonitoring has been shown to effectively reduce BP and improve BP control in younger patients with hypertension, especially when combined with case management [27]. Recent publication of the Systolic Blood Pressure Intervention Trial, a study that demonstrated clinically important benefits to lowering SBP to ≈120 mmHg in high-risk individuals (excluding those with diabetes [10]), also supports the need for close monitoring [70]. Given these low BP targets, careful BP monitoring will be required to operationalize this intervention in current clinical practice.

A critical question is whether BP telemonitoring can be successfully implemented in seniors, who may be less technologically savvy than younger individuals. We propose to test a very simple system that does not require specialized expertise. Usability and acceptability testing constitute a central objective of the trial. Qualitative studies of younger patients and of care providers have, in general, shown that patients find BP telemonitoring usable and acceptable but that providers express concerns about workload, troubleshooting the technology, and increased need for resources [71,72]. This makes rigorous cost-effectiveness analysis essential. It also underscores the importance of minimizing monitoring to include only measurements that are clinically necessary.

Enrolment within the TECHNOMED trial is expected to begin in mid-2016. Recruitment of all 300 subjects is expected by mid-2018. Final results for the main study are anticipated by 2020. We anticipate that this trial will clarify the advantages and disadvantages of BP telemonitoring in this high-risk population with both diabetes and hypertension (see Multimedia Appendix 1).

Conflicts of Interest

TECHNOMED is funded by Canadian Institute for Health Research (CIHR) grant number EH2-143571 and Alberta Innovates Health Solutions grant number 201900506.
RP, SRM, SK, and FAM are supported by an alternative funding plan from the Government of Alberta and the University of Alberta. SK and FM holds salary support awards from Alberta Heritage Foundation for Medical Research and Alberta Innovates-Health Solutions. SRM holds the Endowed Chair in Patient Health Management of the Faculties of Medicine and Dentistry and Pharmacy and Pharmaceutical Sciences, University of Alberta. PB holds an Endowed Chair in Healthcare Solutions provided by CISCO Systems Inc. FAM holds the University of Alberta Chair in Cardiovascular Outcomes Research.

Authors' Contributions

RP drafted the initial study concept and all authors contributed to the study design. RP and PWW wrote the initial draft of the protocol and all authors provided input into revisions and approved the final draft.

Multimedia Appendix 1

CIHR Reviews.

[PDF File (Adobe PDF File), 332KB - resprot_v5i2e107_app1.pdf]

References

1. Gee ME, Janssen I, Pickett W, McAlister FA, Bancej CM, Joffres M, Campbell Norman R C. Prevalence, awareness, treatment, and control of hypertension among Canadian adults with diabetes, 2007 to 2009. Can J Cardiol 2012 May;28(3):367-374. [doi: 10.1016/j.cjca.2011.08.111] [Medline: 22281410]
2. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. JAMA 2015 Feb 10;313(6):603-615. [doi: 10.1001/jama.2014.18574] [Medline: 25668264]
3. Staessen JA, Gasowski J, Wang JG, Thijs L, Den HE, Boissel JP, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. Lancet 2000 Mar 11;355(9207):865-872. [Medline: 10752701]
4. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective SC. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002 Dec 14;360(9349):1903-1913. [Medline: 12493255]
5. Moran AE, Odden MC, Thanataveerat A, Tzong KY, Rasmussen PW, Guzman D, et al. Cost-effectiveness of hypertension therapy according to 2014 guidelines. N Engl J Med 2015 Jan 29;372(5):447-455 [FREE Full text] [doi: 10.1056/NEJMsa1406751] [Medline: 25629742]
6. Daskalopoulou SS, Rabi DM, Zarnke KB, Dasgupta K, Nerenberg K, Cloutier L, Ramesh Prasad G V, Campbell Norman RC, et al. The 2015 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. Can J Cardiol 2015 May;31(5):549-568. [doi: 10.1016/j.cjca.2015.02.016] [Medline: 25936483]

7. Jamerson K, Weber MA, Bakris GL, Dahlöf B, Pitt B, Shi V, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med 2008 Dec 4;359(23):2417-2428. [doi: 10.1056/NEJMoa0806182] [Medline: 19052124]
8. Majumdar S. Antihypertensive treatments for adults with type 2 diabetes. BMJ 2016;352:i560. [Medline: 26867645]
9. Allen M, Kelly K, Fleming I. Hypertension in elderly patients: recommended systolic targets are not evidence based. Can Fam Physician 2013 Jan;59(1):19-21, 22-4 [FREE Full text] [Medline: 23341648]
10. Franklin SS. Elderly hypertensives: how are they different? J Clin Hypertens (Greenwich) 2012 Nov;14(11):779-786 [FREE Full text] [doi: 10.1111/j.1751-7176.2012.00703.x] [Medline: 23126350]
11. Cushman WC, Evans GW, Byington RP, Goff DC, Grimm RH, Cutler JA, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010 Apr 29;362(17):1575-1585 [FREE Full text] [doi: 10.1056/NEJMoa1001286] [Medline: 20228401]
12. Tinetti ME, Han L, Lee David S H, McAvay GJ, Peduzzi P, Gross CP, et al. Antihypertensive medications and serious fall injuries in a nationally representative sample of older adults. JAMA Intern Med 2014 Apr;174(4):588-595 [FREE Full text] [doi: 10.1001/jamainternmed.2013.14764] [Medline: 24567036]
13. Aronow WS, Fleg JL, Pepine CJ, Artinian NT, Bakris G, Brown AS, et al. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents developed in collaboration with the American Academy of Neurology, American Geriatrics Society, American Society for Preventive Cardiology, American Society of Hypertension, American Society of Nephrology, Association of Black Cardiologists, and European Society of Hypertension. J Am Soc Hypertens 2011;5(4):259-352. [doi: 10.1016/j.jash.2011.06.001] [Medline: 21771565]
14. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med 2008 May 1;358(18):1887-1898. [doi: 10.1056/NEJMoa0801369] [Medline: 18378519]
15. Cloutier L, Daskalopoulou SS, Padwal RS, Lamarre-Cliche M, Bolli P, McLean D, et al. A New Algorithm for the Diagnosis of Hypertension in Canada. Can J Cardiol 2015 May;31(5):620-630 [FREE Full text] [doi: 10.1016/j.cjca.2015.02.014] [Medline: 25828374]
16. Conen D, Aeschbacher S, Thijs L, Li Y, Boggia J, Asayama K, et al. Age-specific differences between conventional and ambulatory daytime blood pressure values. Hypertension 2014 Nov;64(5):1073-1079 [FREE Full text] [doi: 10.1161/HYPERTENSIONAHA.114.03957] [Medline: 25185130]
17. ESH/ESC Task Force for the Management of Arterial Hypertension. 2013 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC): ESH/ESC Task Force for the Management of Arterial Hypertension. J Hypertens 2013 Oct;31(10):1925-1938. [doi: 10.1097/HJH.0b013e328364ca4c] [Medline: 24107724]
18. Moltu C, Stefansen J, Svisdahl M, Veseth M. Negotiating the coresearcher mandate - service users' experiences of doing collaborative research on mental health. Disabil Rehabil 2012;34(19):1608-1616. [doi: 10.3109/09638288.2012.656792] [Medline: 22489612]
19. Staessen J, Den HE, Celis H, Fagard R, Keary L, Vandenhoven G, Treatment of Hypertension Based on Home or Office Blood Pressure (THOP) Trial Investigators. Antihypertensive treatment based on blood pressure measurement at home or in the physician's office: a randomized controlled trial. JAMA 2004 Feb 25;291(8):955-964. [doi: 10.1001/jama.291.8.955] [Medline: 14982911]
20. Cappuccio FP, Kerry SM, Forbes L, Donald A. Blood pressure control by home monitoring: meta-analysis of randomised trials. BMJ 2004 Jul 17;329(7458):145 [FREE Full text] [doi: 10.1136/bmj.38121.684410.AE] [Medline: 15194600]
21. Ogedegbe G, Schoenthaler A. A systematic review of the effects of home blood pressure monitoring on medication adherence. J Clin Hypertens (Greenwich) 2006 Mar;8(3):174-180 [FREE Full text] [Medline: 16522994]
22. Agarwal R, Bills J, Hecht Tyler J W, Light R. Role of home blood pressure monitoring in overcoming therapeutic inertia and improving hypertension control: a systematic review and meta-analysis. Hypertension 2011 Jan;57(1):29-38 [FREE Full text] [doi: 10.1161/HYPERTENSIONAHA.110.160911] [Medline: 21115879]
23. McKay DW, Godwin M, Chockalingam A. Practical advice for home blood pressure measurement. Can J Cardiol 2007 May 15;23(7):577-580 [FREE Full text] [Medline: 17534466]
24. Huff LS, Zittleman L, DeAlleaume L, Bernstein J, Chavez R, Sutte C, et al. What keeps patients from adhering to a home blood pressure program? J Am Board Fam Med 2011;24(4):370-379 [FREE Full text] [doi: 10.3122/jabfm.2011.04.100266] [Medline: 21737761]
25. Milot J, Birnbaum L, Larochelle P, Wistaff R, Laskine M, Van NP, et al. Unreliability of home blood pressure measurement and the effect of a patient-oriented intervention. Can J Cardiol 2015 May;31(5):658-663. [doi: 10.1016/j.cjca.2015.03.006] [Medline: 25936491]
26. Myers MG. Limitations of home blood pressure monitoring in clinical practice. Can J Cardiol 2015 May;31(5):583-584. [doi: 10.1016/j.cjca.2015.03.008] [Medline: 25843166]
27. Omboni S, Gazzola T, Carabelli G, Parati G. Clinical usefulness and cost effectiveness of home blood pressure telemonitoring: meta-analysis of randomized controlled studies. J Hypertens 2013 Mar;31(3):455-67; discussion 467. [doi: 10.1097/HJH.0b013e32835ca8dd] [Medline: 23299557]

28. Blood Pressure Lowering Treatment Trialists' Collaboration, Sundström J, Arima H, Woodward M, Jackson R, Karmali K, et al. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. Lancet 2014 Aug 16;384(9943):591-598. [doi: 10.1016/S0140-6736(14)61212-5] [Medline: 25131978]
29. Reboldi G, Gentile G, Angeli F, Ambrosio G, Mancia G, Verdecchia P. Effects of intensive blood pressure reduction on myocardial infarction and stroke in diabetes: a meta-analysis in 73,913 patients. J Hypertens 2011 Jul;29(7):1253-1269. [doi: 10.1097/HJH.0b013e3283469976] [Medline: 21505352]
30. Norris SL, Nichols PJ, Caspersen CJ, Glasgow RE, Engelgau MM, Jack L, et al. The effectiveness of disease and case management for people with diabetes. A systematic review. Am J Prev Med 2002 May;22(4 Suppl):15-38. [Medline: 11985933]
31. Campbell NC, Murray E, Darbyshire J, Emery J, Farmer A, Griffiths F, et al. Designing and evaluating complex interventions to improve health care. BMJ 2007 Mar 3;334(7591):455-459 [FREE Full text] [doi: 10.1136/bmj.39108.379965.BE] [Medline: 17332585]
32. Tricco A, Ivers N, Grimshaw J, Moher D, Turner L, Galipeau J, et al. Effectiveness of quality improvement strategies on the management of diabetes: a systematic review and meta-analysis. Lancet 2012 Jun 16;379(9833):2252-2261. [doi: 10.1016/S0140-6736(12)60480-2] [Medline: 22683130]
33. McAlister FA, Majumdar SR, Padwal RS, Fradette M, Thompson A, Tsuyuki R, et al. The preventing recurrent vascular events and neurological worsening through intensive organized case-management (PREVENTION) trial protocol [clinicaltrials.gov identifier: NCT00931788]. Implement Sci 2010;5:27 [FREE Full text] [doi: 10.1186/1748-5908-5-27] [Medline: 20385021]
34. McAlister FA, Majumdar SR, Padwal RS, Fradette M, Thompson A, Buck B, et al. Case management for blood pressure and lipid level control after minor stroke: PREVENTION randomized controlled trial. CMAJ 2014 May 13;186(8):577-584 [FREE Full text] [doi: 10.1503/cmaj.140053] [Medline: 24733770]
35. Logan AG, Irvine MJ, McIsaac WJ, Tisler A, Rossos PG, Easty A, et al. Effect of home blood pressure telemonitoring with self-care support on uncontrolled systolic hypertension in diabetics. Hypertension 2012 Jul;60(1):51-57 [FREE Full text] [doi: 10.1161/HYPERTENSIONAHA.111.188409] [Medline: 22615116]
36. Moreno L, Dale SB, Chen AY, Magee CA. Costs to Medicare of the Informatics for Diabetes Education and Telemedicine (IDEATel) home telemedicine demonstration: findings from an independent evaluation. Diabetes Care 2009 Jul;32(7):1202-1204 [FREE Full text] [doi: 10.2337/dc09-0094] [Medline: 19366971]
37. Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. J Am Geriatr Soc 1975 Oct;23(10):433-441. [Medline: 1159263]
38. Kroenke K, Strine TW, Spitzer RL, Williams Janet B W, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. J Affect Disord 2009 Apr;114(1-3):163-173. [doi: 10.1016/j.jad.2008.06.026] [Medline: 18752852]
39. National Institute for HealthClinical Excellence. Hypertension. The clinical management of primary hypertension in adults. Clinical Guideline. London: National Clinical Guideline Centre; 2011:127.
40. Dasgupta K, Quinn RR, Zarnke KB, Rabi DM, Ravani P, Daskalopoulou SS, Prasad G V Ramesh, Arnold J Malcolm O, Canadian Hypertension Education Program. The 2014 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. Can J Cardiol 2014 May;30(5):485-501 [FREE Full text] [doi: 10.1016/j.cjca.2014.02.002] [Medline: 24786438]
41. Stergiou GS, Giovas PP, Gkinos CP, Patouras JD. Validation of the Microlife WatchBP Home device for self home blood pressure measurement according to the International Protocol. Blood Press Monit 2007 Jun;12(3):185-188. [doi: 10.1097/MBP.0b013e3280b083ce] [Medline: 17496469]
42. O'Brien E, Mee F, Atkins N, O'Malley K. Accuracy of the SpaceLabs 90207 determined by the British Hypertension Society protocol. J Hypertens 1991 Jun;9(6):573-574. [Medline: 1653299]
43. Freitas S, Simões MR, Alves L, Santana I. Montreal cognitive assessment: validation study for mild cognitive impairment and Alzheimer disease. Alzheimer Dis Assoc Disord 2013;27(1):37-43. [doi: 10.1097/WAD.0b013e3182420bfe] [Medline: 22193353]
44. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005 Aug 30;173(5):489-495 [FREE Full text] [doi: 10.1503/cmaj.050051] [Medline: 16129869]
45. EuroQol Group. 2014. EQ-5D: A standardised instrument for use as a measure of health outcome URL: http://www.euroqol.org/ [accessed 2016-05-12] [WebCite Cache ID 6hSC7Qbij]
46. Kroenke K, Spitzer RL, Williams Janet B W, Monahan PO, Löwe B. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. Ann Intern Med 2007 Mar 6;146(5):317-325. [Medline: 17339617]
47. Maddigan SL, Majumdar SR, Guirguis LM, Lewanczuk RZ, Lee TK, Toth EL, et al. Improvements in patient-reported outcomes associated with an intervention to enhance quality of care for rural patients with type 2 diabetes: results of a controlled trial. Diabetes Care 2004 Jun;27(6):1306-1312. [Medline: 15161780]

48. Majumdar SR, Rowe BH, Folk D, Johnson JA, Holroyd BH, Morrish DW, et al. A controlled trial to increase detection and treatment of osteoporosis in older patients with a wrist fracture. Ann Intern Med 2004 Sep 7;141(5):366-373. [Medline: 15353428]
49. Kahlon S, Pederson J, Majumdar SR, Belga S, Lau D, Fradette M, et al. Association between frailty and 30-day outcomes after discharge from hospital. CMAJ 2015 Aug 11;187(11):799-804 [FREE Full text] [doi: 10.1503/cmaj.150100] [Medline: 26009583]
50. Marshall GN, Hays RD, Mazel R. Health status and satisfaction with health care: results from the medical outcomes study. J Consult Clin Psychol 1996 Apr;64(2):380-390. [Medline: 8871422]
51. Brouwer W, Rutten F, Koopmanschap M. Costing in economic evaluations. In: Drummond M, McGuire A. editors. Economic evaluation in health care: merging theory with practice. Oxford: Oxford University Press; 2001:68.
52. Jacobs P, Roos NP. Standard cost lists for healthcare in Canada. Issues in validity and inter-provincial consolidation. Pharmacoeconomics 1999 Jun;15(6):551-560. [Medline: 10538328]
53. Majumdar S, Johnson, JA, Bowker S. A Canadian consensus for the standardized evaluation of quality improvement interventions in type 2 diabetes. Can J Diab 2005;29:220-229.
54. Graham Timothy A D, Kushniruk AW, Bullard MJ, Holroyd BR, Meurer DP, Rowe BH. How usability of a web-based clinical decision support system has the potential to contribute to adverse medical events. AMIA Annu Symp Proc 2008:257-261 [FREE Full text] [Medline: 18998968]
55. Kushniruk AW, Triola MM, Borycki EM, Stein B, Kannry JL. Technology induced error and usability: the relationship between usability problems and prescription errors when using a handheld application. Int J Med Inform 2005 Aug;74(7-8):519-526. [doi: 10.1016/j.ijmedinf.2005.01.003] [Medline: 16043081]
56. Ash JS, Berg M, Coiera E. Some unintended consequences of information technology in health care: the nature of patient care information system-related errors. J Am Med Inform Assoc 2004;11(2):104-112 [FREE Full text] [doi: 10.1197/jamia.M1471] [Medline: 14633936]
57. Kushniruk AW, Patel VL. Cognitive and usability engineering methods for the evaluation of clinical information systems. J Biomed Inform 2004 Feb;37(1):56-76 [FREE Full text] [doi: 10.1016/j.jbi.2004.01.003] [Medline: 15016386]
58. Kushniruk A. Evaluation in the design of health information systems: application of approaches emerging from usability engineering. Comput Biol Med 2002 May;32(3):141-149. [Medline: 11922931]
59. Kastner M, Lottridge D, Marquez C, Newton D, Straus SE. Usability evaluation of a clinical decision support tool for osteoporosis disease management. Implement Sci 2010;5:96 [FREE Full text] [doi: 10.1186/1748-5908-5-96] [Medline: 21143978]
60. Daniels J, Fels S, Kushniruk A, Lim J, Ansermino JM. A framework for evaluating usability of clinical monitoring technology. J Clin Monit Comput 2007 Oct;21(5):323-330. [doi: 10.1007/s10877-007-9091-y] [Medline: 17701381]
61. W21C. 2014. Human factors and simulation URL: http://w21c.org/research/human-factors-and-simulation [accessed 2016-05-12] [WebCite Cache ID 6hSCQx2Te]
62. Vizri R. Refining the test phase of usability evaluation: how many subjects is enough. Human Factors 1992;34:457-468.
63. Patton M. Qualitative Research and Evaluation Methods. 3rd Edition. California: Sage Publications Inc; 2002.
64. Simpson S, Lier D, Majumdar S, Tsuyuki R, Lewanczuk R, Spooner R, et al. Cost-effectiveness analysis of adding pharmacists to primary care teams to reduce cardiovascular risk in patients with Type 2 diabetes: results from a randomized controlled trial. Diabet Med 2015 Jul;32(7):899-906. [doi: 10.1111/dme.12692] [Medline: 25594919]
65. Cameron C, Coyle D, Ur E, Klarenbach S. Cost-effectiveness of self-monitoring of blood glucose in patients with type 2 diabetes mellitus managed without insulin. CMAJ 2010 Jan 12;182(1):28-34 [FREE Full text] [doi: 10.1503/cmaj.090765] [Medline: 20026626]
66. Cartwright WS. Methods for the economic evaluation of health care programmes, second edition. By Michael F. Drummond, Bernie O'Brien, Greg L. Stoddart, George W. Torrance. Oxford: Oxford University Press, 1997. J Ment Health Policy Econ 1999 Mar 1;2(1):43. [Medline: 11967406]
67. Adler AI, Stratton IM, Neil HA, Yudkin JS, Matthews DR, Cull CA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ 2000 Aug 12;321(7258):412-419 [FREE Full text] [Medline: 10938049]
68. Klarenbach S, Cameron C, Singh S, Ur E. Cost-effectiveness of second-line antihyperglycemic therapy in patients with type 2 diabetes mellitus inadequately controlled on metformin. CMAJ 2011 Nov 8;183(16):E1213-E1220 [FREE Full text] [doi: 10.1503/cmaj.110178] [Medline: 21969406]
69. Mount Hood 4 Modeling Group. Computer modeling of diabetes and its complications: a report on the Fourth Mount Hood Challenge Meeting. Diabetes Care 2007 Jun;30(6):1638-1646. [doi: 10.2337/dc07-9919] [Medline: 17526823]
70. The SPRINT Research Group. A randomized trial of intensive versus standard blood pressure control. N Engl J Med 2015;373:2103-2116.
71. Hanley J, Ure J, Pagliari C, Sheikh A, McKinstry B. Experiences of patients and professionals participating in the HITS home blood pressure telemonitoring trial: a qualitative study. BMJ Open 2013;3(5) [FREE Full text] [doi: 10.1136/bmjopen-2013-002671] [Medline: 23793649]

72. Koopman RJ, Wakefield BJ, Johanning JL, Keplinger LE, Kruse RL, Bomar M, et al. Implementing home blood glucose and blood pressure telemonitoring in primary care practices for patients with diabetes: lessons learned. Telemed J E Health 2014 Mar;20(3):253-260 [FREE Full text] [doi: 10.1089/tmj.2013.0188] [Medline: 24350806]

Abbreviations

ABPM: ambulatory blood pressure monitoring
BP: blood pressure
RCTs: randomized controlled trials
SBP: systolic blood pressure
TECHNOMED: Telemonitoring and Protocolized Case Management for Hypertensive Community-Dwelling Seniors With Diabetes

Edited by G Eysenbach; submitted 18.03.16; peer-reviewed by S Hiremath; comments to author 03.04.16; accepted 03.04.16; published 24.06.16.

Please cite as:
Padwal R, McAlister FA, Wood PW, Boulanger P, Fradette M, Klarenbach S, Edwards AL, Holroyd-Leduc JM, Alagiakrishnan K, Rabi D, Majumdar SR
Telemonitoring and Protocolized Case Management for Hypertensive Community-Dwelling Seniors With Diabetes: Protocol of the TECHNOMED Randomized Controlled Trial
JMIR Res Protoc 2016;5(2):e107
URL: http://www.researchprotocols.org/2016/2/e107/
doi:10.2196/resprot.5775
PMID:27343147

Protocol

Transforming the Patient Role to Achieve Better Outcomes Through a Patient Empowerment Program: A Randomized Wait-List Control Trial Protocol

Lisa Altshuler[1], PhD; Joseph Plaksin[1], BS; Sondra Zabar[1], MD; Andrew Wallach[2], MD; Chester Sawicki[3], BA; Sarita Kundrod[4], BA; Adina Kalet[1], MD, MPH

[1]Program on Medical Education, Innovations and Research (PrMEIR), Division of General Internal Medicine and Clinical Innovation, New York University School of Medicine, New York, NY, United States

[2]Bellevue Hospital Center, Division of General Internal Medicine and Clinical Innovation, New York University School of Medicine, New York, NY, United States

[3]Department of Clinical Affairs and Affiliates, New York University School of Medicine, New York, NY, United States

[4]Department of Psychology, University of Minnesota, Minneapolis, MN, United States

Corresponding Author:
Lisa Altshuler, PhD
Program on Medical Education, Innovations and Research (PrMEIR)
Division of General Internal Medicine and Clinical Innovation
New York University School of Medicine
550 First Avenue
BCD D401
New York, NY, 10016
United States
Phone: 1 (646) 501 4136
Fax: 1 (646) 754 9699
Email: Lisa.Altshuler@nyumc.org

Abstract

Background: In the patient-centered medical home model of health care, both health care providers (HCPs) and patients must understand their respective roles and responsibilities, view the other as a partner, and use communication skills that promote shared decision making. This is particularly necessary in chronic conditions where outcomes depend on behavior change and in underserved populations where the burden of chronic disease is high.

Objective: The objectives of this study are to determine if a Patient Empowerment Program (PEP) (1) is acceptable to patients and feasible across multiple clinical sites; (2) will increase patient preference for control in medical decision making, improve patient perceptions of patient-HCP communication, and increase patient activation; (3) is associated with an increase in diabetes self-management behaviors; and (4) has an effect on hemoglobin A_{1c} (HbA_{1c}) level.

Methods: This study recruited English-speaking adult patients with type 2 diabetes mellitus from three urban clinical sites in New York City and randomized them to an immediate intervention group that completed the PEP intervention or a deferred intervention group that served as a wait-list control and completed the PEP intervention after 3-4 months. The PEP intervention consists of two facilitated small group sessions. Session 1 focuses on defining HCP and patient roles in the medical encounter by introducing ideal communication behaviors in each role and by providing both positive and negative examples of patient-HCP encounters. Session 2 focuses on practicing communication skills by role-playing with actors who serve as standardized health care providers. After the role play, participants set goals for their own health care and for future interactions with their HCPs. Outcome measures include the Patient Activation Measure; Ask, Understand, Remember Assessment; Krantz Health Opinion Survey; SF-12v2 Health Survey; Diabetes Self-Management Questionnaire; and HbA_{1c}. These measures will be assessed at the time of enrollment, after the waiting period (deferred intervention only), and then postintervention at 1 week, 3 months, and 6 months.

Results: Study recruitment occurred from November 2014 to June 2015, with a total of 80 patients enrolled. To date, 45 participants have attended at least one session of the PEP intervention. Further intervention sessions and post-intervention follow-up are ongoing, with data collection set to be completed in April 2016 and results of data analysis available by June 2016.

Conclusions: From preliminary participant self-report data, our PEP intervention is acceptable to low-income, low–health literate patients and feasible to hold across multiple clinical sites. Participants have reported learning specific ways to change their behaviors at their next HCP visit (eg, stating their opinions, asking more questions). With the forthcoming quantitative data on participant attitudinal and behavior change, the PEP intervention may ultimately empower participants within the medical encounter and improve health outcomes.

(JMIR Res Protoc 2016;5(2):e68) doi:10.2196/resprot.5376

KEYWORDS

shared decision making; patient activation; health literacy

Introduction

Background

More than 25.8 million Americans have type 2 diabetes mellitus (T2DM). In 2012, T2DM cost the United States $245 billion in both direct and indirect medical costs [1]. Comparable to the general population, it has been estimated that 10% of the New York City population suffers from T2DM, and patients with diabetes-related disorders occupy half of the hospital beds in the city [2]. The patient-centered medical home (PCMH) model, which strives to provide comprehensive care and improve patient's self-management skills through increasing engagement with health care providers (HCPs), is ideally suited for T2DM care [3-5].

Preparing patients for the PCMH model is challenging because of the inherent power differential between HCPs and patients. Efforts to prepare HCPs to practice in the PCMH model have included strategies for encouraging patient self-care activities and behavior change (eg, tailoring, brief negotiation, motivational interviewing) [6,7]. Interventions have also been developed to educate patients about disease management and increase involvement in their care [8-11]. However, both approaches fail to address the inherent asymmetry in the power dynamics of the physician-patient relationship [12-21]. Increasing patient activation is one method that has been suggested to overcome these barriers. Activated patients are knowledgeable about their health conditions, confident in their ability to manage these conditions, and maintain their health by seeking information and performing health promoting behaviors [22]. In general, more activated patients, as determined by a higher score on the Patient Activation Measure (PAM) [22,23], ask more questions during HCP visits [22-24] and perform more self-management behaviors including diet and exercise [22,23,25-28]. More specifically, patients with T2DM who have higher PAM scores report less difficulty in managing their diabetes than those with lower scores [28]. Furthermore, several interventions that increase patient activation have shown promise for improving outcomes [29-32], most notably in congestive heart failure [29] and T2DM [30].

Standardized patient (SP) training, a well-established, performance-based intervention, offers a compelling method of activating patients to become partners in their health care. Standardized patients are trained to reliably and validly assess HCP clinical competence [33-37] and, as a result, become more activated "real" patients who have higher expectations of HCPs and improved communication with HCPs [38-43]. Additionally, SPs have improved their own health behaviors in terms of weight loss [44] as well as HIV testing and sexually transmitted disease prophylaxis [45]. More recently, these same training methods have been used to train standardized health care providers (SHPs) to assess communication between HCPs of different disciplines (eg, doctors and nurses) as part of interprofessional education [46-48].

Our Patient Empowerment Program (PEP) seeks to adapt the successful SP methodology currently used in HCP education and translate it onto the patient side of the medical encounter [49]. To do so, the PEP incorporates ideas of shared decision making (SDM), involves role-playing, and helps patients develop the skills to give effective feedback to HCPs using validated checklists of observable behaviors. This intervention is both evidence based and theory supported and addresses the needs of multiple stakeholders, including health system quality leaders, HCPs, patient advocates, SP trainers, and patients. We focus on patients with T2DM because of its high prevalence in the population, the need for frequent contact with the health care system, and the numerous aspects of treatment (eg, lifestyle changes, medications, blood glucose monitoring, annual screenings, and so on) that patients must discuss with their HCPs.

Objectives

The objectives of this study are to (1) assess the acceptability and feasibility of implementing the PEP across three urban clinical sites; (2) determine if a PEP will change patient preference for control in medical decision making, improve patient self-efficacy in patient-HCP communication, and increase patient activation; (3) determine if participation in the PEP is associated with an increase in diabetes self-management behaviors; and (4) explore the effect of the PEP on hemoglobin A_{1c} (HbA_{1c}) level.

Methods

Overview

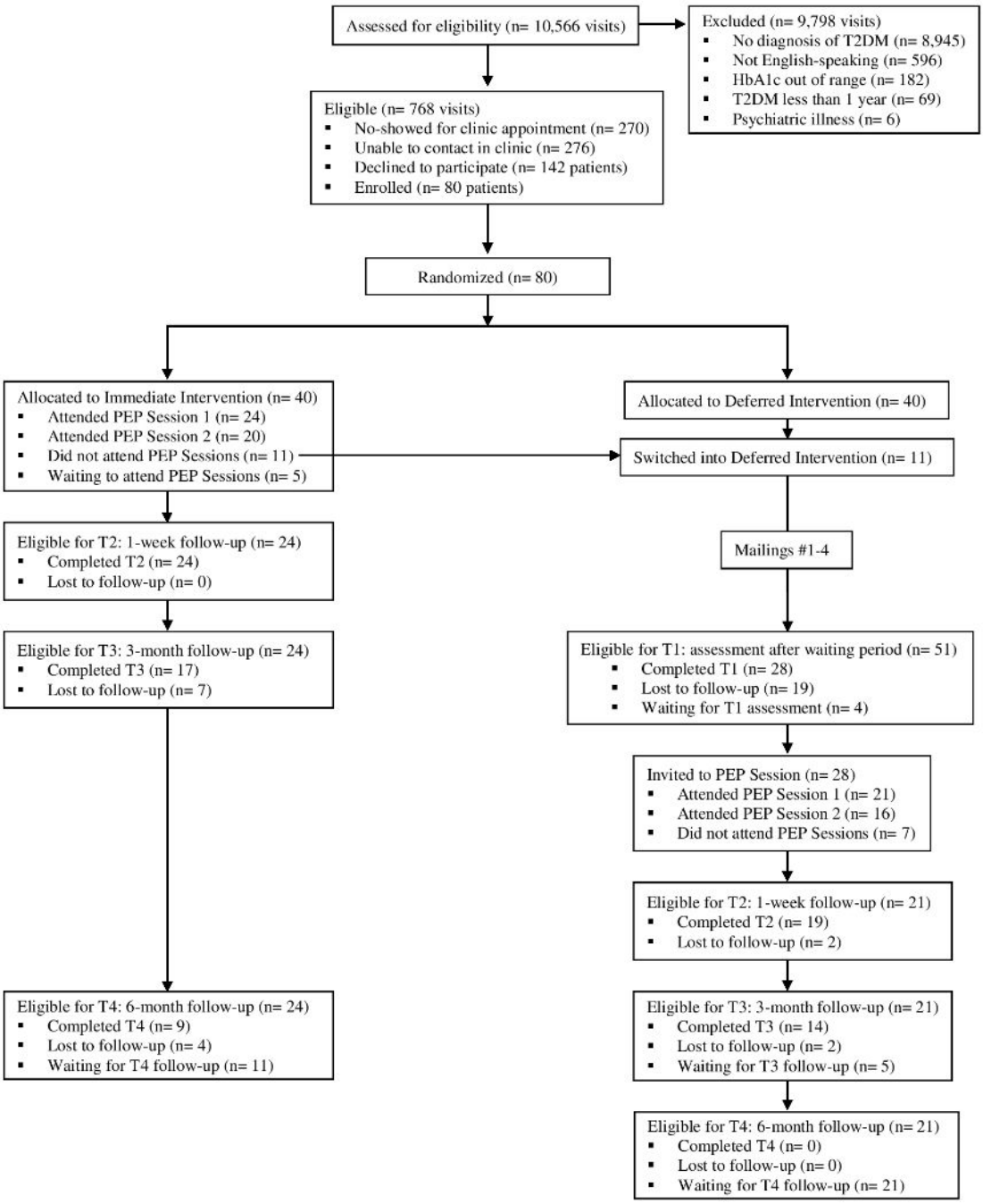
The PEP is a randomized, wait-list control study (see Multimedia Appendix 1) that aims to enhance general communication skills so that patients can participate in SDM during office visits, become activated in their own health care, and better manage their medical conditions.

Patients were recruited in cohorts of 20 and then randomly assigned to attend the PEP intervention immediately (immediate intervention) or after a waiting period (deferred intervention). All participants completed a baseline assessment at the time of enrollment (T0) and will complete follow-up assessments 1

week (T2), 3 months (T3), and 6 months (T4) after completion of the PEP intervention (see Figure 1). Additionally, the deferred intervention group was assessed at the end of the waiting period (T1), immediately before being invited to attend the PEP intervention. The T1 assessment for the deferred intervention group was approximately 3-4 months after randomization and was timed to coincide with the T3 assessment of the immediate intervention group. A wait-list control design was chosen to create a control group with multiple time points of data collection (deferred intervention T0-T1) while still allowing for all participants who enrolled in the study to complete the PEP intervention and post-PEP follow-ups.

Aside from attending the PEP intervention, all participants continued to receive their usual care, including all scheduled primary care and specialty clinic appointments, HbA_{1c} monitoring, and all medications as directed by their physicians.

Figure 1. CONSORT flow diagram. HbA1c: hemoglobin A1c; PEP: Patient Empowerment Program; T2DM: type 2 diabetes mellitus.



Setting

Bellevue Hospital Center, Gouverneur Health, and Woodhull Medical Center are all within the Health and Hospitals Corporation, a large public hospital system in New York City. The adult ambulatory care clinics at these sites serve patients from the local community as well as immigrants from around the world, with English, Spanish, Mandarin, Cantonese, and Bengali among the most common languages spoken. Approximately one-third of patients have Medicaid or are without health insurance and the most common diagnoses in the clinic include obesity, hypertension, heart disease, diabetes, and asthma.

Participants

We recruited patients with T2DM who presented to the adult ambulatory care clinic at each site. Patients eligible for inclusion in the study (1) were at least 18 years old, (2) had a diagnosis of T2DM for at least 1 year, and (3) their most recent HbA_{1c} level was between 6.5% and 11%. Patients were excluded if they (1) were unable to speak English or (2) had a major psychiatric illness that impaired their ability to care for themselves (eg, schizophrenia, uncontrolled bipolar disorder, or uncontrolled depressive disorder).

Recruitment, Randomization, and Retention

Research assistants (RAs) screened all of the clinic appointments each day to identify patients who were eligible for the study. Research assistants then briefly explained the study to all eligible patients who came to their appointment and obtained informed consent from those who decided to enroll (see Figure 1). After obtaining informed consent, RAs read participants a set of questionnaires to complete the initial (T0) assessment (see Table 1).

After 20 participants were enrolled in the study, a Web-based random number generator was used to generate a list of 20 integers between one and two. The list was refreshed until it contained 10 ones and 10 twos. Based on this list, participants were assigned in order of their study identification number to the immediate intervention (1) or deferred intervention (2) group. All participants in the immediate intervention group were contacted by phone to schedule the PEP intervention sessions and all participants in the deferred intervention group were contacted by phone and informed that they would be recontacted in 3-4 months to schedule their PEP intervention sessions.

Participants were compensated for participating in the study. They received US $10 and a MetroCard with US $10 at each of the two PEP intervention sessions. They also received US $60 and a MetroCard with US $10 for completing the study if they attended a post-PEP focus group.

In order to increase retention of deferred intervention participants, they received a letter from our program and an educational handout about T2DM in the mail approximately every 3 weeks. Handouts were sent in the same order and all handouts came from the Diabetes Care and Education website [50]. In total there were four mailings: (1) Nutrition to Help Manage your Diabetes and Weight, (2) Eating Healthy on a Lean Budget, (3) Know Your Blood Sugar Numbers, and (4) Managing and Preventing Hypoglycemia. All four of these handouts were short, only 1-2 pages in length, and contained general information about T2DM that participants should have already obtained from their HCPs as part of their routine treatment. Therefore, we do not expect that receiving these handouts will cause a significant difference in the two randomized groups or otherwise affect the results of the study.

Outcome Measures

Outcome measures for the study primarily consist of self-report questionnaires assessing health attitudes and behaviors (see Table 1). Because of the low literacy of the patient population, RAs read all questionnaires to the participants and then recorded their responses. All questionnaires were asked in the same order and a standardized protocol was created so that all RAs asked and clarified questions in the same manner. Outcome measures were assessed at the time of enrollment (T0), after the waiting period (T1: deferred intervention group only), and postintervention after 1 week (T2), 3 months (T3), and 6 months (T4).

Table 1. Data collection.

Domain	Measures	Timing of assessment			
		Enrollment (T0)	After waiting period (T1) (*deferred only*)	1 week after PEP[a] (T2)	3 and 6 months after PEP (T3, T4)
Demographics	Age, sex Race and ethnicity Education level Annual income	X			
Clinical characteristics	Number of years with diabetes Current diabetes treatment	X			
Health literacy	Newest Vital Sign [51-53]	X			
Patient activation	Patient Activation Measure [23]	X	X	X	X
Ability to obtain information from HCPs[a]	Ask, Understand, Remember Assessment [54]	X	X	X	X
Preference for control in medical decision making	Krantz Health Opinion Survey [55]	X	X	X	X
	Preference Control Scale [56]	X	X	X	X
Disease management	Diabetes Self-Management Questionnaire [57]	X	X		X
Health quality of life	SF-12v2 Health Survey [58]	X	X		X
Biological marker of disease severity	Hemoglobin A_{1c}	X	X		X
PEP intervention feedback	Qualitative data analysis of focus group discussion			X	

[a] PEP: Patient Empowerment Program; HCP: health care provider.

Primary Outcome

The primary outcome of the study is patient activation, as measured by the short form of the PAM [23]. The PAM is a 13-item interval level, unidimensional, Guttman-like scale with four response options, ranging from 1 = disagree strongly to 4 = agree strongly. It has been validated across multiple patient populations and has been shown to be reliable, with Rasch person reliability estimates ranging from .73-.84. The overall score on the PAM ranges from 0-100 and PAM scores can be categorized into four levels of activation. In level one, the lowest level, patients believe taking an active role in their health is important but are unprepared for this role. In level two, patients have some knowledge but still struggle to manage their medical conditions. In level three, patients begin to take action in terms of self-management but do not have the skills to support or sustain their behavior. Finally, in level four, patients have adopted self-management behaviors and work on maintaining them in stressful life situations [23,30].

Secondary Outcomes

Secondary outcomes of the study include the ability to obtain information from HCPs, preferences for information and control in medical decision making, health quality of life, and diabetes self-care behaviors.

The ability of participants to obtain health information from HCPs was assessed by the Ask, Understand, Remember Assessment (AURA) [54]. The AURA is a 4-item interval level scale with four response options, ranging from 1 = disagree a lot to 4 = agree a lot. It is strongly correlated with chronic disease self-efficacy (r = .31) and moderately correlated with disease knowledge (r = .11). It also has good internal consistency reliability, with Cronbach's alpha = .75.

Participants' preferences for information and control in medical decision making were assessed by the Krantz Health Opinion Survey (Krantz) [55] and the Preference Control Scale (PCS) [56]. The Krantz [55] is a 16-item dichotomous (agree/disagree) multidimensional scale containing two subscales: Information and Behavioral Involvement. The Information subscale measures the desire for health information and the Behavioral Involvement subscale measures the desire to engage in health behaviors. The Krantz is moderately correlated (r = .31) with an established health locus of control scale, and test-retest reliability was .74 for the Information subscale, .71 for the Behavioral Involvement subscale, and .59 for the overall scale. The PCS [56] is a 1-item Likert-type interval level scale with five response options. Choices range from "I prefer to make the decision about which treatment I will receive" to "I prefer to leave all decisions regarding treatment to my doctor."

Participants' health quality of life was measured by the SF-12v2 Health Survey [58], a 12-item interval level, multidimensional scale containing a Physical Component summary score and Mental Component summary score. The SF-12v2 Health Survey

has been validated against other physical and mental health scales with Spearman correlation coefficients for each item ρ = .32-.61. It also has high internal consistency reliability (Mosier alpha = .78-.88) and moderate-high test-retest reliability (Physical Component ICC = .78, Mental Component ICC = .60).

Finally, participants' diabetes-specific health behaviors were assessed using the Diabetes Self-Management Questionnaire (DSMQ) [57]. The DSMQ is a 16-item interval level scale with four response options that range from 0 = does not apply to me to 3 = applies to me very much. It includes a Summary Scale as well as four subscales: Glucose Management, Dietary Control, Physical Activity, and Health-Care Use. The DSMQ was validated against a longer diabetes self-care scale and has been shown to significantly correlate with HbA_{1c}. It also has good internal consistency reliability, with Cronbach's alpha = .60-.84.

Exploratory Outcome

HbA_{1c} will serve as an exploratory outcome for the study. HbA_{1c} is exploratory for this study because participants did not undergo HbA_{1c} testing at specific times during the study period. Rather, participants will continue to have HbA_{1c} levels monitored as part of their routine care and the HbA_{1c} closest to enrollment (T0) and each follow-up time point (T1, T3, and T4) will be collected from the electronic medical record (EMR) and used for data analysis. Therefore, it is possible that a significant number of follow-up HbA_{1c} values may be missing or not collected at the time of follow-up and those that are will not correlate precisely to the same time period as the questionnaires.

Potential Confounding Variables

Previous studies have shown that there are numerous confounding variables that affect patients' ability to participate in SDM [15,17,18,59]. In order to account for these variables, demographic information was collected at enrollment (T0). Demographics included age, sex, race/ethnicity, educational attainment, and income level. Clinical characteristics included the number of years diagnosed with diabetes and current diabetes treatment (eg, lifestyle modifications, oral medications, insulin, or both oral medication and insulin).

In the study population, health literacy is also expected to be a significant confounding variable. Health literacy was measured at enrollment (T0) using the Newest Vital Sign (NVS) [51-53]. The NVS is a food label accompanied by 6 questions that are scored dichotomously (correct/incorrect). It has been validated against a longer health literacy questionnaire with an area under the receiver operating characteristic curve of .88. A score of less than 2 has a sensitivity of 72% and a specificity of 87% for predicting low health literacy, while a score of less than 4 has a sensitivity and specificity of 100% and 64%, respectively. The NVS also has good internal consistency reliability, with Cronbach's alpha = .76.

Acceptability and Feasibility of the Intervention

Acceptability and feasibility were judged based on (1) willingness of potential research subjects to enroll in the study, (2) responses to the activities during the PEP sessions, and (3) ability to engage in the role-playing scenarios in PEP session 2. After completion of the PEP intervention, all participants were invited to attend a focus group to discuss their experiences with and reactions to the PEP intervention, which were then audiotaped and transcribed. The transcribed text will be parsed into segments that represent a perspective or theme and each segment will then be independently coded by three readers. Through an iterative process among the coders, a single parsimonious coding scheme will be derived and then applied to all transcripts by the same three coders toward providing a thematic analysis of the data.

Intervention: Patient Empowerment Program

Our PEP is a two-session course led by a clinical health psychologist (LA) and assisted by research staff (JP, SK, and CS). Each session is 2 hours in length and the two sessions are held approximately 1 week apart. The PEP intervention is designed to be a group experience, with 2-6 participants attending each session. Ideally, the same participants who attended session 1 will return for session 2, but because of the limited availability of both research staff as well as participants, it is expected that this may not always be the case.

PEP Intervention Development

The PEP intervention curriculum (see Table 2) and materials for each PEP session were developed with input from patients as well as HCPs across all levels of training. Input was obtained via focus groups, all led by a clinical health psychologist (LA). Six focus groups for patients with T2DM (n=26) were held across all three study sites. In these groups, patients discussed their experiences with HCPs, difficulties managing diabetes, and opinions about participating in the PEP. This information was used to create content for video clips of patient-HCP interactions and cases for role-playing scenarios with SHPs. Overwhelmingly, patients reported that they thought it would be beneficial to participate in a program like PEP [60].

Focus groups were also held with internal medicine attending physicians (n=11), primary care residents (n=16), and medical students with at least 1 year experience on clinical rotations (n=11). In these groups, HCPs discussed their experiences with patients and expectations for patient engagement/activation. Overwhelmingly, HCPs reported preferring patients who were more informed about their medical conditions, who raised questions or concerns during the office visits, and who performed self-management behaviors in between appointments to those who were less activated [61].

After these focus groups were completed and intervention materials were created, 6 patients from the focus groups were invited to complete a beta test of the PEP intervention. During the beta test, they provided feedback about timing of the sessions, realism of the video clips, and feasibility of asking patients to complete a 10-minute role-play scenario with SHPs. Their feedback was used to revise all materials before recruitment for the PEP intervention began.

Table 2. Patient Empowerment Program intervention curriculum.

	Session 1		Session 2	
Session Element	Part 1	Part 2	Part 1	Part 2
Time	1 hour	1 hour	1 hour	1 hour
Task	Learn disease-specific case & HCP[a] checklist	Use checklist to rate video interactions	Practice case with SHPs[a]	Plan to apply model to own health care
Goal	Set standards for high-quality HCP and activated patient behaviors	Understand range of provider behaviors Learn to accurately describe provider behavior	Experience models of physician-patient interactions Shift social dynamic by empowering patient	Increase patient activation
Target	Learn standards for HCP behaviors: listen, ask questions, develop shared goals Learn standards for patient behaviors: share information, make choices, negotiate with provider	Learn to recognize elements of good/poor shared decision making and communication Practice describing HCP and patient behavior	Learn to be an active partner in health care encounters Give constructive feedback to providers	Reflect on lessons learned Set individualized goals for own health care and interaction with HCP
Theory	Develop cognitive framework for health care interactions	Vicarious learning of interpersonal skills in exam room	Behavioral rehearsal Experiential learning	Behavioral intentions

[a] HCP: health care provider; SHP: standardized healthcare provider

Intervention Standardization and Fidelity

In order to standardize the intervention, a curriculum and detailed manual were created. A group of 7 actors with previous SP experience were trained to play SHPs at the beginning of the study and reoriented to each case by an SP trainer before each intervention session. Throughout the intervention sessions, participants were asked to rate each activity to determine if the learning goals were being achieved, using a simple visual Likert scale with responses ranging from 0 = not at all to 3 = very much. All PEP intervention sessions were also audiotaped so that they could be transcribed to evaluate consistency across each run of the intervention.

Patient Empowerment Program Session 1

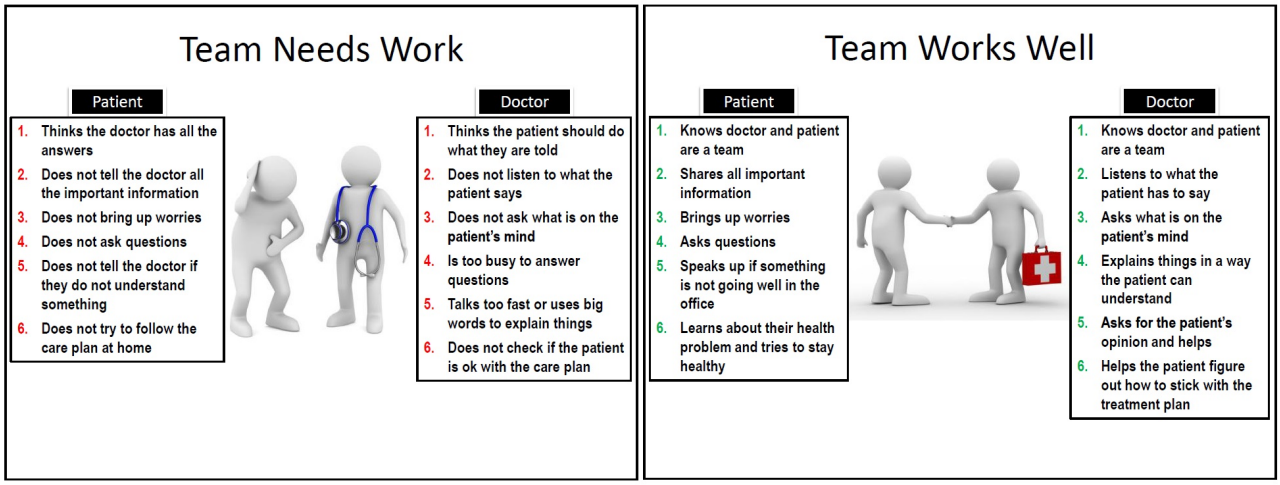
In the beginning of PEP session 1, participants discussed their experiences with HCPs and beliefs about the role of the patient and HCP in the medical encounter. Two posters were used to frame this discussion (see Figure 2), which describe specific behaviors of an effective patient-HCP team (ie, Team Works Well) and one that is not effective (ie, Team Needs Work). This framework was used to anchor discussions of the video clips and role-playing scenarios throughout the remainder of the PEP intervention.

Participants then watched three pairs of video clips of patient-HCP interactions. These video clips were created using actors who were experienced SPs and to represent a range of sex, race, and ethnicity for both the patient and HCP. Each pair of video clips represented a different aspect of a conversation between a patient and HCP, including (1) HCP taking the patient's medical history, (2) HCP providing information, and (3) decision making about the treatment plan. All visits were designed as follow-up visits, implying an ongoing relationship between patient and HCP within the interactions.

The first video in each pair represented a negative example of communication. In these videos, the patients were passive and did not voice their perspective or engage actively with the HCP. The HCPs, while trying to be helpful and sympathetic, were rushed, followed their own agendas, and acted with some sense that they knew the best approach. After the video clip, participants rated both the patient’s and HCP’s communication based on behaviors listed on the Team Works Well poster and discussed what each party could have done to improve the communication and the quality of the visit.

The second video in each pair was example of positive communication in the same situation. The patients in these videos were more activated and engaged with their HCPs, while the HCPs demonstrated a patient-centered approach. Similar to the first video, afterwards participants rated the patient and HCP and then had a brief discussion about what was different or improved.

Figure 2. Framework for patientÃƒÆ'Ã†â€™Ãƒâ€šÃ‚Â¢ÃƒÆ'Ã‚Â¢Ã¢â€šÂ¬Ã…¡Ãƒâ€šÃ‚Â¬Ã…¡ÃƒÆ'Ã‚Â¢Ã¢â€šÂ¬Ã¢â€žÂ¢Ã¢â€šÂ¬Ã…“health care provider interactions.



Patient Empowerment Program Session 2

PEP session 2 gave participants the opportunity to practice the communication skills that were discussed in session 1. Participants were first split into pairs to complete a brief role-play scenario with SHPs. While one participant was role-playing, the other observed and rated both the participant and the SHP in real time. The observing participant then led a debriefing of the scenario in order to practice giving feedback. After the debriefing, the participants switched places and the second participant completed a different role-play scenario.

In the second part of PEP session 2, participants applied what they learned to an individualized 10-minute role-play scenario with a SHP, created specifically for each participant based on self-reported difficulties with diabetes. Common topics for this scenario included struggles with adhering to a healthy diet, difficulties performing frequent finger sticks to monitor blood glucose, and overall frustration when trying to control blood sugar numbers. Research personnel observed these role-plays and led a debriefing afterward. PEP session 2 concluded with a group discussion about lessons learned from the role-plays and each participant worked with a member of the research staff to create an individualized action plan for both diabetes self-care and future medical encounters. All ideas for the action plan were participant generated, but research staff provided feedback on the feasibility of their goals and brought up potential barriers to those goals when participants were unable to identify any on their own.

Post-PEP Focus Group

Approximately 1 week after the completion of PEP session 2 all participants were invited to attend a focus group. The goals of focus group were to (1) collect the first set of follow-up questionnaires, (2) gather qualitative data on intervention, and (3) get feedback on each element of the PEP curriculum.

Follow-Up

After completion of the PEP intervention, participants will be followed up for 6 months and will complete repeat assessments at 1 week (T2), 3 months (T3), and 6 months (T4) after the PEP intervention (see Table 1). The T2 assessment will take place either at the beginning of the focus group, to avoid any bias introduced by discussing the PEP intervention again, or by telephone for any participants who do not come to the focus group. The T3 and T4 follow-ups will occur by telephone and any concurrent HbA_{1c} available at these times will be collected from the EMR.

Sample Size

Prior studies have pilot-tested interventions to increase patient activation and found that PAM scores increased by a range of 4-8 points [30,31]. This difference was statistically significant, is thought to be clinically significant, and translates to a moderate effect size, Cohen's d=0.48. Given the repeated-measures design of the study, setting alpha = .05 and beta = .2, and using the effect size calculated from the literature, the required sample size will be n=36 patients. It is our goal to have 40 participants complete the PEP intervention.

In anticipation of significant participant dropout over the course of the study, we aimed to enroll 40 patients from Bellevue Hospital Center, 20 from Gouverneur Health, and 20 from Woodhull Medical Center. From these patients, it was our goal that 20 from Bellevue Hospital Center and 10 each from Gouverneur Health and Woodhull Medical Center would complete the PEP intervention. Because of these concerns about dropout, all participants who were randomized to the immediate intervention group but unable to attend the PEP intervention at that time were contacted for the T1 assessment with the deferred intervention group and invited back to attend the PEP intervention as part of that group (see Figure 1).

Data Analysis

First, descriptive statistics including mean, standard deviation, range, skewness, and kurtosis for all continuous variables as well as frequencies for all categorical variables will be calculated at each time point (T0-T4). Because of concerns about the relatively small sample size and low literacy/health literacy, the normality of all continuous variables will be assessed both graphically with histograms as well as statistically using the Shapiro-Wilk and Kolmogorov-Smirnov tests, and

transformations will be made if necessary. Then we will assess for any baseline (T0) differences between two separate groups: (1) the randomly determined immediate intervention and deferred intervention groups and (2) all participants who attended the PEP intervention and those who did not. Both of these analyses will be conducted using chi-square test for categorical variables and either independent samples *t* test or Wilcoxon rank sum test for continuous variables.

Next, analyses will be conducted within each intervention group to evaluate for any effect of the PEP intervention on the primary, secondary, and exploratory outcomes using chi-square test for categorical variables (eg, PAM level, PCS) and either repeated-measures *t* test or Wilcoxon signed rank test for continuous variables (eg, PAM score, AURA, Krantz, SF-12v2 Health Survey, DSMQ, and HbA_{1c}). Initial assessment (T0) will be compared with each of the post-PEP assessments (T2-T4) for each variable. For the deferred intervention group, initial assessment (T0) will be compared with the assessment at the end of the waiting period (T1), which will then be compared with each post-PEP assessment (T2-T4).

After analyzing each group individually, the groups will be combined in order to have a larger sample size for pre- and post-PEP comparisons. Pre-PEP intervention data for these analyses will consist of data from enrollment (T0) for participants in the immediate intervention group and data collected at the end of the waiting period (T1) for participants in the deferred intervention group. Repeated-measures analyses will be conducted on the primary, secondary, and exploratory outcomes as described above and pre-PEP data (either T0 or T1) will be compared with each post-PEP assessment (T2-T3).

Finally, multivariate analyses will be conducted using a series of generalized mixed-effects models to determine what effect patient characteristics, group membership, and time have on each continuous outcome measure. In each model, the dependent variable will be the outcome measure (eg, PAM, AURA, Krantz, SF-12v2 Health Survey, DSMQ, and HbA_{1c}). Independent variables will include participant characteristics such as age, sex, race/ethnicity, education level, annual income, number of years with T2DM, and health literacy as measured by the NVS. Other independent variables will include group (immediate vs deferred intervention) and time (T0-T4).

Results

Recruitment for this study began in November 2014. As of June 2015, we met our enrollment goal of 80 patients. However, because of differences in site policies, the distribution of enrolled participants does not match our initial goals. By site, we have enrolled 40 participants from Bellevue Hospital Center, 31 from Gouverneur Health, and 9 from Woodhull Medical Center. As Woodhull Medical Center is located in a different part of New York City and serves a slightly different patient population, we plan to return to that site within the next few months to recruit an additional 11 patients.

Out of these 80 participants enrolled, the 71 from Bellevue Hospital Center and Gouverneur Health have been invited to attend the PEP intervention. Because of staff turnover and site-specific policies, we have as of yet been unable to hold any PEP intervention sessions at Woodhull Medical Center. Of the 71 participants invited to attend the PEP intervention, 45 have attended PEP session 1, 36 have attended the full PEP intervention, and 33 have returned for the post-PEP focus group. Of the 11 participants switched from the immediate intervention group to the deferred intervention group, 6 completed the T1 assessment and 3 attended at least one session of the PEP intervention. Coding and thematic analysis of the focus group discussions is not completed, but participants have reported that the PEP intervention was not only acceptable but a valuable experience that made them feel more empowered in their own health care. Several participants have even reported seeing their HCPs after completing the PEP intervention and changing their behaviors in the visit, which resulted in improvement in the quality of their visit.

Follow-up data collection is still underway and all patients who attended at least PEP session 1 will be called for all follow-up data points. Follow-up data collection is scheduled to conclude in April 2016 and the results of our data analysis are expected to be available by June 2016.

Discussion

Although there have been significant shifts in the power hierarchy between HCPs and patients, there continues to be an asymmetry that makes it difficult for patients to engage in true SDM as envisioned by the PCMH model. Little is understood about how to best activate patients to make the most of their visits with HCPs. With input from both patients and HCPs, we have developed an innovative PEP that seeks to prepare patients with T2DM to be better partners in their care and collaborate effectively with HCPs. We focused on improving patients' communication skills in the context of the medical encounter by discussing behavioral descriptors for activated patients and then using performance-based training, adapted from SP methodology, to develop these skills.

Study enrollment and implementation of the PEP intervention have been shown to be feasible across multiple hospital sites and acceptable to patients. Participants were able to engage in the skills development tasks and to self-reflect on their experiences with HCPs. Initial qualitative responses from participants were positive and collection of quantitative post-PEP data will conclude over the next few months, which will allow us to assess the effect of this intervention on patient activation and self-reported measures of diabetes care.

Conflicts of Interest

None declared.

Multimedia Appendix 1

CONSORT-EHEALTH checklist V1.6.2 [62].

[PDF File (Adobe PDF File), 182KB - resprot_v5i2e68_app1.pdf]

References

1. American DA. Economic costs of diabetes in the U.S. in 2012. Diabetes Care 2013 Apr;36(4):1033-1046 [FREE Full text] [doi: 10.2337/dc12-2625] [Medline: 23468086]
2. City University of New York Campaign Against Diabetes. 2007. Reversing the Diabetes and Obesity Epidemics in New York City URL: https://www.monroecollege.edu/uploadedFiles/_Site_Assets/PDF/diabetes_prevention_report.pdf [accessed 2016-04-06] [WebCite Cache ID 6gZWvaZmb]
3. Scholle SH, Torda P, Peikes D, Han E, Genevro J. Patient Centered Medical Home. Rockville, MD: Agency for Healthcare Research and Quality; 2010. Engaging Patients and Families in the Medical Home URL: https://pcmh.ahrq.gov/page/engaging-patients-and-families-medical-home [accessed 2016-04-06] [WebCite Cache ID 6gZWwptbo]
4. Committee on Quality of Healthcare in America. Crossing the Quality Chasm: A New Health System for the 21st Century. Washington (DC): National Academies Press (US); 2001. URL: https://www.nationalacademies.org/hmd/~/media/Files/Report%20Files/2001/Crossing-the-Quality-Chasm/Quality%20Chasm%202001%20%20report%20brief.pdf [WebCite Cache ID 6giUTtgNq]
5. IOM Executive Office. Partnering with Patients to Drive Shared Decisions, Better Value, and Care Improvement: Workshop Proceedings. 2013 Nov 11 Presented at: Building the Patient and Family Advisory Leadership Network for Better Care; 2013; Washington, DC p. 205 URL: http://www.nap.edu/ [WebCite Cache ID 6giUgTclz]
6. Davis K, Schoenbaum SC, Audet A. A 2020 vision of patient-centered primary care. J Gen Intern Med 2005 Oct;20(10):953-957 [FREE Full text] [doi: 10.1111/j.1525-1497.2005.0178.x] [Medline: 16191145]
7. Judson T, Detsky A, Press M. Encouraging Patients to Ask Questions: How to Overcome “White-Coat Silence. ” JAMA 2013;309(22):2325-2326. [Medline: 23757079]
8. Greenfield S, Kaplan S, Ware JE. Expanding patient involvement in care. Effects on patient outcomes. Ann Intern Med 1985 Apr;102(4):520-528. [Medline: 3977198]
9. Greenfield S, Kaplan SH, Ware JE, Yano EM, Frank HJ. Patients' participation in medical care: effects on blood sugar control and quality of life in diabetes. J Gen Intern Med 1988;3(5):448-457. [Medline: 3049968]
10. McDonald KM, Bryce CL, Graber ML. The patient is in: patient involvement strategies for diagnostic error mitigation. BMJ Qual Saf 2013 Oct;22 Suppl 2:ii33-ii39 [FREE Full text] [doi: 10.1136/bmjqs-2012-001623] [Medline: 23893394]
11. Elwyn G, Scholl I, Tietbohl C. “Many miles to go …”: a systematic review of the implementation of patient decision support interventions into routine clinical practice. BMC Med Inform Decis Mak 2013;13(Suppl 2):S14. [Medline: 24625083]
12. Anderson RM, Funnell MM. Negotiating behavior changes with patients who have diabetes: negotiation or coercion? Diabetes Management 2012 Jan;2(1):41-46. [doi: 10.2217/dmt.11.65]
13. Frosch DL, May SG, Rendle Katharine A S, Tietbohl C, Elwyn G. Authoritarian physicians and patients' fear of being labeled 'difficult' among key obstacles to shared decision making. Health Aff (Millwood) 2012 May;31(5):1030-1038 [FREE Full text] [doi: 10.1377/hlthaff.2011.0576] [Medline: 22566443]
14. Schouten BC, Meeuwesen L. Cultural differences in medical communication: a review of the literature. Patient Educ Couns 2006 Dec;64(1-3):21-34. [doi: 10.1016/j.pec.2005.11.014] [Medline: 16427760]
15. Joseph-Williams N, Elwyn G, Edwards A. Knowledge is not power for patients: a systematic review and thematic synthesis of patient-reported barriers and facilitators to shared decision making. Patient Educ Couns 2014 Mar;94(3):291-309. [doi: 10.1016/j.pec.2013.10.031] [Medline: 24305642]
16. Peek ME, Odoms-Young A, Quinn MT, Gorawara-Bhat R, Wilson SC, Chin MH. Race and shared decision-making: perspectives of African-Americans with diabetes. Soc Sci Med 2010 Jul;71(1):1-9 [FREE Full text] [doi: 10.1016/j.socscimed.2010.03.014] [Medline: 20409625]
17. Peek ME, Wilson SC, Gorawara-Bhat R, Odoms-Young A, Quinn MT, Chin MH. Barriers and facilitators to shared decision-making among African-Americans with diabetes. J Gen Intern Med 2009 Oct;24(10):1135-1139 [FREE Full text] [doi: 10.1007/s11606-009-1047-0] [Medline: 19578818]
18. Protheroe J, Brooks H, Chew-Graham C, Gardner C, Rogers A. 'Permission to participate?' A qualitative study of participation in patients from differing socio-economic backgrounds. J Health Psychol 2013 Aug;18(8):1046-1055. [doi: 10.1177/1359105312459876] [Medline: 23104997]
19. Willems S, De MS, Deveugele M, Derese A, De MJ. Socio-economic status of the patient and doctor-patient communication: does it make a difference? Patient Educ Couns 2005 Feb;56(2):139-146. [doi: 10.1016/j.pec.2004.02.011] [Medline: 15653242]
20. Alexander JA, Hearld LR, Mittler JN, Harvey J. Patient-physician role relationships and patient activation among individuals with chronic illness. Health Serv Res 2012 Jun;47(3 Pt 1):1201-1223 [FREE Full text] [doi: 10.1111/j.1475-6773.2011.01354.x] [Medline: 22098418]

21. Légaré F, Ratté S, Gravel K, Graham ID. Barriers and facilitators to implementing shared decision-making in clinical practice: update of a systematic review of health professionals' perceptions. Patient Educ Couns 2008 Dec;73(3):526-535. [doi: 10.1016/j.pec.2008.07.018] [Medline: 18752915]
22. Hibbard JH, Stockard J, Mahoney ER, Tusler M. Development of the Patient Activation Measure (PAM): conceptualizing and measuring activation in patients and consumers. Health Serv Res 2004 Aug;39(4 Pt 1):1005-1026 [FREE Full text] [doi: 10.1111/j.1475-6773.2004.00269.x] [Medline: 15230939]
23. Hibbard JH, Mahoney ER, Stockard J, Tusler M. Development and testing of a short form of the patient activation measure. Health Serv Res 2005 Dec;40(6 Pt 1):1918-1930 [FREE Full text] [doi: 10.1111/j.1475-6773.2005.00438.x] [Medline: 16336556]
24. Mosen DM, Schmittdiel J, Hibbard J, Sobel D, Remmers C, Bellows J. Is patient activation associated with outcomes of care for adults with chronic conditions? J Ambul Care Manage 2007 Mar;30(1):21-29. [Medline: 17170635]
25. Harvey L, Fowles JB, Xi M, Terry P. When activation changes, what else changes? the relationship between change in patient activation measure (PAM) and employees' health status and health behaviors. Patient Educ Couns 2012 Aug;88(2):338-343. [doi: 10.1016/j.pec.2012.02.005] [Medline: 22459636]
26. Greene J, Hibbard JH. Why does patient activation matter? An examination of the relationships between patient activation and health-related outcomes. J Gen Intern Med 2012 May;27(5):520-526 [FREE Full text] [doi: 10.1007/s11606-011-1931-2] [Medline: 22127797]
27. Hibbard JH, Mahoney ER, Stock R, Tusler M. Do increases in patient activation result in improved self-management behaviors? Health Serv Res 2007 Aug;42(4):1443-1463 [FREE Full text] [doi: 10.1111/j.1475-6773.2006.00669.x] [Medline: 17610432]
28. Rask KJ, Ziemer DC, Kohler SA, Hawley JN, Arinde FJ, Barnes CS. Patient activation is associated with healthy behaviors and ease in managing diabetes in an indigent population. Diabetes Educ 2009;35(4):622-630. [doi: 10.1177/0145721709335004] [Medline: 19419972]
29. Shively MJ, Gardetto NJ, Kodiath MF, Kelly A, Smith TL, Stepnowsky C, et al. Effect of patient activation on self-management in patients with heart failure. J Cardiovasc Nurs 2013;28(1):20-34. [doi: 10.1097/JCN.0b013e318239f9f9] [Medline: 22343209]
30. Hibbard JH, Greene J, Tusler M. Improving the outcomes of disease management by tailoring care to the patient's level of activation. Am J Manag Care 2009 Jun;15(6):353-360 [FREE Full text] [Medline: 19514801]
31. Deen D, Lu W, Rothstein D, Santana L, Gold MR. Asking questions: the effect of a brief intervention in community health centers on patient activation. Patient Educ Couns 2011 Aug;84(2):257-260. [doi: 10.1016/j.pec.2010.07.026] [Medline: 20800414]
32. Maranda MJ, Deen D, Elshafey S, Herrera M, Gold MR. Response to a patient activation intervention among Spanish-speaking patients at a community health center in New York City. J Health Care Poor Underserved 2014 May;25(2):591-604. [doi: 10.1353/hpu.2014.0110] [Medline: 24858870]
33. Barrows HS. An overview of the uses of standardized patients for teaching and evaluating clinical skills. AAMC. Acad Med 1993 Jun;68(6):443-51; discussion 451. [Medline: 8507309]
34. Stillman PL, Regan MB, Philbin M, Haley HL. Results of a survey on the use of standardized patients to teach and evaluate clinical skills. Acad Med 1990 May;65(5):288-292. [Medline: 2337429]
35. Tamblyn R, Abrahamowicz M, Dauphinee D, Wenghofer E, Jacques A, Klass D, et al. Physician scores on a national clinical skills examination as predictors of complaints to medical regulatory authorities. JAMA 2007 Sep 5;298(9):993-1001. [doi: 10.1001/jama.298.9.993] [Medline: 17785644]
36. Klass D, De CA, Fletcher E, King A, Macmillan M. Development of a performance-based test of clinical skills for the United States Medical Licensing Examination. Federation Bulletin 1998;85(3):177-185.
37. Grand'Maison P, Lescop J, Rainsberry P, Brailovsky CA. Large-scale use of an objective, structured clinical examination for licensing family physicians. CMAJ 1992 May 15;146(10):1735-1740 [FREE Full text] [Medline: 1596809]
38. Plaksin J, Nicholson J, Kundrod S, Zabar S, Kalet A, Altshuler L. The Benefits and Risks of Being a Standardized Patient: A Narrative Review of the Literature. Patient 2016 Feb;9(1):15-25. [doi: 10.1007/s40271-015-0127-y] [Medline: 26002043]
39. Woodward CA, Gliva-McConvey G. The effect of simulating on standardized patients. Acad Med 1995 May;70(5):418-420. [Medline: 7748389]
40. Wallach PM, Elnick M, Bognar B, Kovach R, Papadakis M, Zucker S, et al. Standardized patients' perceptions about their own health care. Teach Learn Med 2001;13(4):227-231. [doi: 10.1207/S15328015TLM1304_03] [Medline: 11727388]
41. Gillespie C, Bruno JH, Kalet A. What standardised patients tell us about 'activating' patients. Med Educ 2009 Nov;43(11):1112-1113. [doi: 10.1111/j.1365-2923.2009.03502.x] [Medline: 19874523]
42. Boerjan M, Boone F, Anthierens S, van WE, Deveugele M. The impact of repeated simulation on health and healthcare perceptions of simulated patients. Patient Educ Couns 2008 Oct;73(1):22-27. [doi: 10.1016/j.pec.2008.05.028] [Medline: 18650054]
43. Bokken L, van DJ, Rethans J. The impact of simulation on people who act as simulated patients: a focus group study. Med Educ 2006 Aug;40(8):781-786. [doi: 10.1111/j.1365-2929.2006.02529.x] [Medline: 16869924]

44. Wagenschutz H, Ross PT, Bernat CK, Lypson ML. Impact of repeated health behavior counseling on women portraying an overweight standardized patient. J Nutr Educ Behav 2013;45(5):466-470. [doi: 10.1016/j.jneb.2013.01.011] [Medline: 23466127]
45. Triviño X, Ferrer L, Bernales M, Cianelli R, Moore P, Peragallo N. Effect of emotionally complex roles on HIV-related simulated patients. Hisp Health Care Int 2013;11(2):72-77. [doi: 10.1891/1540-4153.11.2.72] [Medline: 24830729]
46. Gillespie C, Adams J, Hanley K, Wagner E, Shaker-Brown A, Naidu M, et al. 'We might as well be speaking different languages': an innovative interprofessional education tool to teach and assess communication skills critical to patient safety. BMJ STEL 2015 Aug 25;1(2):54-60. [doi: 10.1136/bmjstel-2014-000014]
47. Lifchez SD, Cooney CM, Redett RJ. The Standardized Professional Encounter: A New Model to Assess Professionalism and Communication Skills. J Grad Med Educ 2015 Jun;7(2):230-233. [doi: 10.4300/JGME-D-14-00275.1] [Medline: 26221440]
48. Aeder L, Altshuler L, Kachur E, Langenau E. MedEdPORTAL Publications. 2012 May 2. Fostering an Atmosphere of Professionalism in a Residency Program: Learning How to Address the Unprofessional Behavior of Colleagues Through OSCEs URL: https://www.mededportal.org/publication/9168 [accessed 2016-04-07] [WebCite Cache ID 6gaS5zArR]
49. Coleman EA. Extending simulation learning experiences to patients with chronic health conditions. JAMA 2014 Jan 15;311(3):243-244. [doi: 10.1001/jama.2013.283057] [Medline: 24343769]
50. Diabetes Care and Education. Patient Education Handouts URL: http://www.dce.org/publications/education-handouts/ [accessed 2016-04-05] [WebCite Cache ID 6ggh6zsKj]
51. Powers BJ, Trinh JV, Bosworth HB. Can this patient read and understand written health information? JAMA 2010 Jul 7;304(1):76-84. [doi: 10.1001/jama.2010.896] [Medline: 20606152]
52. PR Newswire. 2005 Dec 6. University of Arizona Researcher Develops New Tool for Rapid Assessment of Health Literacy Skills URL: http://www.prnewswire.com/news-releases/university-of-arizona-researcher-develops-new-tool-for-rapid-assessment-of-health-literacy-skills-55364172.html [accessed 2016-04-06] [WebCite Cache ID 6gZZrlCK8]
53. Weiss BD, Mays MZ, Martz W, Castro KM, DeWalt DA, Pignone MP, et al. Quick assessment of literacy in primary care: the newest vital sign. Ann Fam Med 2005;3(6):514-522 [FREE Full text] [doi: 10.1370/afm.405] [Medline: 16338915]
54. Clayman ML, Pandit AU, Bergeron AR, Cameron KA, Ross E, Wolf MS. Ask, understand, remember: a brief measure of patient communication self-efficacy within clinical encounters. J Health Commun 2010;15 Suppl 2:72-79 [FREE Full text] [doi: 10.1080/10810730.2010.500349] [Medline: 20845194]
55. Krantz DS, Baum A, Wideman MV. Assessment of Preferences for self-treatment and information in health care. J Pers Soc Psychol 1980 Nov;39(5):977-990. [Medline: 7441487]
56. Degner LF, Kristjanson LJ, Bowman D, Sloan JA, Carriere KC, O'Neil J, et al. Information needs and decisional preferences in women with breast cancer. JAMA 1997 May 14;277(18):1485-1492. [Medline: 9145723]
57. Schmitt A, Gahr A, Hermanns N, Kulzer B, Huber J, Haak T. The Diabetes Self-Management Questionnaire (DSMQ): development and evaluation of an instrument to assess diabetes self-care activities associated with glycaemic control. Health Qual Life Outcomes 2013;11:138 [FREE Full text] [doi: 10.1186/1477-7525-11-138] [Medline: 23937988]
58. Cheak-Zamora NC, Wyrwich KW, McBride TD. Reliability and validity of the SF-12v2 in the medical expenditure panel survey. Qual Life Res 2009 Aug;18(6):727-735. [doi: 10.1007/s11136-009-9483-1] [Medline: 19424821]
59. Saha S, Beach MC. The impact of patient-centered communication on patients' decision making and evaluations of physicians: a randomized study using video vignettes. Patient Educ Couns 2011 Sep;84(3):386-392 [FREE Full text] [doi: 10.1016/j.pec.2011.04.023] [Medline: 21600723]
60. Plaksin J, Kundrod S, Hu H. Patient-Reported Barriers to Shared Decision-Making (SDM): Targets for Behavioral Intervention. 2015 Apr 22 Presented at: Society for General Internal Medicine (SGIM) 38th Annual Meeting; April 22, 2015; Toronto, ON, Canada.
61. Kundrod S, Plaksin J, Wallach A, Zabar S, Altshuler L, Kalet A. Barriers to Patient EmpowermentShared Decision-Making (SDM): Healthcare Provider (HCP) Perspectives. 2015 Apr 22 Presented at: Society for General Internal Medicine (SGIM) 38th Annual Meeting; April 22, 2014; Toronot, ON, Canada.
62. Eysenbach G, Consort- E. CONSORT-EHEALTH: improving and standardizing evaluation reports of Web-based and mobile health interventions. J Med Internet Res 2011;13(4):e126 [FREE Full text] [doi: 10.2196/jmir.1923] [Medline: 22209829]

Abbreviations

AURA: Ask, Understand, Remember Assessment
DSMQ: Diabetes Self-Management Questionnaire
EMR: electronic medical record
HbA1c: hemoglobin A1c
HCP: health care provider
Krantz: Krantz Health Opinion Survey

NVS: Newest Vital Sign
PAM: Patient Activation Measure
PCMH: patient-centered medical home
PCS: Preference Control Scale
PEP: Patient Empowerment Program
RA: research assistant
SDM: shared decision-making
SHP: standardized health care provider
SP: standardized patient
T2DM: type 2 diabetes mellitus

Edited by G Eysenbach; submitted 30.11.15; peer-reviewed by E Ross, J Gee; comments to author 20.01.16; accepted 09.02.16; published 21.04.16.

Please cite as:
Altshuler L, Plaksin J, Zabar S, Wallach A, Sawicki C, Kundrod S, Kalet A
Transforming the Patient Role to Achieve Better Outcomes Through a Patient Empowerment Program: A Randomized Wait-List Control Trial Protocol
JMIR Res Protoc 2016;5(2):e68
URL: http://www.researchprotocols.org/2016/2/e68/
doi:10.2196/resprot.5376
PMID:27103306

Protocol

A Guided Workbook Intervention (WorkPlan) to Support Work-Related Goals Among Cancer Survivors: Protocol of a Feasibility Randomized Controlled Trial

Pernille Luxhøj Woods[1], MSci; Lauren Schumacher[1], MSc; Steven S Sadhra[2], BSc, PhD; Andrew J Sutton[3], PhD; Anjali Zarkar[4], MD, MRCP, FRCR; Pauline Rolf[1], BA, MA, PGCE; Elizabeth A Grunfeld[1], BSc, MSc, PhD

[1]Coventry University, Centre for Technology Enabled Health Research, Coventry, United Kingdom

[2]University of Birmingham, Occupational and Environmental Medicine, Institute of Clinical Sciences, Birmingham, United Kingdom

[3]University of Leeds, Leeds Institute of Health Sciences, Leeds, United Kingdom

[4]University Hospitals Birmingham National Health Service Foundation Trust, Oncology, Queen Elizabeth Hospital, Birmingham, United Kingdom

Corresponding Author:
Elizabeth A Grunfeld, BSc, MSc, PhD
Coventry University
Centre for Technology Enabled Health Research
Richard Crossman Building (4th Floor)
Priory Street
Coventry,
United Kingdom
Phone: 44 247 765 9968
Fax: 44 247 765 5840
Email: beth.grunfeld@coventry.ac.uk

Abstract

Background: Returning to and staying at work following illness is associated with better physical and psychological functioning. Not working has been shown to be associated with reduced self-esteem, lowered self-efficacy, and decreased belief in one's ability to return to the workplace. Although there is a growing body of research looking at what predicts return to work following cancer treatment, there are fewer studies examining interventions targeting return to work.

Objective: The primary objective is to assess the feasibility and acceptability of a theoretically led workbook intervention designed to support cancer patients in returning to work to inform a fully powered randomized controlled trial (RCT).

Methods: This is a multicenter feasibility RCT where the main analysis uses a qualitative approach. Sixty participants (aged 18-65 years) who have received a diagnosis of cancer and who intend to return to work will be randomized to either the WorkPlan intervention group or a usual care group (ratio 1:1). Participants in the intervention group will receive a guided workbook intervention (which contains activities aimed at eliciting thoughts and beliefs, identifying targets and actions, and concrete steps to achieve goals) and will receive telephone support over a 4-week period. The primary outcome measure is time taken to return to work (in days), and secondary outcome measures include mood, quality of life, illness perceptions, and job satisfaction. Data will be collected through postal questionnaires administered immediately postintervention and at 6- and 12-month follow-ups. In addition, interviews will be undertaken immediately postintervention (to explore acceptability of the intervention and materials) and at 12-month follow-up (to explore perceptions of participation in the trial and experiences of returning to work).

Results: Enrollment for the study will be completed in May 2016. Data analysis will commence in April 2017, and the first results are expected to be submitted for publication in late 2017.

Conclusions: Currently no standardized return-to-work intervention based on targeting cancer patient beliefs is in existence. If the intervention is shown to be feasible and acceptable, the results of this study will inform a future full RCT with the potential to provide a valuable and cost-efficient tool in supporting cancer survivors in the return-to-work process.

Trial Registration: International Standard Randomized Controlled Trial Number (ISRCTN): ISRCTN56342476; http://www.isrctn.com/ISRCTN56342476 (Archived by WebCite at http://www.webcitation.org/6gblhEPXd).

(JMIR Res Protoc 2016;5(2):e75) doi:10.2196/resprot.5300

KEYWORDS

oncology; cancer; return to work; intervention; protocol; RCT

Introduction

Overview

Returning to and staying in work following illness is associated with better physical and psychological functioning. Not working has been shown to be associated with reduced self-esteem, lowered self-efficacy, and decreased belief in one's ability to return to the workplace [1]. Employment is important not only for individual and societal economic reasons [2] but because being out of work is thought to cause, contribute to, and aggravate adverse health outcomes [3,4]. Furthermore, work is an important component of quality of life [5]. The relationship between unemployment and negative health outcomes is thought to be mediated by factors such as socioeconomic status, financial anxiety, and a stress pathway involving physical changes including hypertension and lowered immunity [6,7]. Although there is a growing body of research looking at what predicts return to work (most commonly defined as returning to work quicker and improved self-reported ability to undertake one's role, or workability) following cancer treatment, there are fewer studies examining interventions targeting return to work.

Over 100,000 people of working age receive a diagnosis of cancer each year in the United Kingdom [8]. Earlier diagnosis and improvements in treatment survival rates have led to an increase in the number of cancer survivors. UK policy reviews have highlighted a need for more research into the challenges of living with cancer [9,10]. For many cancer survivors returning to work is a realistic outcome. Many patients do well following treatment; however, some experience ongoing negative outcomes from the disease or treatment (including pain, fatigue, and low mood) that may impact everyday functioning, including work [11]. Over a quarter of cancer survivors report high symptom burden one year post-diagnosis, even after treatment termination [12]. In addition, many cancer survivors still undergo some form of treatment/monitoring for substantial periods of time following termination of active treatment. Return to work rates of between 23% and 75% have been reported [13], and cancer patients are 1.4 times more likely to be unemployed than healthy individuals [4]. Furthermore, return-to-work rates have been shown to vary across cancer types [14], and longer return to work times have been reported among patients undergoing certain treatments (surgery/chemotherapy) [15], experiencing fatigue [16], or reporting a nonsupportive work environment [17]. Although some cancer types have a high return-to-work rate, we know that across cancer types we see a significant proportion of patients return to work too early or in an inappropriate manner, which results in them taking additional sick leave or leaving the workplace [16]. In addition, a large proportion of cancer patients report modifications in working hours, wages, and work patterns as well as reporting perceived reductions in workability [13]. Cancer survivors have been shown to have similar work-disability levels to those reported in other chronic conditions (eg, stroke, diabetes, heart disease, arthritis) but significantly higher work-disability levels when compared with age-matched adults with no reported chronic condition [18]. This supports the finding that cancer survivors often report difficulties in achieving productivity levels similar to healthy counterparts [19].

Predictors of longer time to return to work include a range of disease and treatment, work-related and psychological factors [20]. The relative role of each of these factors is difficult to determine because few studies directly compare these factors or they focus on either a single cancer type or a mixed-cancer sample. However, a recent study [14] examined these factors across four distinct cancer types and identified that, in addition to optimal symptom management and appropriate workplace adaptations, specific cancer (ie, beliefs about the consequences of cancer) and treatment-related (ie, beliefs about controlling the effects of cancer at work) perceptions predicted return to work.

Cancer patients have reported apprehensions about returning to work related to concerns about ongoing treatments and their level of physical fitness [21]. In addition, depressive symptoms are associated with reduced return-to-work rates, and partial or full resumption of work may help alleviate depressive symptoms by challenging dysfunctional beliefs [22]. Research from noncancer disease groups also supports the importance of psychological factors in the return to work process. Among patients diagnosed with coronary heart disease, depression has been shown to impact functional recovery and predict failure or delay in returning to work [23,24]. Perceptions of illness [25,26,27] and work-related disability (independent of physician report of disability) [28] are also predictive of reemployment and occupational functioning.

In the field of cancer, a number of intervention and trial protocols have been published. Such interventions include a 12-week occupational physician-led intervention focused on increasing physical activity in cancer survivors to support return to work [29]; a case management approach focusing on signposting/referring patients to services (eg, physiotherapy and occupational or psychological therapy) that may support return to work [30]; and a tool that cancer survivors use to guide discussions about working [31]. Although this tool was initially well received, it focused on guiding questions during interactions with employers and healthcare professionals and not on beliefs and barriers that impact workability and work behavior. A recent Cochrane systematic review identified the need for more high-quality randomized controlled trials (RCTs) to enhance return to work among cancer patients [32]. Last, a recent metasynthesis of qualitative research studies highlighted the need for vocational interventions with cancer patients to be person-centred and for such interventions to acknowledge the role of social, clinical, and work-related factors [33].

Current Study

Feasibility studies are conducted before a main study and are used to estimate key parameters to support the design of a full RCT [34]. This feasibility randomized controlled study will trial and evaluate the WorkPlan guided workbook intervention, a theoretically led intervention aimed at targeting known

psychological factors to improve work-related outcomes among cancer survivors. The primary objective of the study is to trial the workbook intervention and data collection materials to ensure that the materials are acceptable to participants and that participants are able to provide full answers. This objective will be met through five aims.

In aim 1, data collection materials will be trialed to ensure that the materials are acceptable to participants. We will identify whether the materials are acceptable to participants and whether participants understand and are able to complete the required tasks.

In aim 2, the recruitment process and feasibility of recruiting participants into the study will be tested. We will observe whether we are able to meet the required monthly recruitment targets, identify which methods of recruitment are most successful in attracting participants into the study, and determine if changes could be made to future studies to improve recruitment.

In aim 3, we will test the acceptability of the randomization process among participants. As part of the final interview process we will discuss the randomization process with participants to determine the level of understanding and satisfaction with the information provided.

In aim 4, we will determine retention in control and intervention groups to the 12-month follow-up. Where possible we will determine reasons for attrition in both arms.

In aim 5, we will conduct the groundwork necessary to obtain data that will be required in the definitive trial to enable a full cost-effectiveness analysis. Measures to be used in a full trial will be administered for acceptability.

The study is registered with the UK Clinical Research Network (UKCRN ID: 19013) and the International Standard Randomized Controlled Trial Number registry [ISRCTN: 56342476]. The protocol version is 4.1, date 11.11.2015. The recruitment status is open (participants are currently being recruited and enrolled into the study).

Methods

Eligibility Criteria

Inclusion criteria: patients who have received a diagnosis of breast, gynecological, urological, or bowel cancer that has not been classified as metastatic disease or recurrence; are at least 2 weeks posttreatment initiation; are aged 18 to 65 years; were working at the time of diagnosis; and are not currently working but intend to return to work.

Participants will be recruited to the study from multiple UK hospital sites. We aim to recruit 60 participants who will be randomized into either the intervention or the usual care group. There are currently no clear guidelines for estimating an appropriate sample size for feasibility studies. This is not a hypothesis testing study; the sample size is based on pragmatic assumptions around feasible recruitment figures and the number of participants required to estimate the key parameters around the feasibility of a full RCT.

WorkPlan Intervention

The WorkPlan package is theoretically led and based around the self-regulation model [35] and goal setting theory [36], which have been applied previously in return-to-work interventions. WorkPlan was developed around an intervention mapping methodology used for designing and implementing complex interventions or programs (interventions that comprise a number of separate elements essential to the functioning of the intervention as a whole). WorkPlan is delivered as a 4-week guided workbook intervention consisting of structured sections and activities to provide guidance and support to patients. The workbook is broken down into 4 chapters that participants are encouraged to work through in turn during each week of the intervention period. The workbook comprises activities aimed at eliciting thoughts/beliefs, identifying targets/actions, and adopting concrete steps to achieve goals. Participants incorporate all elements from the workbook into a personal "return-to-work" plan which they are encouraged to create in the fourth and final week. A resources section is included to signpost participants toward relevant avenues of further support. Multiple copies of the return-to-work planning page will be available to encourage changes to be made when necessary, and these plans can be used as a tool when meeting with employers to aid discussion around returning to work. An intervention manual has also been developed to be used by the researchers during the delivery of the intervention.

Intervention Group

Patients in the intervention group will be guided through the initial exercises and given a detailed overview of the workbook. They will be encouraged to discuss the workbook with their partner, family, or friends. Telephone support calls will be made by the researchers at 2 and 4 weeks during the intervention period to discuss progress. The workbook is used during the introductory session, at home during the intervention period, and as a reminder during the return to work process.

Usual Care Group

Participants will receive usual care which focuses on clinical care and optimal symptom management and will be offered the workbook at the end of the study. In order to prevent participants from undertaking activities in the workbook, the following precautions have been included in the design: (1) the information sheets and prerandomization discussion do not include the content or focus of the intervention and (2) the workbook will not be made available until the participant's 12-month follow-up.

Participants in either group may access other information and support relating to work posttreatment but will be asked to record any resources or information they receive or access during the trial.

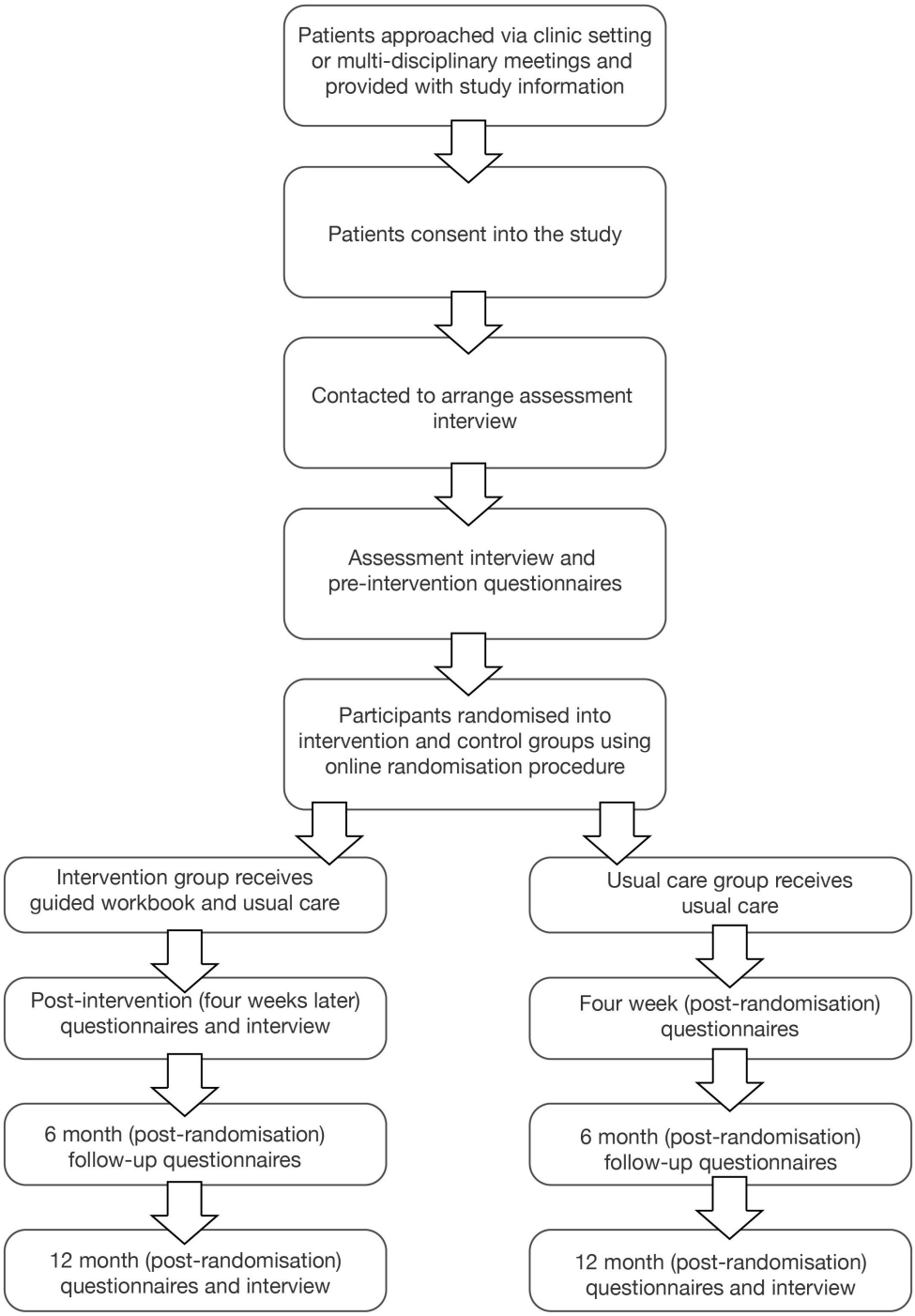
Procedure

Participants will be recruited when they are at least 2 weeks posttreatment initiation (Figure 1). Patients will be identified through breast, gynecological, colorectal, or urological cancer clinics; through multidisciplinary team meetings; and by placing posters in clinics, chemotherapy suites, and computerized tomography scan waiting areas. Clinicians will have leaflets and information packs outlining the study and providing contact

details available for patients. Study materials have been translated into the five most commonly spoken languages among people of working age in Birmingham (2011 Census): Bengali, Chinese (standard), Polish, Punjabi, and Urdu. Interpreters will be provided if required.

Potential participants will be provided with contact details and asked to contact one of the researchers by telephone or email. Details for the project website will also be displayed on the leaflets and posters, where potential participants can access further information about the study. Patients who express interest in the study will be provided with an information sheet and eligibility screening questionnaire. Eligible participants will be sent an invitation to be interviewed at the hospital or over the telephone; a researcher will outline the study and randomization process, explain the patient information sheet, and obtain written consent (if explained via telephone, researchers will obtain verbal consent after explaining the study and will ask participants to return a written consent form by postal mail). If participants provide additional consent, the researchers will inform their general practitioner about participation in the study. Participants will receive £20 when they complete the assessment interview to cover time and travel expenses.

Figure 1. Study flowchart showing allocation to groups.



Allocation and Stratification

The researchers will randomize participants into one of the two arms using a central online and text system, Sealed Envelope (Sealed Envelope Ltd), at a ratio of 1:1 between the intervention group and usual care group. During the randomization process, participants will be stratified by age (18-50 or 51-65 years) and cancer type (breast, bowel, gynecological, or urological). Patients with different cancer diagnoses may have specific impairments or side effects due to the location of the cancer or the treatments received. Hence, stratifying for cancer type balances out any effects that might be due to this variable. Treatments undertaken during the follow-up period will be monitored in both arms of the trial. Participants are informed about their group allocation (guided intervention or usual care), and participants allocated to the usual care group will be informed that they will be offered the workbook after the 12-month follow-up.

Blinding

The researchers will be aware of group allocation at randomization and during follow-up in order to provide telephone support to participants in the intervention group. However, the principal investigator will be blind to participant group allocation to reduce bias when analyzing data.

Data Collection

Study Outcomes

The main outcome measures of a full RCT will be used (eg, number of days to return to work and satisfaction with the return-to-work process). At each time point, participants will be asked to recall the date of return to work (paid or unpaid employment, different job, reduced hours/salary, full-time or part-time). Any changes in working status and duties will be documented as will specific reasons for nonreturn to work (eg, unavailability of job, ongoing medical concerns) to determine whether to incorporate specific reasons for nonreturn as measures in a full trial. Secondary outcome measures include mood, satisfaction with return to work, and satisfaction with the return-to-work process. Although not appropriate for a feasibility trial, we would aim to undertake subgroup analysis of the primary outcome measure by cancer type/site in a future definitive RCT.

Data will be collected at 4 time points during the study: baseline, 4 weeks (postintervention), and 6- and 12-month follow-ups. At each time point participants will complete the following questionnaires:

- Illness Perceptions Questionnaire-Revised [37]
- Brief Illness Perception at Work Scale [38]
- Hospital Anxiety and Depression Scale [39]
- Work Ability Index [40]
- Satisfaction with return to work if returned to work (single item)
- Satisfaction with Work Scale [41] (if returned to work)
- EQ-5D-5L (Quality of Life) [42]
- Visual Analogue Scale measure of Quality of Life (single item) [43]

Questionnaire packs will be mailed to participants with a prepaid self-addressed envelope. In addition, participants will be asked to provide details of their use of services and information via text message. A maximum of 4 text messages will be sent to participants at the end of each month for the duration of the study to gather information on their current work status and healthcare utilization. Monthly intervals were chosen because research shows that memory of general practitioner appointments is around 4 weeks, so we could not rely on accurate recall of healthcare utilization at 6-month follow-ups [44,45]. The text-based service can also be used for reminders to participants to complete and return questionnaire packs if there is missing data.

Interviews

Twenty participants from the intervention group will be interviewed postintervention and 12 months postrandomization, and 20 participants from the usual care group will be interviewed 12 months postrandomization. Participants will be asked to participate sequentially until the recruitment target is reached. Interviews will be conducted over the telephone or face to face, depending on the participant's preference. The postintervention interview will focus on gaining perceptions of (1) how the intervention was delivered; (2) aspects of the intervention individuals found useful; and (3) compliance with the intervention, how aspects of the intervention were used, and recommendations for change. The 12-month interview will explore (1) experiences of the randomization process, (2) general perceptions of the trial, and (3) the personal return-to-work process of each individual. Members of both groups will be asked about their experiences and how this may have impacted their return to work as well as any additional support received regarding return to work.

Data Management

To maintain confidentiality, all participants will be given a unique identifier that will be used on all hard copy and database records. Patient names will not be used. Clinical and research government guidelines will be followed for safe and confidential storage of participant personal data (such as password-protected data files), to which only the research team directly involved in the study will have access. If a participant withdraws from the study, identifiable data which has already been collected with consent would be retained and used in the study, but no further data would be collected from the participant.

Analysis Plan

Qualitative Analysis

Although this is a mixed-methods study, the main focus of the analysis of the study will be qualitative. Interviews will be recorded, transcribed verbatim, and analyzed using the framework method [46] to identify emergent themes.

Quantitative Analysis

The purpose of this feasibility study is not hypothesis testing. Furthermore, it is anticipated that the sample size will be underpowered to undertake the full analysis that would be used in a full trial (analysis of covariance adjusting for baseline values). Baseline characteristics will be reported as mean and

standard deviations or medians and interquartile ranges for continuous data and as n (%) for categorical data. Differences between the intervention and control groups for the primary outcome measure will be examined. Secondary outcome measures will be assessed using independent samples *t* tests (significance level set at .05).

Economic Analysis

Although an economic evaluation is not suitable in the context of a feasibility trial, we will undertake a descriptive economic analysis focusing on the resource usage of the intervention (intervention materials, time, follow-ups/support), self-reported indirect costs including paid sick days/unemployment benefits, and healthcare utilization. The EQ-5D-5L will be used to inform the changes in quality of life over time, and these can contribute to the calculation of quality-adjusted life years in a full economic evaluation.

Data Monitoring

This is a feasibility trial, so a data monitoring committee will not be convened. However, the project steering committee will review safety and efficacy data throughout the trial. Personal data will be accessed by the research team only and will be stored for 12 months after the study has ended and then moved to a secure archiving facility for 5 years.

Ethics

Ethical approval for this study has been obtained from West Midlands–Solihull (National Research Ethics Service) Research Ethics Committee (Reference: 15/WM/0166). The principal investigator will communicate any amendments to protocol to members of the research team, who will inform trial participants by postal mail if relevant.

Harms

Because the trial focuses on a workbook-based intervention aimed at promoting return to work, we do not envisage any adverse events or a need to stop the trial prematurely. It is unlikely that the intervention would cause distress, although participants may experience distress while discussing their work in the context of having experienced cancer. Procedures will be in place for participants to access psychological support services if required.

Dissemination Policy

Results from the study will be reported and disseminated through publication in peer-reviewed scientific journals and presentations at relevant conferences. A lay summary of the findings of the study will be mailed or emailed to the participants if they express interest.

Results

The project was funded in March 2015, and enrollment will be completed in May 2016. Data analysis will commence in April 2017, and the first results are expected to be submitted for publication in late 2017.

Discussion

Principle Considerations

There is currently no available standardized return-to-work intervention focused on targeting cancer patient beliefs. Previous research [47,48] has demonstrated that both cancer patients and organizations report that such an intervention would be invaluable to facilitate return to work and ensure work retention. Undertaking a feasibility study is critical to inform the planning of a larger, fully powered RCT to improve work-related outcomes among cancer survivors. The results of the study will be used to modify the trial materials and methodology if required and determine likely recruitment and retention rates for a larger trial. If appropriate, the results of the feasibility study will be used to estimate a sample size calculation for a future (appropriately powered) RCT of the intervention with a longer follow-up period. If a fully powered RCT were to demonstrate that the WorkPlan intervention is more effective in supporting return to work than usual care, this would allow us to implement a valuable, cost-efficient tool to support people who have received a diagnosis of cancer in planning and achieving supported return to work as well as greater satisfaction with work and the return-to-work process.

Methodological Considerations

One strength of this study is that it uses a theoretically based intervention. The study follows the best practice guidelines set out by the Medical Research Council, the UK national funding agency, in the development and evaluation of complex interventions [49] and published recommendations for pilot studies [50-53]. The intervention package was developed in several stages. A review of the literature identified that few studies focusing on return to work had targeted participant beliefs and yet the role of beliefs in the performance of numerous behaviors, including return to work, has previously been documented [54,55]. A prospective questionnaire study was developed and administered to identify which clinical, work-related, and psychological variables influence the return-to-work process among cancer patients. As part of this study, qualitative interviews were undertaken to gain further information about the patients' vocational aspirations, perceptions of the process of returning to work, and beliefs regarding their ability to return to work. The study demonstrated the role played by illness perceptions and beliefs about the impact of illness on return to work as well as differences in predictive factors across cancer types [14,56,57]. The results of this research were used to map the intervention components through an intervention mapping methodology used for designing and implementing complex interventions or programs. It has been used for over 20 years for systematically designing multifaceted programs involving numerous interventions directed at various individuals and environments [58]. This methodology is suited to the development of a return-to-work program because it is a complex intervention requiring a tailored and multifaceted approach. Further strengths of the study: chosen self-reported outcome measures relate directly to the components addressed through the intervention, resources are available to support a diverse sample within the study, and a qualitative analysis approach will be used. Qualitative methods

are increasingly applied in the developmental stages of RCTs of complex interventions [58]. Qualitative methods are often used to evaluate participants' understanding and experience of an intervention. Individual in-depth interviews allow exploration of why some participants may respond more positively to the intervention and what modifications may be required to suit different groups of participants (eg, differences between cancer types and occupation types, specific gender-based needs).

Conclusion

This feasibility study may be the first step in the development of an intervention that provides long-term benefits and may have some immediate benefits for the sample who participate. The intervention will provide cancer survivors with the skills and confidence to manage their return to work. The intervention may improve long-term job retention among cancer survivors with the potential to be adapted for other conditions. Furthermore, the intervention may have long-term implications for improving psychological outcomes among cancer survivors through improvements in well-being, mood, and physical functioning, all of which could impact the utilization of national health services.

Acknowledgments

This trial is funded by the Research for Patient Benefit Programme: PB-PG-0613-31088A (National Institute for Health Research). The primary sponsor is Coventry University. The sponsor is responsible for ensuring that appropriate arrangements are in place for the initiation, management, and financing of the project and that appropriate insurances are in place.

Conflicts of Interest

None declared.

Multimedia Appendix 2

Approval letter of support from NIHR (RfPB) for the application for funding. Includes committee comments from their review of the application which have all been addressed.

[PDF File (Adobe PDF File), 235KB - resprot_v5i2e75_app2.pdf]

References

1. Creed PA, Bloxsome TD, Johnston K. Self-esteem and self-efficacy outcomes for unemployed individuals attending occupational skills training programs. Community Work Fam 2001 Dec;4(3):285-303. [doi: 10.1080/01405110120089350]
2. Coats D, Max C. Healthy work: productive workplaces--Why the UK needs more "good jobs". 2005. URL: http://www.theworkfoundation.com/downloadpublication/report/77_77_healthy%20work.pdf [accessed 2015-10-12] [WebCite Cache ID 6cDsXqVAg]
3. Murphy G, Athanasou J. The effects of unemployment on mental health. J Occup Organ Psychol 1999 Mar;72(1):83-99. [doi: 10.1348/096317999166518]
4. de Boer AG, Taskila T, Ojajärvi A, van Dijk F, Verbeek JH. Cancer survivors and unemployment: a meta-analysis and meta-regression. JAMA 2009 Feb 18;301(7):753-762. [doi: 10.1001/jama.2009.187] [Medline: 19224752]
5. Bowling A. What things are important in people's lives? A survey of the public's judgements to inform scales of health related quality of life. Soc Sci Med 1995 Nov;41(10):1447-1462. [Medline: 8560313]
6. Jin RL, Shah CP, Svoboda TJ. The impact of unemployment on health: a review of the evidence. CMAJ 1995 Sep 1;153(5):529-540 [FREE Full text] [Medline: 7641151]
7. Fryers T, Melzer D, Jenkins R. Social inequalities and the common mental disorders: a systematic review of the evidence. Soc Psychiatry Psychiatr Epidemiol 2003 May;38(5):229-237. [doi: 10.1007/s00127-003-0627-2] [Medline: 12719837]
8. Cancer Research UK. UK cancer incidence statistics by age. 2004. URL: http://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/age?a=5441%2818/08/2011%29 [accessed 2015-10-14] [WebCite Cache ID 6cH93k1y8]
9. Improving outcomes: a strategy for cancer.: UK Department of Health; 2011. URL: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213785/dh_123394.pdf [accessed 2015-10-12] [WebCite Cache ID 6cDwiNAZs]
10. Better Cancer Care, An Action Plan.: Scottish Government; 2008. URL: http://www.gov.scot/Resource/Doc/242498/0067458.pdf [accessed 2015-10-12] [WebCite Cache ID 6cDwqIj8a]
11. Taskila T, de Boer AG, van Dijk FJH, Verbeek JH. Fatigue and its correlates in cancer patients who had returned to work: a cohort study. Psychooncology 2011 Nov;20(11):1236-1241. [doi: 10.1002/pon.1843] [Medline: 20821375]
12. Shi Q, Smith TG, Michonski JD, Stein KD, Kaw C, Cleeland CS. Symptom burden in cancer survivors 1 year after diagnosis: a report from the American Cancer Society's Studies of Cancer Survivors. Cancer 2011 Jun 15;117(12):2779-2790 [FREE Full text] [doi: 10.1002/cncr.26146] [Medline: 21495026]
13. Mehnert A. Employment and work-related issues in cancer survivors. Crit Rev Oncol Hematol 2011 Feb;77(2):109-130. [doi: 10.1016/j.critrevonc.2010.01.004] [Medline: 20117019]

14. Cooper AF, Hankins M, Rixon L, Eaton E, Grunfeld EA. Distinct work-related, clinical and psychological factors predict return to work following treatment in four different cancer types. Psychooncology 2013 Mar;22(3):659-667. [doi: 10.1002/pon.3049] [Medline: 22434715]
15. Bradley CJ, Neumark D, Luo Z, Bednarek HL. Employment-contingent health insurance, illness, and labor supply of women: evidence from married women with breast cancer. Health Econ 2007 Jul;16(7):719-737. [doi: 10.1002/hec.1191] [Medline: 17177273]
16. Taskila T, Lindbohm ML. Factors affecting cancer survivors' employment and work ability. Acta Oncol 2007;46(4):446-451. [doi: 10.1080/02841860701355048] [Medline: 17497311]
17. Spelten ER, Sprangers MA, Verbeek JH. Factors reported to influence the return to work of cancer survivors: a literature review. Psychooncology 2002;11(2):124-131. [Medline: 11921328]
18. Short PF, Vasey JJ, Belue R. Work disability associated with cancer survivorship and other chronic conditions. Psychooncology 2008 Jan;17(1):91-97 [FREE Full text] [doi: 10.1002/pon.1194] [Medline: 17429835]
19. Taskila-Brandt T, Martikainen R, Virtanen SV, Pukkala E, Hietanen P, Lindbohm M. The impact of education and occupation on the employment status of cancer survivors. Eur J Cancer 2004 Nov;40(16):2488-2493. [doi: 10.1016/j.ejca.2004.06.031] [Medline: 15519524]
20. Steiner JF, Cavender TA, Main DS, Bradley CJ. Assessing the impact of cancer on work outcomes: what are the research needs? Cancer 2004 Oct 15;101(8):1703-1711 [FREE Full text] [doi: 10.1002/cncr.20564] [Medline: 15386303]
21. Maunsell E, Brisson C, Dubois L, Lauzier S, Fraser A. Work problems after breast cancer: an exploratory qualitative study. Psychooncology 1999;8(6):467-473. [Medline: 10607979]
22. Brenninkmeijer V, Houtman I, Blonk R. Depressed and absent from work: predicting prolonged depressive symptomatology among employees. Occup Med (Lond) 2008 Jun;58(4):295-301 [FREE Full text] [doi: 10.1093/occmed/kqn043] [Medline: 18434294]
23. Abbott J, Berry N. Return to work during the year following first myocardial infarction. Br J Clin Psychol 1991 Sep;30 (Pt 3):268-270. [Medline: 1933046]
24. Söderman E, Lisspers J, Sundin O. Depression as a predictor of return to work in patients with coronary artery disease. Soc Sci Med 2003 Jan;56(1):193-202. [Medline: 12435561]
25. Maeland JG, Havik OE. Psychological predictors for return to work after a myocardial infarction. J Psychosom Res 1987;31(4):471-481. [Medline: 3668885]
26. Petrie KJ, Weinman J, Sharpe N, Buckley J. Role of patients' view of their illness in predicting return to work and functioning after myocardial infarction: longitudinal study. BMJ 1996 May 11;312(7040):1191-1194 [FREE Full text] [Medline: 8634561]
27. Hlatky MA, Boothroyd D, Horine S, Winston C, Brooks MM, Rogers W, et al. Employment after coronary angioplasty or coronary bypass surgery in patients employed at the time of revascularization. Ann Intern Med 1998 Oct 1;129(7):543-547. [Medline: 9758574]
28. Mittag O, Kolenda KD, Nordman KJ, Bernien J, Maurischat C. Return to work after myocardial infarction/coronary artery bypass grafting: patients' and physicians' initial viewpoints and outcome 12 months later. Soc Sci Med 2001 May;52(9):1441-1450. [Medline: 11286367]
29. Groeneveld IF, de Boer AG, Frings-Dresen MH. A multidisciplinary intervention to facilitate return to work in cancer patients: intervention protocol and design of a feasibility study. BMJ Open 2012;2(4) [FREE Full text] [doi: 10.1136/bmjopen-2012-001321] [Medline: 22786950]
30. Hubbard G, Gray NM, Ayansina D, Evans JM, Kyle RG. Case management vocational rehabilitation for women with breast cancer after surgery: a feasibility study incorporating a pilot randomised controlled trial. Trials 2013;14:175 [FREE Full text] [doi: 10.1186/1745-6215-14-175] [Medline: 23768153]
31. Munir F, Kalawsky K, Wallis DJ, Donaldson-Feilder E. Using intervention mapping to develop a work-related guidance tool for those affected by cancer. BMC Public Health 2013;13:6 [FREE Full text] [doi: 10.1186/1471-2458-13-6] [Medline: 23289708]
32. de Boer AG, Taskila T, Tamminga SJ, Frings-Dresen MH, Feuerstein M, Verbeek JH. Interventions to enhance return-to-work for cancer patients. Cochrane Database Syst Rev 2011 Feb(2):CD007569. [doi: 10.1002/14651858.CD007569.pub2] [Medline: 21328297]
33. Wells M, Williams B, Firnigl D, Lang H, Coyle J, Kroll T, et al. Supporting 'work-related goals' rather than 'return to work' after cancer? A systematic review and meta-synthesis of 25 qualitative studies. Psychooncology 2013 Jun;22(6):1208-1219. [doi: 10.1002/pon.3148] [Medline: 22888070]
34. Arain M, Campbell MJ, Cooper CL, Lancaster GA. What is a pilot or feasibility study? A review of current practice and editorial policy. BMC Med Res Methodol 2010;10:67 [FREE Full text] [doi: 10.1186/1471-2288-10-67] [Medline: 20637084]
35. Leventhal H, Nerenz DR, Steele DJ. Illness representations and coping with health threats. In: Baum A, Taylor SE, Singer JE, editors. Handbook of Psychology and Health. Vol IV: Social Psychological Aspects of Health. Hillsdale NJ: Erlbaum; 1984:219-252.
36. Locke EA. Toward a theory of task motivation and incentives. Organ Behav Hum Perform 1968 May;3(2):157-189. [doi: 10.1016/0030-5073(68)90004-4]

37. Moss-Morris R, Weinman J, Petrie K, Horne R, Cameron L, Buick D. The Revised Illness Perception Questionnaire (IPQ-R). Psychology & Health 2002 Jan;17(1):1-16. [doi: 10.1080/08870440290001494]
38. Grunfeld EA, Low E, Cooper AF. Cancer survivors' and employers' perceptions of working following cancer treatment. Occup Med (Lond) 2010 Dec;60(8):611-617 [FREE Full text] [doi: 10.1093/occmed/kqq143] [Medline: 20855546]
39. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983 Jun;67(6):361-370. [Medline: 6880820]
40. Tuomi K, Ilmarinen J, Jahkola A, Katajarinne L, Tulkki A. Work Ability Index. 2nd revised edition. Helsinki: Finnish Institute of Occupational Health; 1998.
41. Gagné M, Bérubé N, Donia M, Houlfort N, Koestner R. Validation of the satisfaction with work scale. 2007 Presented at: Proceedings of the Annual Conference of the Association for Administrative Sciences of Canada (ASAC); 2007; Ontario, Canada p. 2-5.
42. EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. Health Policy 1990 Dec;16(3):199-208. [Medline: 10109801]
43. de Boer AG, van Lanschot JJ, Stalmeier PF, van Sandick J, Hulscher JB, de Haes JC, et al. Is a single-item visual analogue scale as valid, reliable and responsive as multi-item scales in measuring quality of life? Qual Life Res 2004 Mar;13(2):311-320. [Medline: 15085903]
44. Bhandari A, Wagner T. Self-reported utilization of health care services: improving measurement and accuracy. Med Care Res Rev 2006 Apr;63(2):217-235. [doi: 10.1177/1077558705285298] [Medline: 16595412]
45. Severens JL, Mulder J, Laheij RJ, Verbeek AL. Precision and accuracy in measuring absence from work as a basis for calculating productivity costs in The Netherlands. Soc Sci Med 2000 Jul;51(2):243-249. [Medline: 10832571]
46. Ritchie J, Spencer L. Qualitative data analysis for applied policy research. In: Bryman A, Burgess RG, editors. Analysing qualitative data. London: Routledge; 1993:173-194.
47. Grunfeld EA, Rixon L, Eaton E, Cooper AF. The organisational perspective on the return to work of employees following treatment for cancer. J Occup Rehabil 2008 Dec;18(4):381-388. [doi: 10.1007/s10926-008-9152-1] [Medline: 19003524]
48. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M, Medical Research Council Guidance. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ 2008;337:a1655 [FREE Full text] [Medline: 18824488]
49. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. J Eval Clin Pract 2004 May;10(2):307-312. [doi: 10.1111/j.2002.384.doc.x] [Medline: 15189396]
50. Leon AC, Davis LL, Kraemer HC. The role and interpretation of pilot studies in clinical research. J Psychiatr Res 2011 May;45(5):626-629 [FREE Full text] [doi: 10.1016/j.jpsychires.2010.10.008] [Medline: 21035130]
51. Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios LP, et al. A tutorial on pilot studies: the what, why and how. BMC Med Res Methodol 2010;10:1 [FREE Full text] [doi: 10.1186/1471-2288-10-1] [Medline: 20053272]
52. Bowen DJ, Kreuter M, Spring B, Cofta-Woerpel L, Linnan L, Weiner D, et al. How we design feasibility studies. Am J Prev Med 2009 May;36(5):452-457 [FREE Full text] [doi: 10.1016/j.amepre.2009.02.002] [Medline: 19362699]
53. Petrie KJ, Cameron LD, Ellis CJ, Buick D, Weinman J. Changing illness perceptions after myocardial infarction: an early intervention randomized controlled trial. Psychosom Med 2002;64(4):580-586. [Medline: 12140347]
54. Broadbent E, Ellis CJ, Thomas J, Gamble G, Petrie KJ. Further development of an illness perception intervention for myocardial infarction patients: a randomized controlled trial. J Psychosom Res 2009 Jul;67(1):17-23. [doi: 10.1016/j.jpsychores.2008.12.001] [Medline: 19539814]
55. Grunfeld EA, Cooper AF. A longitudinal qualitative study of the experience of working following treatment for gynaecological cancer. Psychooncology 2012 Jan;21(1):82-89. [doi: 10.1002/pon.1874] [Medline: 21105181]
56. Grunfeld EA, Drudge-Coates L, Rixon L, Eaton E, Cooper AF. "The only way I know how to live is to work": a qualitative study of work following treatment for prostate cancer. Health Psychol 2013 Jan;32(1):75-82. [doi: 10.1037/a0030387] [Medline: 23316855]
57. Bartholomew LK, Parcel GS, Kok GJ, Gottlieb NH. Intervention Mapping: Designing Theory and Evidence-Based Health Promotion Programs. Mountain View, CA: Mayfield Publishing Company; 2001.
58. Murtagh MJ, Thomson RG, May CR, Rapley T, Heaven BR, Graham RH, et al. Qualitative methods in a randomised controlled trial: the role of an integrated qualitative process evaluation in providing evidence to discontinue the intervention in one arm of a trial of a decision support tool. Qual Saf Health Care 2007 Jun;16(3):224-229 [FREE Full text] [doi: 10.1136/qshc.2006.018499] [Medline: 17545351]

Abbreviations

RCT: randomized controlled trial

Edited by G Eysenbach; submitted 29.10.15; peer-reviewed by J Verbeek, A Weinberg; comments to author 20.12.15; revised version received 27.01.16; accepted 28.01.16; published 03.05.16.

Please cite as:
Woods PL, Schumacher L, Sadhra SS, Sutton AJ, Zarkar A, Rolf P, Grunfeld EA
A Guided Workbook Intervention (WorkPlan) to Support Work-Related Goals Among Cancer Survivors: Protocol of a Feasibility Randomized Controlled Trial
JMIR Res Protoc 2016;5(2):e75
URL: http://www.researchprotocols.org/2016/2/e75/
doi:10.2196/resprot.5300
PMID:27143229

Protocol

Effects of a Community-Based, Post-Rehabilitation Exercise Program in COPD: Protocol for a Randomized Controlled Trial With Embedded Process Evaluation

Laura Desveaux[1,2,3,4], MSc PT, PhD; Marla K Beauchamp[1,5], MSc PT, PhD; Annemarie Lee[1], PT, PhD; Noah Ivers[3,6,7], MD, PhD; Roger Goldstein[1,8,9], MD; Dina Brooks[1,4,8], PT, PhD

[1]West Park Healthcare Centre, Department of Respiratory Medicine, Toronto, ON, Canada
[2]Institute for Health System Solutions and Virtual Care, Women's College Hospital, Toronto, ON, Canada
[3]Women's College Research Institute, Toronto, ON, Canada
[4]Rehabilitation Sciences Institute, University of Toronto, Toronto, ON, Canada
[5]School of Rehabilitation Science, McMaster University, Hamilton, ON, Canada
[6]Women's College Hospital, Family Practice Health Centre, Toronto, ON, Canada
[7]University of Toronto, Department of Family and Community Medicine, Toronto, ON, Canada
[8]University of Toronto, Department of Physical Therapy, Toronto, ON, Canada
[9]University of Toronto, Department of Medicine, Toronto, ON, Canada

Corresponding Author:
Dina Brooks, PT, PhD
University of Toronto
Department of Physical Therapy
160-500 University Ave.
Toronto, ON, M5G 1V7
Canada
Phone: 1 416 978 1739
Fax: 1 416 946 8562
Email: dina.brooks@utoronto.ca

Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a leading cause of death across the world and will become increasingly common with an aging population. Pulmonary rehabilitation (PR) is an evidence-based, nonpharmacological intervention for individuals with COPD, targeting the secondary impairments of the disease. Although the benefits of participation in PR are well established, improvements in exercise tolerance and health status typically deteriorate following discharge. Challenges with long-term adherence to recommended exercise regimens are thought to explain much of this decline. Therefore, we developed a community-based exercise maintenance program for patients with COPD following discharge from PR.

Objectives: This manuscript (1) outlines the intervention, (2) describes how its effectiveness is being evaluated in a pragmatic randomized controlled trial, and (3) summarizes the embedded process evaluation aiming to understand key barriers and facilitators for implementation in new environments.

Methods: Participating centers refer eligible individuals with COPD following discharge from their local PR program. Consenting patients are assigned to a year-long community exercise program or usual care using block randomization and stratifying for supplemental oxygen use. Patients in the intervention arm are asked to attend an exercise session at least twice per week at their local community facility where their progress is supervised by a case manager. Each exercise session includes a component of aerobic exercise, and activities designed to optimize balance, flexibility, and strength. All study participants will have access to routine follow-up appointments with their respiratory physician, and additional health care providers as part of their usual care. Assessments will be completed at baseline (post-PR), 6, and 12 months, and include measures of functional exercise capacity, quality of life, self-efficacy, and health care usage. Intervention effectiveness will be assessed by comparing functional exercise capacity between intervention and control groups. A mixed-methods process evaluation will be conducted to better understand intervention implementation, guided by Normalization Process Theory and the Consolidated Framework for Implementation Research.

Results: Based on results from our pilot work, we anticipate a maintenance of exercise capacity and improved health-related quality of life in the intervention group, compared with a decline in exercise capacity in the usual care group.

Discussion: Findings from this study will improve our understanding of the effectiveness of community-based exercise programs for maintaining benefits following PR in patients with COPD and provide information on how best to implement them. If effective, the intervention represents an opportunity to transition patients from institutionally-based rehabilitative management to community-based care. The results of the process evaluation will contribute to the science of translating evidence-based programs into regular practice.

(JMIR Res Protoc 2016;5(2):e63) doi:10.2196/resprot.5435

KEYWORDS

COPD; pulmonary rehabilitation; exercise training; maintenance; community

Introduction

Background

Chronic obstructive pulmonary disease (COPD) is a leading cause of death across the world [1] and will become increasingly common with an aging population. The prevalence of COPD increases with age and is highest in individuals aged 65 years and over [2], with a current prevalence of 20% in this age group [3]. The natural course of COPD is that of progressive worsening of airflow limitation, repeated exacerbations, respiratory failure, and premature death. Among the major chronic illnesses in Canada, COPD accounts for the highest rate of hospital admissions [4]. Coupled with the knowledge that COPD is a common and costly condition [5], long-term strategies to improve health outcomes and prevent functional decline are likely to result in a decrease in health resource usage [6].

It is well established that pulmonary rehabilitation (PR) for those who suffer from COPD results in short-term improvements in dyspnea, exercise capacity, and health-related quality of life (HRQL). However, benefits achieved through PR tend to diminish over time [7,8], often to the point that outcomes return to preintervention levels within 12 months [9,10]. Nonadherence to a maintenance home exercise program is a key factor associated with the decline in outcomes [9,11], with a 50% reduction in adherence only 9 months after completion of intensive rehabilitation, according to patient self-report [11]. While patients are encouraged to adhere to their home exercise program upon discharge, many have difficulty maintaining their exercise routine after the transition from a hospital-based rehabilitation setting to a community setting. The benefit of rehabilitation is further diminished as patients who develop acute exacerbations struggle to return to their previous level of exercise without professional guidance [11].

Consequently, there is a growing interest in developing innovative follow-up strategies to promote long-term exercise maintenance. Supervised exercise programs delivered following PR appeal to individuals with COPD [12] and are more effective than usual care for preserving exercise capacity in the medium term [13] Studies that have examined post-rehabilitation maintenance programs in patients with COPD have not shown consistent positive effect [14,15]. The optimal method for preventing functional decline following PR remains unclear, especially in individuals with moderate and severe COPD who experience frequent exacerbations.

Data from a systematic review [13] suggests that maintenance programs with higher exercise frequency and those that involved health care support, particularly after exacerbations, provided the greatest benefit. These findings complement patient-reported barriers and facilitators from qualitative work, suggesting program proximity and a scheduled, group-based format supervised by an individual who could facilitate rapid access to a health care professional were key features to promote adherence to community-based programs [16]. The potential benefits of community-based programs extend beyond the exercise component to include opportunities for social interaction among individuals who face similar challenges in their day-to-day lives and potential follow-up for those who do not adhere. An important advantage of this type of model is the transfer of wellness maintenance away from a medical environment to a fully integrated community setting.

In light of these findings, we developed a post-PR community-based exercise maintenance program for patients with COPD and completed a pilot at a single community site. Results from our pilot study demonstrated the program was feasible and well-tolerated by participants [12]. In contrast with previous studies evaluating community-based programs post-PR, our pilot work noted sustained significant improvements in physical function and HRQL at both 6 months and 1 year following PR [17]. With the success of the pilot program, a randomized controlled trial is required to determine the effectiveness of this maintenance strategy. The overall aim of this study is to evaluate the effectiveness of a post-rehabilitation community-based exercise maintenance program that uses existing community resources to provide individuals with COPD the opportunity to exercise in a community rather than an institutional setting. This research has the potential to not only prevent functional decline in those with COPD but also to improve their HRQL. Specific objectives are below:

Objectives

1. To evaluate the effects of a 1-year community-based maintenance exercise program on functional exercise capacity in individuals with moderate to severe COPD who have completed a course of PR.
2. To determine the effects after 1 year of this intervention on secondary outcomes including HRQL, functional strength, self-reported functional status, adherence to exercise and self-efficacy.

3. To conduct a process evaluation to understand how the intervention was operationalized at each site and to identify factors that facilitated or impeded the implementation process.

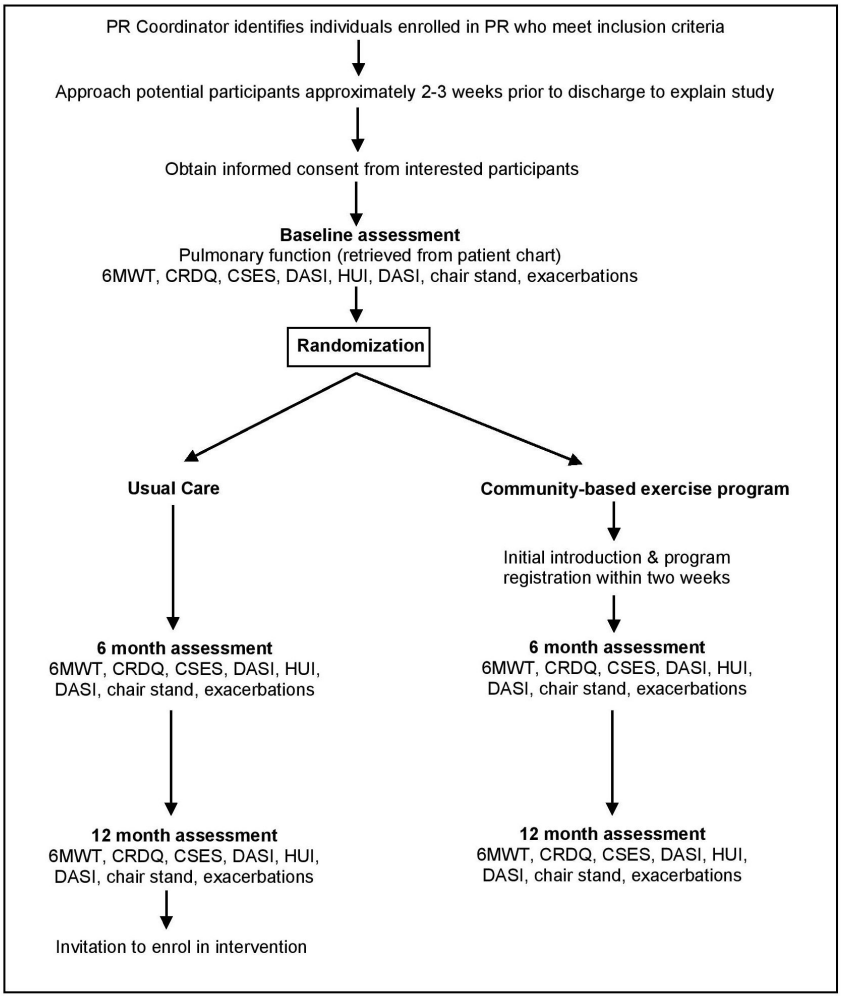
Methods

Study Design

The proposed study design is a two-arm, multicenter randomized controlled trial with blinding of both the outcome assessor and data analyst. A detailed participant flow chart can be found in Figure 1.

The protocol received ethics approval from the Joint Bridgepoint/West Park/Toronto Central Community Care Access Centre Research Ethics Board (REB); the Trillium Health Partners REB; the Lakeridge Health REB; the University Health Network REB; and the St. Joseph's Care Group REB. The trial is registered with ClinicalTrials [NLM Identifier: NCT01942499].

Figure 1. Participant flow chart (6MWT, six-minute walk test; CRDQ, chronic respiratory disease questionnaire; CSES, COPD self-efficacy scale; DASI, duke activity status index; HUI, health utility index; PR, pulmonary rehabilitation including all core components of exercise, education, self management and psychological support, in keeping with international guidelines).



Setting

In the province of Ontario, many health care services are covered under the Ontario Health Insurance Program (OHIP), a government-run health plan that is publicly funded. OHIP covers medically necessary services provided by physicians, including basic and emergency services, specialist visits, and formal rehabilitation (which includes PR). Community-based exercise programs are not covered under OHIP, and can be found in both municipal and private facilities.

Participants

Individuals with COPD will be considered eligible for the study if they: (1) have moderate to severe COPD based on international (GOLD) criteria [18], (2) are clinically stable as determined by their respirologist, (3) have completed PR within the previous 2 weeks, and (4) are able to provide their own informed consent. Participants will be given written study information for review and will completed a written consent form prior to study enrollment. All participants will be under the active care of a respirologist.

Individuals will be excluded if they have associated medical conditions that significantly limit their ability to exercise. Specifically, participants who report a history of significant cardiovascular disease (ie, congestive cardiac failure, history of cardiac arrest, acute myocardial infarction within the preceding 3 months, symptomatic ischaemic cardiac disease,

or uncontrolled systemic hypertension) or report severe nonrespiratory symptoms during exercise will be excluded from the study. Participants receiving mechanical ventilation and those who are unable or unwilling to attend the community-based exercise program or follow-up assessment sessions will also be excluded.

Allocation

A computer-generated randomization schedule using variable block size will be created. A member of the research team will consecutively randomize participants using sealed, opaque envelopes. Randomization will be stratified by the use of supplemental oxygen to minimize the impact of this factor, as it has been shown to influence the response to PR [19] and improve the total distance achieved during the 6-minute walk test (6MWT) by 12 to 59 m [20,21].

Intervention

The course of PR completed by both groups is in accordance with international guidelines [8] and will consist of all core components of rehabilitation including exercise, education, self-management, and nutrition, as well as psychological support. Thus, all participants will possess the tools and knowledge necessary to manage their condition prior to enrolment in the community maintenance program. Post-PR, participants randomized to the intervention group will receive the community-based maintenance exercise program for 12 months.

Control: Usual Care

Patients in both groups will receive usual care by their family physician and respiratory specialist (ie, medical care or prescriptions will not be standardized). Post-PR, they will receive the standard home exercise instructions and regular appointments with a physical therapist to review their program and address any outstanding issues.

Intervention: Community-Based Exercise Program

The intervention group will receive the same usual care and follow-up as the control group. In addition, they will be enrolled in a community-based maintenance exercise program for 12 months. Participants will be asked to attend a minimum of two sessions per week and are able to attend more frequently if they so choose. Each session will be approximately 60 minutes in duration. The exercise program will be delivered at one of seven community centers affiliated with the study; location selection will be based on the patient's preference and proximity to their home. Each participant will receive a full, 1-year membership to the community center as part of the study.

Group-based classes led by a certified fitness instructor will be offered at least twice per week, although participants will have the option of attending the community center at an alternative time if they are unable to attend the group class. Participants who attend the center outside of class times will have access to a certified fitness instructor for supervision. Fitness instructors will be certified by the Canadian Society for Exercise Physiology, the principal body for physical activity, health and fitness research, and personal training in Canada. Educational materials and training workshops regarding issues pertinent to supervising patients with COPD during exercise, symptom management, and guidelines for training progression will be provided to fitness instructors prior to launching the study.

The content of each exercise program will be individualized according to each participant's specific needs. Each exercise session will include a component of aerobic exercise such as walking or cycling, upper-limb resistance exercise (eg, free weights for bicep curls and triceps extensions), and activities designed to optimize balance, flexibility and strength (eg, functional exercises such as minisquats, stairs, basic stretches, core strengthening) based on PR guidelines (see Table 1 for an example). In addition to attending the twice weekly exercise program, participants will be encouraged to continue with their home exercise program consisting of aerobic exercise and strengthening. As we expect an inherent degree of variability in program delivery across sites, individual program details will be evaluated and reported as part of the process evaluation in order to capture variation across sites.

Table 1. Example of exercise program at community center.

Type	Approximate duration	Potential activities
Warm up	10 minutes	Gentle stretches for all major muscle groups (neck, shoulders, arms, hamstrings, quadriceps, and calves); marching on the spot to increase heart rate.
Aerobic training	20-30 minutes	Walking along a designated track with rests as needed, cycling and/or treadmill.
Functional exercises to promote strength and balance	20-30 minutes	Free weights and 'wall climbing' for upper extremity; mini-squats, stairs, hip abduction and hip extension while holding onto the back of a chair (therabands available to add resistance) for lower extremity; basic balance exercises such as practicing tandem stance, standing on one leg, walking on different surfaces (with mats and rails available for safety).
Cool down	10 minutes	Gentle stretches for all major muscle groups (neck, shoulders, arms, hams, quads, and calves); slow walking to decrease heart rate.

The case manager, a member of the research team and a clinically trained physiotherapist, will have training in pulmonary rehabilitation and be familiar with the rehabilitation programs offered at each site. The case manager will collaborate with the patient's PR physiotherapist and community center fitness instructor to establish the initial frequency, intensity, and training modalities for the community exercise program, tailored to the individual's capacity. During the 12-month community-based program, the case manager will remain in communication with participants and fitness staff via a study

phone-line and email. Participants attending exercise classes will be asked to contact the case manager by telephone after an absence of more than 1 week, due to illness or other reasons, so that support may be provided in managing exacerbations and resuming regular exercise. If significant new health problems arise, participants will be encouraged to return to their family doctor or respiratory specialist for review. Preliminary results from our pilot study demonstrated that the case manager was only accessed on occasions where a patient required additional support in managing exacerbations and where the medical safety of the patient was unclear to the fitness instructor. Feedback from focus groups with participants indicated that the presence of a case manager was a valued component of the model [12]. The role of the case manager moves this model into an integrated care strategy by providing patients and fitness staff with access to a health care professional when needed.

Outcomes

Primary Outcome

Six-Minute Walk Test

The 6MWT is a valid, responsive, interpretable, self-paced test that quantifies functional exercise capacity in terms of the distance walked in 6 minutes (6-minute walk distance) in patients with COPD [22]. The test will be performed over a 30-m level, straight course within an enclosed corridor, using the protocol described by the American Thoracic Society [22]. Outcome assessors will receive standardized training and will be blinded to group allocation. The measurement properties of this test have been well established in the COPD population [23]. A minimum important difference (MID) for the 6MWT is 54 m [24].

Secondary Outcomes

Chronic Respiratory Disease Questionnaire

Health-related quality of life will be measured using the Chronic Reparatory Disease Questionnaire (CRQ). The CRQ is a disease-specific instrument evaluating four domains that are considered important to individuals with chronic airflow limitation [25,26]. Participants will be required to quantify events and experiences that have taken place over the 2-week period preceding administration of the questionnaire. It includes 20 questions in four domains: dyspnea, fatigue, emotional function, and mastery. Answers are scored on a 7-point scale ranging from 1 (maximum impairment) to 7 (no impairment). The results are expressed as the mean score for each domain and the mean overall score. The MID for the CRQ is a change (improvement or deterioration) of 0.5 per item [27]. The CRQ is valid, responsive and interpretable when used among patients with COPD [25-27].

Duke Activity Status Index

The Duke Activity Status Index (DASI) is a 12-item questionnaire that requires only simple yes/no responses and takes less than 5 minutes to complete [28]. The questionnaire includes activities representative of personal care, ambulation, household tasks, sexual function, and recreational activities. The DASI has high criterion validity for predicting functional outcomes in patients with moderate to severe COPD [29] and was responsive to change in our pilot study [17].

Lower Extremity Functional Strength

The repeated chair stand test (number of sit-to-stands the subject can complete in a 30-second time-period) will be used as a measure of functional lower body strength. Reliability and validity of this measure has been previously evaluated in community-dwelling older adults [30] and in people with COPD [31] and it has been shown to be correlated to maximal voluntary force from a seated leg press [30,31].

Self-Efficacy

Behavioural modification is embedded in the rehabilitation process. Bandura describes the concept of self-efficacy as the 'belief in one's capabilities to organise and execute the course of action required to produce given attainments' [32]. A specific self-efficacy scale has been designed and validated for COPD, the COPD self-efficacy scale (CSES) [33], and was recently shown to be responsive to the effects of PR [34]. It is a 34-item questionnaire divided into five sections, one of which pertains to exercise.

Exacerbations

Acute exacerbations will be defined based on symptoms according to the criteria described by Anthonisen and colleagues [35], which are increased dyspnea with changes in sputum purulence or volume lasting at least 2 consecutive days. We will use intervention-based criteria for classifying the exacerbation as mild, moderate, or severe, depending on whether they are managed at home with no additional health care contact (mild), at home with unscheduled health care contact or the initiation of oral corticosteroids or antibiotics (moderate), or in the emergency room or hospital (severe) [35]. Patients will be asked to self-report this information at each assessment.

Data Analysis

Descriptive summary statistics will be reported using means and standard deviations, with median values as indicated for nonparametric data. The primary analysis will use a generalized linear model to examine the effect of treatment, time (follow-up at 6 and 12 months), and the interaction between treatment group and time. Values at baseline will be used as a covariate in this analysis. Secondary analyses will include adjustment for other baseline variables including age, sex, forced expiratory volume$_1$, and exacerbations. The generalized linear model creates a working covariance matrix for the model parameters that deals with missing data, including patients who do not complete all follow-up measures. The model uses all data in calculating a net effect of intervention versus control at 12 months and an estimate of precision (95% confidence interval) at that final follow-up. This analytic strategy will be used for all continuous variables that are primary or secondary measures of outcome (ie, 6MWD, CRQ domains, CSES, DASI, chair stand test). Data will be analyzed using the Statistical Package for the Social Sciences, version 22.0, with significance set at $P<0.05$.

Sample Size Calculation

Sample size calculations are based on the primary outcome measure, the 6MWT. We calculated sample size using a paired samples t-test. As the repeated measures analysis of the variance will be a more powerful analysis than a t-test, our sample size is a conservative estimate. Furthermore, as we will use baseline scores as a covariate in our planned analysis, we will be using within participant variability as our error (and not within participant variability), making our estimate even more conservative. A sample size estimation based on the knowledge of the differences in 6MWD that represent a clinically important difference (54 m and standard deviation of 86 m [15]), type I error of 0.05 and a power of 80%, revealed the need for a sample size of 40 in each group for a total of 80 participants. From our previous experience in this population, we estimate the rates of noncompliance and loss to follow-up to be 15% to 20% (8-10 participants per group). Therefore, we will aim to recruit 100 participants.

Process Evaluation

The process evaluation was informed by the MRC Guidance on Process Evaluations of complex interventions [36] and will focus on the evaluation of fidelity and implementation context. Intervention fidelity will be monitored throughout the study through semiannual check-ins with community facilities. Facilities will explicitly outline the operationalization of the intervention at their respective facility, including frequency, duration, supervision, attendance monitoring, and individual program components. Implementation will be explored through the integration of two frameworks: (1) Normalization Process Theory (NPT) [37] will be used to understand how the intervention was operationalized and (2) the Consolidated Framework for Implementation Research (CFIR) [38] will be used to evaluate contextual factors that influence the adoption, implementation, and maintenance of the intervention.

NPT is an established framework for understanding how and whether complex interventions become embedded in routine practice (ie, normalized) [37].This approach is ideally suited to this study as it entails numerous individuals, professionals, and organizations that may impact the effectiveness of a community-based exercise program. A quantitative questionnaire [39] will be administered following completion of the study. The questionnaire will evaluate the extent to which individuals involved in delivering the intervention (ie, PR and community center staff) make sense of the work of implementing and integrating the intervention (coherence); how they engage with it (cognitive participation); how they enact it (collective action); and how they appraise its effects (reflexive monitoring).

The CFIR will be used to develop a semistructured interview guide; PR coordinators and staff involved in referring participants, as well as managers, and fitness instructors from each community site will be invited to participate. Interviews will be conducted during the post-implementation phase and will elicit information relating to the experience of implementing and administering the intervention. Perspectives around program sustainability in order to inform broader implementation, should the program be effective, will also be explored.

For quantitative data (eg, survey results) descriptive analyses, including frequencies, means, and percentages will be performed using the Statistical Package for the Social Sciences version 22.0. Summary indices will be calculated for each NPT construct in order to evaluate the degree to which the intervention has become part of routine practice. Qualitative data collected during interviews will be audio recorded and transcribed verbatim. After reading the transcripts several times to become familiar with the text, codes will be identified and subsequently categorized into different themes [40]. Analysis will involve mapping the themes to the CFIR Framework to identify points of convergence (pattern matching) and divergence (examining alternative explanations). Sampling will continue until saturation is reached. Qualitative analysis will be performed using NVivo software.

Results

The trial is currently recruiting participants and will continue until the proposed sample size is reached. Approximately one-half of the required participants are enrolled in the study to date, indicating that data collection is likely to continue until 2018. Fidelity to the implementation process across all five hospitals and seven community sites is being monitored throughout the study. The rest of the process evaluation will commence in 2016.

Discussion

Trial Implications

This study will determine the effectiveness of a community-based maintenance exercise intervention for preserving functional exercise capacity following PR in patients with moderate to severe COPD. Upon completion, this study will be the first multicenter, randomized controlled trial of community-based maintenance programs following PR. Furthermore, this is the first study of maintenance exercise in COPD that includes a formal process evaluation, which will identify context-specific factors related to program implementation, thereby facilitating the uptake of the program into new environments. The intervention is fairly simple to implement, can be delivered in existing community settings, and requires minimal health system support. Although several studies have reported limited success with maintenance exercise programs following PR [11,14,15,41], the intervention outlined in this study is positioned for improved outcomes as we have incorporated previously identified elements of successful maintenance exercise programs and are building on an effective model of maintenance from our pilot study [17]. Specifically, our delivery model includes a higher exercise frequency [13], supervised exercise [12,16], program proximity [12,16], and health care professional support [12,13,16].

If participation in a community-based maintenance exercise program results in improved maintenance of functional exercise capacity compared with standard care, this approach will represent an innovative (and relatively inexpensive) strategy to optimize the maintenance of gains made during PR. Our project is particularly relevant for guiding both clinical and policy-based decision-making, given the large population of adults with moderate and severe COPD who cannot be served on an ongoing

basis by existing PR programs. Furthermore, a community-based approach using case managers could offer a scalable approach for maintaining well-being across multiple disease-conditions post-rehabilitation.

Conclusions

In conclusion, this study will provide definitive evidence on the effectiveness of a community-based maintenance exercise program for patients with COPD. The intervention involved in the current study was designed to address factors that contribute to success previously identified in the literature within the constraints of existing community resources to maximize generalizability. The addition of a process evaluation is an added strength that will offer insight into the factors that may impede or facilitate the implementation of the program. Data from this evaluation will provide information around the potential application of the intervention across different health care and community settings.

Acknowledgments

Funding for this study is provided by the Canadian Institutes of Health Research and the Ontario Thoracic Society. During the project development and launch, LD was affiliated with West Park Healthcare Centre and supported by Canadian Respiratory Health Professionals and Ontario Respiratory Care Society Fellowships. MB is supported by the Canadian Institutes of Health Research and DB is supported by a Canada Research Chair. NI is supported by New Investigator Awards from the Canadian Institutes of Health Research and the Department of Family and Community Medicine at the University of Toronto. RG is supported by the NSA Chair in Respiratory Rehabilitation Research.

Authors' Contributions

DB, RG, and MB conceived of the study, participated in its design, and helped to draft the protocol. LD participated in the design, conceived the process evaluation, led the planning of the study, and drafted the protocol. AL was involved in the management of the study and helped to draft the protocol. NI helped to develop the process evaluation and draft the protocol. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

CIHR Operating Grant Reviews.

[PDF File (Adobe PDF File), 267KB - resprot_v5i2e63_app1.pdf]

References

1. Mathers C, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006;3:e442 [FREE Full text] [doi: 10.1371/journal.pmed.0030442] [Medline: 17132052]
2. Hurd S. The impact of COPD on lung health worldwide: epidemiology and incidence. Chest 2000;117(2 Suppl):1S-4S. [Medline: 10673465]
3. Institute for Clinical Evaluative Sciences. Prevalence of Chronic Obstructive Pulmonary Disease, Ontario 1996/97 to 2009/10. Toronto, ON: Institute for Clinical Evaluative Sciences; 2010:1-10.
4. Canadian Institute of Health Information. Health Indicators 2008. Ottawa, ON: Canadian Institute of Health Information; 2008. URL: https://secure.cihi.ca/free_products/HealthIndicators2008_ENGweb.pdf [accessed 2016-04-01] [WebCite Cache ID 6gRfJAsWB]
5. Mittmann N, Kuramoto L, Seung SJ, Haddon JM, Bradley-Kennedy C, Fitzgerald JM. The cost of moderate and severe COPD exacerbations to the Canadian healthcare system. Respir Med 2008;102:413-421 [FREE Full text] [doi: 10.1016/j.rmed.2007.10.010] [Medline: 18086519]
6. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, BOLD Collaborative Research Group. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet 2007;370:741-750. [doi: 10.1016/S0140-6736(07)61377-4] [Medline: 17765523]
7. Lacasse Y, Martin S, Lasserson TJ, Goldstein RS. Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease. A Cochrane systematic review. Eura Medicophys 2007;43:475-485 [FREE Full text] [Medline: 18084170]
8. Ries A, Bauldoff G, Carlin B, Casaburi R, Emery C, Mahler D, et al. Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based clinical practice guidelines. Chest 2007;131(5 Suppl):4S-42S. [doi: 10.1378/chest.06-2418] [Medline: 17494825]
9. Griffiths TL, Burr ML, Campbell IA, Lewis-Jenkins V, Mullins J, Shiels K, et al. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. Lancet 2000;355:362-368. [Medline: 10665556]

10. Ries AL, Kaplan RM, Limberg TM, Prewitt LM. Effects of pulmonary rehabilitation on physiologic and psychosocial outcomes in patients with chronic obstructive pulmonary disease. Ann Intern Med 1995;122:823-832. [Medline: 7741366]
11. Brooks D, Krip B, Mangovski-Alzamora S, Goldstein R. The effect of postrehabilitation programmes among individuals with chronic obstructive pulmonary disease. Eur Respir J 2002;20:20-29 [FREE Full text] [Medline: 12166571]
12. Desveaux L, Rolfe D, Beauchamp M, Goldstein R, Brooks D. Participant experiences of a community-based maintenance program post-pulmonary rehabilitation. Chron Respir Dis 2014;11:23-30. [doi: 10.1177/1479972313516880] [Medline: 24431408]
13. Beauchamp MK, Evans R, Janaudis-Ferreira T, Goldstein RS, Brooks D. Systematic review of supervised exercise programs after pulmonary rehabilitation in individuals with COPD. Chest 2013;144:1124-1133. [doi: 10.1378/chest.12-2421] [Medline: 23429931]
14. Wilson AM, Browne P, Olive S, Clark A, Galey P, Dix E, Wilson Edward C F, et al. The effects of maintenance schedules following pulmonary rehabilitation in patients with chronic obstructive pulmonary disease: a randomised controlled trial. BMJ Open 2015;5:e005921 [FREE Full text] [doi: 10.1136/bmjopen-2014-005921] [Medline: 25762226]
15. Busby AK, Reese RL, Simon SR. Pulmonary Rehabilitation Maintenance Interventions: A Systematic Review. Am J Hlth Behav 2014;38:321-330. [doi: 10.5993/ajhb.38.3.1]
16. Desveaux L. Community-Based Physical Activity Following Rehabilitation in Chronic Disease. Toronto, ON: University of Toronto Press; 2016.
17. Beauchamp MK, Francella S, Romano JM, Goldstein RS, Brooks D. A novel approach to long-term respiratory care: results of a community-based post-rehabilitation maintenance program in COPD. Respir Med 2013;107:1210-1216 [FREE Full text] [doi: 10.1016/j.rmed.2013.04.014] [Medline: 23706779]
18. GIobal Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Diseas. 2013. URL: http://www.goldcopd.com/Guidelines/guidelines-resources.html [accessed 2016-04-01] [WebCite Cache ID 6gRfiXi1u]
19. Dyer F, Callaghan J, Cheema K, Bott J. Ambulatory oxygen improves the effectiveness of pulmonary rehabilitation in selected patients with chronic obstructive pulmonary disease. Chron Respir Dis 2012;9:83-91. [doi: 10.1177/1479972312438702] [Medline: 22452975]
20. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J 2014;44:1428-1446. [doi: 10.1183/09031936.00150314] [Medline: 25359355]
21. Singh SJ, Puhan MA, Andrianopoulos V, Hernandes NA, Mitchell KE, Hill CJ, et al. An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease. Eur Respir J 2014;44:1447-1478. [doi: 10.1183/09031936.00150414] [Medline: 25359356]
22. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-117. [doi: 10.1164/ajrccm.166.1.at1102] [Medline: 12091180]
23. Solway S, Brooks D, Lacasse Y, Thomas S. A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. Chest 2001;119:256-270. [Medline: 11157613]
24. Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH. Interpreting small differences in functional status: the Six Minute Walk test in chronic lung disease patients. Am J Respir Crit Care Med 1997;155:1278-1282. [doi: 10.1164/ajrccm.155.4.9105067] [Medline: 9105067]
25. Lacasse Y, Wong E, Guyatt G, Goldstein R. Health status measurement instruments in chronic obstructive pulmonary disease. Can Respir J 1997;4:152-164.
26. Guyatt G, Berman L, Townsend M, Pugsley S, Chambers L. A measure of quality of life for clinical trials in chronic lung disease. Thorax 1987;42:773-778 [FREE Full text] [Medline: 3321537]
27. Lacasse Y, Wong E, Guyatt G. A systematic overview of the measurement properties of the Chronic Respiratory Questionnaire. Can Respir J 1997;4:131-139.
28. Hlatky MA, Boineau RE, Higginbotham MB, Lee KL, Mark DB, Califf RM, et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). Am J Cardiol 1989;64:651-654. [Medline: 2782256]
29. Carter R, Holiday DB, Grothues C, Nwasuruba C, Stocks J, Tiep B. Criterion validity of the Duke Activity Status Index for assessing functional capacity in patients with chronic obstructive pulmonary disease. J Cardiopulm Rehabil 2002;22:298-308. [Medline: 12202852]
30. Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. Res Q Exerc Sport 1999;70:113-119. [doi: 10.1080/02701367.1999.10608028] [Medline: 10380242]
31. Benton MJ, Alexander JL. Validation of functional fitness tests as surrogates for strength measurement in frail, older adults with chronic obstructive pulmonary disease. Am J Phys Med Rehabil 2009;88:579-583; quiz 584. [doi: 10.1097/PHM.0b013e3181aa2ff8] [Medline: 19542782]
32. Bandura A. Self-Efficacy: The Exercise of Control. New York: W.H. Freeman; 1997.
33. Wigal JK, Creer TL, Kotses H. The COPD Self-Efficacy Scale. Chest 1991;99:1193-1196. [Medline: 2019177]

34. Heppner PS, Morgan C, Kaplan RM, Ries AL. Regular walking and long-term maintenance of outcomes after pulmonary rehabilitation. J Cardiopulm Rehabil 2006;26:44-53. [Medline: 16617228]
35. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 1987;106:196-204. [Medline: 3492164]
36. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical Research Council guidance. BMJ 2015;350:h1258 [FREE Full text] [Medline: 25791983]
37. Murray E, Treweek S, Pope C, MacFarlane A, Ballini L, Dowrick C, et al. Normalisation process theory: a framework for developing, evaluating and implementing complex interventions. BMC Med 2010;8:63 [FREE Full text] [doi: 10.1186/1741-7015-8-63] [Medline: 20961442]
38. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. Implement Sci 2009;4:50 [FREE Full text] [doi: 10.1186/1748-5908-4-50] [Medline: 19664226]
39. Finch TL, Rapley T, Girling M, Mair FS, Murray E, Treweek S, et al. Improving the normalization of complex interventions: measure development based on normalization process theory (NoMAD): study protocol. Implement Sci 2013;8:43 [FREE Full text] [doi: 10.1186/1748-5908-8-43] [Medline: 23578304]
40. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology 2006;3:77-101. [doi: 10.1191/1478088706qp063oa]
41. Spencer LM, Alison JA, McKeough ZJ. Maintaining benefits following pulmonary rehabilitation: a randomised controlled trial. Eur Respir J 2010;35:571-577 [FREE Full text] [doi: 10.1183/09031936.00073609] [Medline: 19643944]

Abbreviations

6MWT: 6-minute walk test
CFIR: consolidated framework for implementation research
COPD: chronic obstructive pulmonary disease
CRQ: chronic respiratory disease questionnaire
CSES: COPD self-efficacy scale
DASI: duke activity status index
HRQL: health-related quality of life
MID: minimum important difference
NPT: normalization process theory
OHIP: Ontario Health Insurance Program
PR: pulmonary rehabilitation
REB: research ethics board

Edited by G Eysenbach; submitted 11.12.15; peer-reviewed by M Stickland, E Marziali, L Spencer; comments to author 30.01.16; revised version received 10.02.16; accepted 10.02.16; published 11.05.16.

Please cite as:
Desveaux L, Beauchamp MK, Lee A, Ivers N, Goldstein R, Brooks D
Effects of a Community-Based, Post-Rehabilitation Exercise Program in COPD: Protocol for a Randomized Controlled Trial With Embedded Process Evaluation
JMIR Res Protoc 2016;5(2):e63
URL: http://www.researchprotocols.org/2016/2/e63/
doi:10.2196/resprot.5435
PMID:27169436

Protocol

The Mobile Solutions for Immunization (M-SIMU) Trial: A Protocol for a Cluster Randomized Controlled Trial That Assesses the Impact of Mobile Phone Delivered Reminders and Travel Subsidies to Improve Childhood Immunization Coverage Rates and Timeliness in Western Kenya

Dustin G Gibson[1], MS, PhD; E. Wangeci Kagucia[1], MHS; Benard Ochieng[2], MS; Nisha Hariharan[1], MSPH; David Obor[2], MS; Lawrence H Moulton[1], PhD; Peter J Winch[1], MPH, MD; Orin S Levine[1], PhD; Frank Odhiambo[2], PhD; Katherine L O'Brien[1], MPH, MD; Daniel R Feikin[3], MSPH, MD

[1]Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States

[2]Health and Demographic Surveillance System Branch, Kenya Medical Research Institute and Centers for Disease Control and Prevention Public Health Collaboration, Kisian, Kenya

[3]Division of Viral Diseases, Centers For Disease Control and Prevention, Atlanta, GA, United States

Corresponding Author:
Dustin G Gibson, MS, PhD
Department of International Health
Johns Hopkins Bloomberg School of Public Health
615 N Wolfe St
Baltimore, MD, 21205
United States
Phone: 1 443 287 8763
Fax: 1 410 614 1419
Email: dgibso28@jhu.edu

Abstract

Background: Text message (short message service, SMS) reminders and incentives are two demand-side interventions that have been shown to improve health care–seeking behaviors by targeting participant characteristics such as forgetfulness, lack of knowledge, and transport costs. Applying these interventions to routine pediatric immunizations may improve vaccination coverage and timeliness.

Objective: The Mobile Solutions for Immunization (M-SIMU) trial aims to determine if text message reminders, either with or without mobile phone–based incentives, sent to infant's parents can improve immunization coverage and timeliness of routine pediatric vaccines in rural western Kenya.

Methods: This is a four-arm, cluster, randomized controlled trial. Villages are randomized to one of four study arms prior to enrollment of participants. The study arms are: (1) no intervention (a general health-related text message will be texted to this group at the time of enrollment), (2) text message reminders only, (3) text message reminders and a 75 Kenyan Shilling (KES) incentive, or (4) text message reminders and a KES200 incentive. Participants assigned to study arms 2-4 will receive two text message reminders; sent 3 days before and one day before the scheduled immunization visit at 6, 10, and 14 weeks for polio and pentavalent (containing diphtheria, tetanus, pertussis, hepatitis B, and *Haemophilus influenza* type b antigens) type b antigens) vaccines, and at 9 months for measles vaccine. Participants in incentive arms will, in addition to text message reminders as above, receive mobile phone–based incentives after each timely vaccination, where timely is defined as vaccination within 2 weeks of the scheduled date for each of the four routine expanded program immunization (EPI) vaccination visits. Mother-infant pairs will be followed to 12 months of age where the primary outcome, a fully immunized child, will be ascertained. A fully immunized child is defined as a child receiving vaccines for bacille Calmette-Guerin, three doses of pentavalent and polio, and measles by 12 months of age. General estimating equation (GEE) models that account for clustering will be employed for primary outcome analyses.

Results: Enrollment was completed in October 2014. Twelve month follow-up visits to ascertain immunization status from the maternal and child health booklet were completed in February 2016.

Conclusions: This is one of the first studies to examine the effect of text message reminders on immunization coverage and timeliness in a lower income country and is the first study to assess the effect of mobile money-based incentives to improve immunization coverage.

Trial Registration: Clinicaltrials.gov NCT01878435; https://clinicaltrials.gov/ct2/show/NCT01878435 (Archived by WebCite at http://www.webcitation.org/6hQlwGYJR)

(JMIR Res Protoc 2016;5(2):e72) doi:10.2196/resprot.5030

KEYWORDS

text message; reminders; SMS; M-PESA; Kenya; mobile; conditional cash transfer; CCT; incentive; measles; mHealth; immunization; pentavalent

Introduction

The decade from 2010 to 2019 has been dubbed the "Decade of Vaccines" with renewed focus on immunization by major international groups like World Health Organization, United Nations Children's Emergency Fund, the Global Alliance for Vaccines, and the Bill and Melinda Gates Foundation [1-3]. A key component in the Global Vaccine Action Plan is the recognition that both demand- and supply-side deficiencies need to be addressed in order to achieve universal immunization [4]. Ensuring more infants receive timely vaccination is a major component in efforts to reduce child mortality by two-thirds and achieve Millennium Development Goal 4 [5]. Every year, immunization programs are estimated to save over 2.5 million lives globally [6], with the majority of deaths averted occurring in Africa [7].

Timely vaccination is important for several reasons. First, the diseases that pediatric vaccines protect against often have highest morbidities and mortalities at earlier stages of life. Delays of infant immunization have been associated with increased cases of pertussis [8,9], hepatitis B [10], and *Haemophilus influenza* type b [11]. Second, timely vaccination heightens population herd immunity levels [12], thereby protecting those that are too young to be vaccinated or are medically contraindicated. Delays in vaccination lessen population coverage and create a pool of susceptible individuals, thereby increasing the pathogen's ability to spread and theoretically increasing the risk of exposure.

Interventions to improve immunization coverage and timeliness are important because approximately 1 in 13 children in Kenya and 1 in 5 children in our study site, Siaya County in western Kenya, will die before their 5th birthday, with the majority of deaths attributed to infectious diseases [13,14]. Many of these deaths are preventable by vaccination, yet many children in Kenya are not vaccinated or are vaccinated late [15,16].

Two demand-side interventions, text message (short message service, SMS) reminders [17-22] and small monetary incentives [23-25], have been shown to motivate positive health behaviors in resource constrained settings. Moreover, text message reminders have been shown to modestly improve immunization coverage in the United States [26-29]; however, the efficacy of text message reminders to improve immunization coverage in sub-Saharan Africa, until recently [30,31], has neither been evaluated nor used in conjunction with monetary incentives. This randomized controlled trial will test whether text messaging reminders, either with or without mobile phone-based incentives, can improve timeliness and coverage of routine pediatric immunizations.

Critically, the success of our pilot study in a neighboring division, Karemo, shows that a mobile phone-based system that delivers incentives and text messaging reminders is technically feasible and welcomed by the community [32]. Lessons and challenges learned from the pilot study will be incorporated into the design of the current cluster randomized controlled trial.

The Mobile Solutions for Immunizations (M-SIMU) study is a four-arm, cluster, randomized controlled trial, which evaluates the impact of providing caregivers text message reminders and monetary incentives on the proportion of children that are fully vaccinated by 12 months of age.

Methods

Study Design

The M-SIMU study is a four-arm, cluster, randomized controlled trial to evaluate the impact of text message reminders and monetary incentives on pediatric immunization coverage and timeliness in rural western Kenya. Villages, as defined by the Kenyan Medical Research Institute and (KEMRI) and Centers for Disease Control and Prevention (CDC) Health and Demographic Surveillance System (HDSS), are the units of randomization. Villages will be randomized to one of four study arms in a 1:1:1:1 allocation ratio (Figure 1). The study arms include: (1) control, (2) text message reminders, (3) text message reminders plus a 75 Kenyan Shillings incentive (KES; KES85 = US$1 as of August 2015) and, (4) text message reminders plus a KES200 incentive. Text message reminders are sent three days and one day before pentavalent vaccination visits scheduled at 6, 10, and 14 weeks, and measles vaccination at 9 months of age. Incentives are delivered to the participant's mobile phone if the participant's child is brought for immunization within 2 weeks of the scheduled date. All eligible mothers/caretakers residing within a study village will be assigned to the study arm that the village was allocated.

Setting and Participants

The M-SIMU study is located in Rarieda and Gem Districts of Siaya County, Kenya. Malaria, tuberculosis, and human

immunodeficiency virus transmission are highly prevalent in this rural setting [33]. In 2008, the under-5 mortality rate was 212 deaths per 1000 live births, with pneumonia and diarrhea as common causes of childhood mortality [13].

The study site is nested within boundaries defined by KEMRI/CDC HDSS. Since 2001, the HDSS systematically collects information on births, deaths, migration, morbidity, and demographics every 4 months for a population of over 220,000 people. Within the HDSS, several disease specific studies have been conducted, including randomized controlled trials for bed-net efficacy, and rotavirus vaccine efficacy [34,35].

Prior to enrollment of the randomized controlled trial, a baseline survey was conducted in the study villages to obtain recent estimates of vaccination coverage for sample size calculation and to collect sociodemographic variables, such as mobile phone ownership and distance to nearest health facility, to perform a restricted randomization of study villages [16]. Additionally, three focus group discussions with 10 to 15 mothers who have a child 12- to 23-months-old were conducted to solicit local and contextual-specific feedback on the content and timing of the text message reminders, incentive amounts, willingness to receive reminders and incentives, and to anticipate any problems or complications associated with delivering text message reminders and incentives.

Villages are included in the cluster randomized controlled trial if they are located within either Gem or Asembo HDSS boundaries. Villages are excluded from the M-SIMU study if there are active immunization intervention/programs (e.g., nongovernmental organizations conducting immunization-related activities, outreach immunization clinics, etc.) that might confound study outcomes. Sample size calculations were conducted to determine the number of villages needed to be able to detect a 15% absolute difference in full immunization coverage at 12 months of age between control and intervention arms.

To ensure accurate population numbers, KEMRI/CDC HDSS casually employs ‘village reporters’ to identify births, deaths, and pregnancies within their community. For the M-SIMU trial, village reporters will be provided a simple mobile phone and trained to send a birth or death notification text message to the RapidSMS server, a free and open-source platform. The notification text message will include the study village and compound number. The RapidSMS server then automatically relays the notification to a field-based Community Interviewer (CI). Following receipt of a birth notification, the CI will visit the newborn’s compound to explain the trial and screen the mother/caretaker for the following eligibility criteria described in Textbox 1.

Textbox 1. Criteria for participant enrollment into the Mobile Solutions for Immunization (M-SIMU) trial.

Inclusion criteria:

- Mother of infant aged 0- to 4-weeks during the study period
- Current resident of one of the study villages
- Willing to sign informed consent for the study

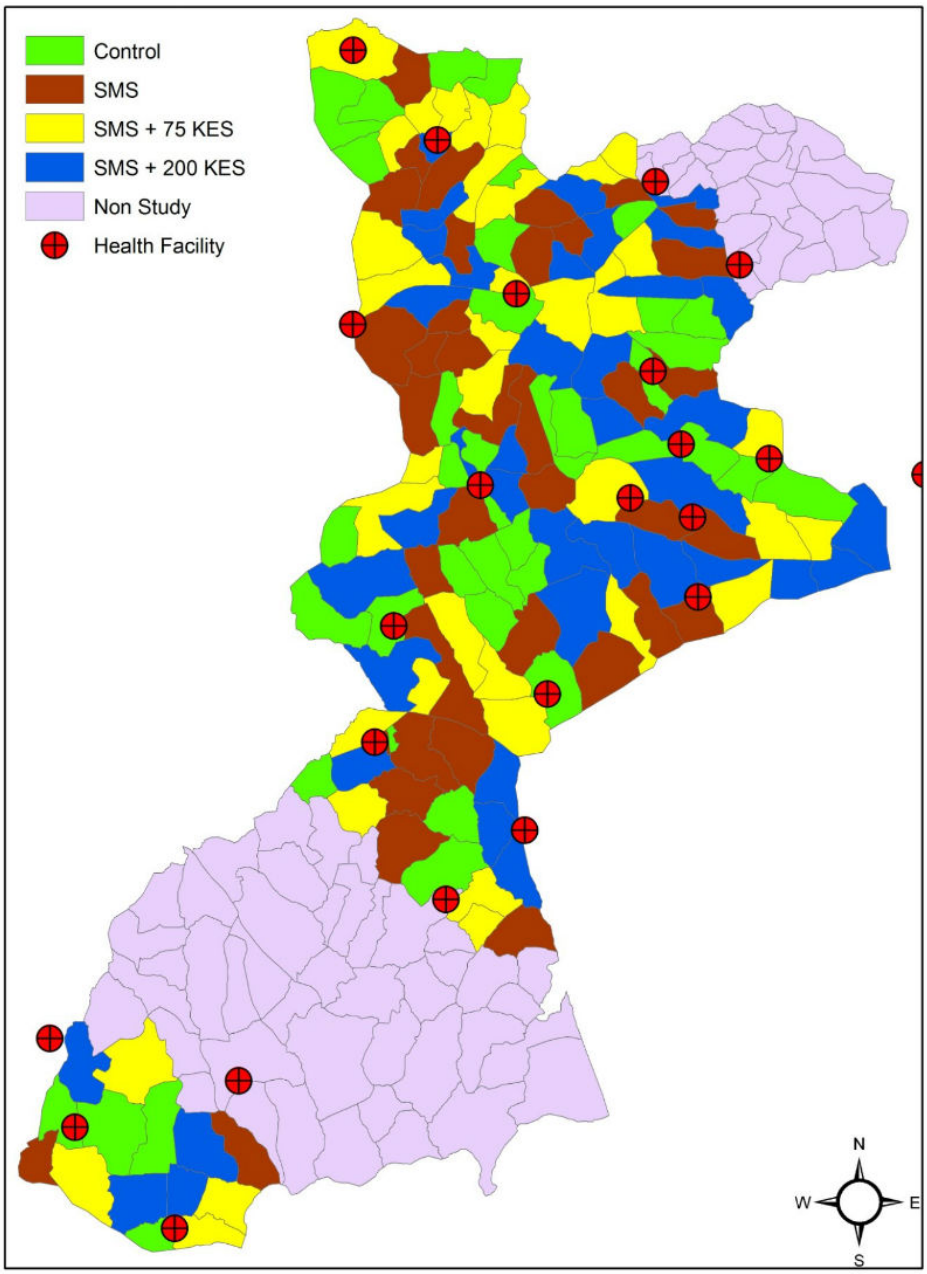
Exclusion criteria:

- Plans to move out of the study area in the next 6 months
- Has already received immunizations other than birth dose of bacille Calmette-Guerin or polio
- Will not bring infant to an M-SIMU identified clinic (Figure 2)

Mothers are eligible independent of mobile phone ownership. Mothers only need to have access to a mobile phone, whereby access is defined by the mother and could include someone that lives in household, compound, or a neighbor. If no mobile phone can be identified, the mother may use the CI’s phone.

Eligible mothers will be required to provide both oral and written informed consent to the CI. Upon providing consent, the CI will send an enrollment text message to the RapidSMS server containing the mother’s village and compound number, the phone number that can be used to receive text message reminders, the child’s date of birth, the preferred language to receive text message reminders (English, Kiswahili, or Dholuo), and the baby’s first and last name. Upon completion of a successful enrollment text message, the RapidSMS server sends a personalized text message to the mother welcoming her to the study (see Table 1).

Figure 2. Map of villages coded by study arm.



Interventions

The interventions, text message reminders and incentives, are designed to motivate mothers and increase demand for routine pediatric immunizations.

Text message reminders are a component of all three intervention arms and will be sent to the mobile phone number participants identified at enrollment. Text message reminders will be sent using RapidSMS on both 3 and 1 days before the scheduled immunization visits at 6, 10, and 14 weeks for the three doses of pentavalent vaccine and at 9 months for measles as per Kenyan Expanded Programme on Immunization (KEPI) guidelines. Text message reminders will be sent as in English, Kiswahili, or Dholuo language according to the mother's preference as indicated at enrollment. If a pentavalent vaccination is given later than the scheduled date, then text message reminders for the subsequent pentavalent dose will be reprogrammed to occur at 4 weeks from the date of vaccine receipt, as per KEPI guidelines. As an example, if a child receives pentavalent1 at 8 weeks of age (scheduled to be given at 6 weeks), the immunization reminders for pentavalent2 will be sent when the child is 12-weeks old (instead of the KEPI schedule of 10 weeks).

Text message reminders are composed of a core text and a motivational saying (See Table 1). The core message states which vaccine is due, and if the participant is in an incentive arm, reminds the mother how much money she will receive if the child is vaccinated in a timely manner. The motivational sayings attached at the end of the text message were chosen from the results of focus group discussions held with caregivers of children aged 12- to 23-months old. The four sayings are "Vaccines save Kenyan babies lives," "Baby < INSERT BABY FIRST NAME> is happy when healthy "Most <INSERT DISTRICT: ASEMBO or GEM> babies get vaccinated, be one

of them," and "Vaccines are available now." For each vaccine dose, one of the four motivational sayings is randomly selected, with replacement, by the RapidSMS software. The same motivational saying is used for the 3- and 1-days reminder for that particular vaccine dose.

Mobile phone–based monetary incentives are a component of study arms numbers three and four. In both arms, the conditions and delivery of the incentive are identical; only the incentive amount differs. In addition to receiving text message reminders, mothers will receive either KES75 (arm #3;) or KES200 (arm #4) on their mobile phone for each timely dose of pentavalent and measles vaccine, defined as vaccination within 2 weeks of the scheduled date (i.e., pentavalent1 at 6 weeks, pentavalent2 four weeks after pentavalent1 received, pentavalent3 four weeks after pentavalent2 received, and measles at 9 months). If a mother brings her child for vaccination any time 2 weeks after the scheduled date, no incentive will be transferred. Mobile-money incentives will be transferred using the preferred mobile money network of the participant and are aimed to be delivered within 24 hours of a timely vaccination.

Figure 1. CONSORT diagram of study design.

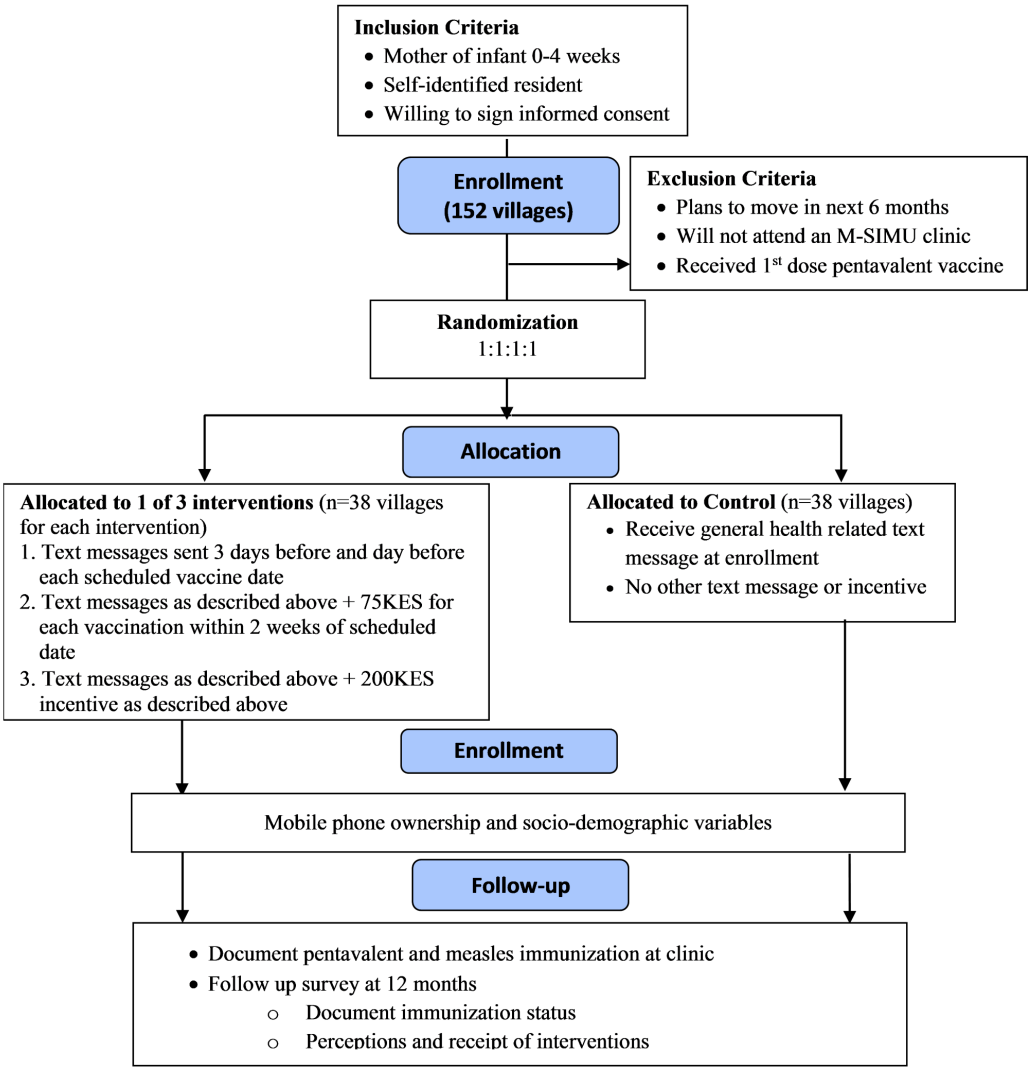


Table 1. Content of text message reminders sent to participant's mobile phones.

Message Type	Message Timing	Arm 1: Control	Arm 2 : Reminders Only	Arm 3: Reminders + KES75 Incentive	Arm 4: Reminders + 200KES Incentive
Enrollment message	Enrollment	Thank you for enrolling Baby <BABY'S FIRST NAME> to the KEMRI/CDC M-SIMU study. The greatest wealth is health.	Thank you for enrolling your child in the KEMRI/CDC M-SIMU study. You will get periodic reminders for Baby <BABY'S FIRST NAME>'s vaccinations. The greatest wealth is health.	Thank you for enrolling your child in the KEMRI/CDC M-SIMU study. You will get periodic reminders for Baby <BABY'S FIRST NAME>'s vaccinations. The greatest wealth is health.	Thank you for enrolling your child in the KEMRI/CDC M-SIMU study. You will get periodic reminders for Baby <BABY'S FIRST NAME>'s vaccinations. The greatest wealth is health.
3-day reminder message	3 days before EPI due date	No message	Tell Mama <BABY'S FIRST NAME> that <VACCINE NAME> vaccine is due this week. <MOTIVATIONAL MESSAGE>	Tell Mama <BABY'S FIRST NAME>> that <VACCINE NAME> vaccine is due this week. You get KES75 if Baby vaccinated in next 2 weeks. <MOTIVATIONAL MESSAGE>	Tell Mama <BABY'S FIRST NAME> that <VACCINE NAME> vaccine is due this week. You get KES200 if Baby vaccinated in next 2 weeks. <MOTIVATIONAL MESSAGE>
1-day reminder message	1 day before the EPI due date	No message	Tell Mama <BABY's FIRST NAME> that <VACCINE NAME> vaccine is due this week. Go to the clinic if you haven't already. <MOTIVATIONAL MESSAGE>	Tell Mama <BABY'S FIRST NAME> that <VACCINE NAME> vaccine is due this week. Go to the clinic if you haven't already. <MOTIVATIONAL MESSAGE>	Tell Mama <BABY'S FIRST NAME> that<VACCINE NAME> vaccine is due this week. Go to the clinic if you haven't already. <MOTIVATIONAL MESSAGE>
Motivational message	1 of 4 motivational messages randomly selected and appended to the end of the 3- and 1-day reminders; Motivational message is the same for the 1st and 3rd day reminder of the specific vaccine dose	No message	1. Vaccines save Kenyan babies lives; 2. <Most DISTRICT: ASEMBO OR GEM> babies get vaccinated, be one of them; 3. Baby < BABY'S FIRST NAME > is happy when healthy; or 4. Vaccines are available now.		

The incentive amounts in arms three and four were guided by opinions of mothers, village reporters, and local transport costs. The intent of the incentive is to help offset the costs associated with transportation to the clinic. The transaction costs associated with mobile-money transactions will be borne by the study, such that mothers will receive the full amount indicated. Enrolled mothers will be able to change the mobile phone number for receiving text message reminders and incentives when visiting any M-SIMU clinic.

Control

Mothers residing in control arm villages will receive a congratulatory text message at enrollment with a general-health related saying, "The greatest wealth is health" (See Table 1). No additional text messages or incentives will be sent to mothers.

At the 12 month follow-up visit conducted at the enrolled mother's household, a CI will refer mothers of under-vaccinated children from any arm to the nearest clinic.

Primary Objective

The study is powered to determine if text message reminders, with or without incentives, increase the percentage of fully immunized children (FIC) by 15% as compared with control group children at 12 months of age. A fully immunized child is defined as having received one dose of bacille Calmette-Guerin, three doses of pentavalent and polio vaccines, and one dose of measles vaccine.

Secondary Objectives

The study assesses several secondary objectives that primarily focus on timely receipt of individual vaccines and effect modifiers on the primary outcome. These secondary objectives include:

1. To determine if FIC coverage measured at 10 months of age varies by study arm;

2. To determine if the proportion of children vaccinated within 2 weeks of each scheduled vaccine date differs by study arm;

3. To determine if the proportion of children who drop-out in vaccination between first and third pentavalent dose differs by study arm;

4. To determine if measles and or pentavalent3 vaccine coverage varies by study arm;

5. To determine if there is a differential effect on vaccine coverage based on mobile phone ownership (owned vs shared) or on residential distance from a health facility.

6. To determine whether other indicators of health status, such as height-for-age, bed-net usage, vitamin A coverage, retention of the maternal and child health card, and all-cause mortality vary by study arm; and

7. To evaluate the direct costs for each intervention arm per additional child vaccinated beyond the status quo (ie, control group).

Randomization

This constrained randomization was conducted using GAUSS Mathematical and Statistical System. The GAUSS program iterated until 5000 acceptable randomizations were found that met the following criteria: (1) +/− relative 10% over all 152 villages for the means of the variables: full immunization coverage, phone ownership, distance to the nearest clinic, and village population of children 12- to 23- months-old, and (2) +/− relative 25% within each region for the means of the variables: full immunization coverage and phone ownership.

The randomization was also stratified on region such that each study arm contained 30 villages from Gem and eight villages from Asembo region. Data for the randomization came from the baseline survey described previously.

A simple random sample of n=1000 was taken from the 5000 valid randomization sequences. The 1000 sequences were labeled with a three-digit number, 000 to 999. Each sequence allocated 38 villages to one of four groupings (A-D).

Villages were randomized to study arms in a public ceremony attended by location chiefs and Community Advisory Board members on September 12, 2013 (Figure 2). Ten soccer balls were labeled with numbers zero through nine and placed in a cloth sack. Three location chiefs each drew one labeled ball, with replacement, such that a three-digit number, equating to a randomization sequence, was generated. Villages were placed into four groups based on the randomization sequence drawn. Then, four soccer balls labeled with the study arms (#1: control; #2: SMS; #3: KES75; and #4: KES200) were placed in a different cloth sack. A representative from each of the four groupings (A-D) drew one ball, without replacement, to determine the study arm assigned to all villages within the grouping. A similar randomization scheme for a cluster trial was successfully conducted in Zambia [36]. Due to the nature of the intervention and study design, study participants will know their study arm allocation.

Data Collection

The study is designed to minimally interfere with routine care–seeking behaviors of mothers and routine delivery of care by health practitioners. Participants are interviewed, at most, six times. All participants are interviewed at enrollment when the infant is between 0- and 4-weeks old and at follow-up when the infant is 12-months old. Mothers that bring their child for immunization at an M-SIMU clinic will be interviewed by study staff at each immunization visit (up to four visits).

CIs will administer the enrollment survey using the ODK Collect software on a simple smartphone. Mobile phone literacy, demographics, vaccine perceptions, transportation, and socioeconomic status will be collected at enrollment.

A KEMRI/CDC health facility recorder (HFR) will be stationed at each health facility to document enrolled infants' immunization. For all enrolled children, the HFR will send a text message to the RapidSMS server. This text message contains the child's study identification, the date of vaccination, which vaccine was received, and the new phone number if the mother has changed phone lines. If the mother is in an incentive arm (#3 or #4) and the child is vaccinated within 2 weeks of scheduled date, an incentive will be transferred to the phone number designated by the mother. After sending the vaccine receipt text message, HFRs will interview participants to collect means and costs of transportation and other clinic-related expenses for future cost-effective analyses.

For clinics where few immunizations are given per day, there will be no permanent HFR stationed due to financial constraints. Rather, HFRs from neighboring clinics or MOH staff, will visit these smaller clinics at the end of the day, collect immunization information for enrolled mother-infant pairs, and send the vaccine receipt SMS text message to the RapidSMS system. The M-SIMU trial will collect immunization from 24 clinics whose catchment areas envelope study villages (see Figure 2).

When enrolled children reach 12 months of age, CIs will conduct in-home follow up visits to document immunization status using the child's maternal and child health (MCH) booklet and to collect information on mothers' perceptions of the intervention(s).

Data Analysis

The analysis and reporting of results will be conducted in accordance with the **Consolidated Standards of Reporting Trials**guidelines adapted for cluster, randomized trials [37]. A blinded statistician will conduct analyses for primary and secondary outcomes. The primary analyses will be conducted with intention-to-treat principles. The primary outcome, FIC at 12 months of age, will be defined as a binary variable. Risk ratios for achieving FIC by 12 months of age will be calculated for the intervention arms as compared with the control arm. Due to the high number of clusters per study arm, individual level analyses using general estimating equations (GEE) with an exchangeable correlation matrix to account for correlation within clusters will be preferred over cluster level comparisons [38]. As a secondary analysis of the primary outcome, time-to-immunization curves will be constructed using the Kaplan-Meier method and study arms will be compared using the Cox model with frailty or robust variance estimator accounting for cluster. The 25th, 50th, and 75th percentiles for time to immunization and the number of days delayed, in relation to the EPI due date, will also be reported for each vaccine and by study arm. Lastly, adjusted analyses will be conducted if randomization results in imbalanced groups on key demographic variables. Effect estimates will be presented in whole and stratified on mobile phone ownership and clinic proximity. Mobile phone ownership will be defined as a binary variable ('owns a mobile phone' or 'doesn't own a mobile

phone'). Socioeconomic quintile scores will be computed using a multiple correspondence analysis of household assets, livestock, water source, and cooking fuel [39]. Straight-line distances from the participant's household to the nearest health facility will be calculated using ArcView Geographic Information Systems. An alpha of 0.05 will be assumed for all statistical tests of significance.

Sample Size

The primary objective is to increase the proportion of infants that are fully immunized at 12 months of age by 15% (eg, a difference between 70% in the control arm and 85% in an intervention arm). There are few interventions available to public health officials that can rapidly raise immunization coverage by this amount so we expect that this size of an effect will represent a meaningful public health impact and could motivate decision makers to adopt this intervention. Type 1 error (alpha) and our power to detect a 15% difference (1-beta) were set to 0.05 and 0.80, respectively.

Village-level immunization coverage estimates were collected during the baseline survey. The baseline survey indicated that approximately 70% (1243/1681) of children were fully immunized by 12 months of age. This estimate was used for assumptions on control arm immunization coverage. Village size (m) was calculated using the most recent HDSS birth cohort data for our study area and assuming 1-year enrollment. Because our sample size per village varies, we computed the harmonic mean for village size, calculated to be 16 children per village. [40].

An important parameter in cluster sample size calculations is *k*, the between cluster coefficient of variation. Although our baseline survey indicated a *k*of 0.14, for sample size calculations we used a conservative estimate of 0.25.

We expect that the percentage of children who will not be enrolled due to not meeting eligibility criteria or refusal will be approximately 10% and the number who will be lost to follow-up after enrollment before 12 months of age, due to death, outmigration, and other reasons, will be 15%. Therefore, we used a 25% reduction from the birth cohort size to determine the number of villages we will enroll in the study.

In order to ascertain a 15% difference between control and intervention arms, 152 villages will be included in the study (38 villages per arm).

Ethical Considerations

The study protocol received ethical clearance from the Scientific Steering Committee (SSC), the KEMRI-Nairobi Ethical Review Committee (ERC; SSC#2409), Johns Hopkins University Bloomberg School of Public Health (deferred ethical clearance to KEMRI-ERC), and the Centers for Disease Control and Prevention (deferred ethical clearance to KEMRI-ERC). The trial is registered with ClinicalTrials.gov [NCT 01878435, June 10, 2013]. The study's principal investigators are authors DF and KO from Johns Hopkins University and FO from KEMRI/CDC.

Results

The baseline survey was conducted March to April 2013 where it was found that 95% (2243/2393) of mothers owned or had access to a mobile phone within the compound. Focus group discussions were conducted in June 2013 to contextualize and adapt the interventions to the community's needs and to identify the incentive amounts. The randomized-controlled trial completed enrollment in October of 2014. Twelve month follow-up visits to ascertain enrolled participants' immunization status using the MCH booklet were completed in February, 2016.

Discussion

Supply side strategies to improve immunization, such as improving cold chain capacity, increasing procurement, and staff training, have been effective, but immunization gaps persist. Demand side interventions, such as text message reminders and incentives, that target cost of transport, vaccine fears and perception, and forgetfulness may play a more prominent role in reaching the "last mile" with timely immunizations.

Despite a lack of rigorous scientific evidence of effectiveness, mHealth and conditional cash transfer programs continue to spread throughout Africa [41-43]. This is the first randomized study to evaluate the impact of text message reminders and mobile money incentives on immunization coverage within sub-Sahara Africa. Evidence generated by this project will assist decision makers in the Kenyan Ministry of Health, as well as those in other African countries, before committing the investment, time, and effort that will be necessary to scale-up these programs. Moreover, this project has the opportunity to demonstrate the potential of mobile phone technologies in achieving the Millennium Development Goal of reducing childhood mortality in Africa. We anticipate results in 2016.

Acknowledgments

We thank the Gem and Asembo communities, KEMRI/CDC-Kisumu and project staff. The authors also thank Maurice Ombok for preparing the randomization map. The M-SIMU study is dedicated to the late Dan Odipo Orao; a motivated student, a loving husband, a caring father, a hard-working colleague, and a dear friend. Funding was obtained through the Bill & Melinda Gates Foundation (BMGF) and awarded to the International Vaccine Access Center (IVAC) at the Johns Hopkins University Bloomberg School of Public Health.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer review summary report from scientific steering committee.

[PDF File (Adobe PDF File), 57KB - resprot_v5i2e72_app1.pdf]

References

1. Gates Foundation. Decade of vaccines. Lancet Infect Dis 2010;10:139. [doi: 10.1016/S1473-3099(10)70033-5] [Medline: 20185087]
2. Alonso PL, de Quadros Ciro A, Robert M, Lal AA. Decade of Vaccines. Editorial. Vaccine 2013;31 Suppl 2:B3-B4. [doi: 10.1016/j.vaccine.2013.02.035] [Medline: 23598490]
3. Berkley S, Chan M, Elias C, Fauci A, Lake A, Phumaphi J. Decade of Vaccines. Foreword. Vaccine 2013;31 Suppl 2:B1-B2. [doi: 10.1016/j.vaccine.2013.02.014] [Medline: 23598469]
4. GAVI. Global Vaccine Action Plan. Decade of vaccine collaboration. Vaccine 2013;31 Suppl 2:B5-B31. [Medline: 23734366]
5. Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, Bassani DG, Child Health Epidemiology Reference Group of WHO and UNICEF. Global, regional, and national causes of child mortality in 2008: a systematic analysis. Lancet 2010;375:1969-1987. [doi: 10.1016/S0140-6736(10)60549-1] [Medline: 20466419]
6. WHO, UNICEF, World B. State of the World's Vaccines and Immunization 2009. Geneva: World Health Organization; 2009.
7. Lee LA, Franzel L, Atwell J, Datta SD, Friberg IK, Goldie SJ, et al. The estimated mortality impact of vaccinations forecast to be administered during 2011-2020 in 73 countries supported by the GAVI Alliance. Vaccine 2013;31 Suppl 2:B61-B72. [doi: 10.1016/j.vaccine.2012.11.035] [Medline: 23598494]
8. Grant CC, Roberts M, Scragg R, Stewart J, Lennon D, Kivell D, et al. Delayed immunisation and risk of pertussis in infants: unmatched case-control study. BMJ 2003;326:852-853. [doi: 10.1136/bmj.326.7394.852] [Medline: 12702617]
9. Kolos V, Menzies R, McIntyre P. Higher pertussis hospitalization rates in indigenous Australian infants, and delayed vaccination. Vaccine 2007;25:588-590. [doi: 10.1016/j.vaccine.2006.08.022] [Medline: 16971026]
10. Inskip HM, Hall AJ, Chotard J, Loik F, Whittle H. Hepatitis B vaccine in the Gambian Expanded Programme on Immunization: factors influencing antibody response. Int J Epidemiol 1991;20:764-769. [Medline: 1835452]
11. von KR, Böhm O, Windfuhr A. Haemophilus influenzae b-vaccination: the urgency for timely vaccination. Eur J Pediatr 1997;156:282-287. [Medline: 9128812]
12. Akmatov MK, Kretzschmar M, Krämer A, Mikolajczyk RT. Timeliness of vaccination and its effects on fraction of vaccinated population. Vaccine 2008;26:3805-3811. [doi: 10.1016/j.vaccine.2008.05.031] [Medline: 18565626]
13. Hamel MJ, Adazu K, Obor D, Sewe M, Vulule J, Williamson JM, et al. A reversal in reductions of child mortality in western Kenya, 2003-2009. Am J Trop Med Hyg 2011;85:597-605 [FREE Full text] [doi: 10.4269/ajtmh.2011.10-0678] [Medline: 21976557]
14. Kenya National Bureau of Statistics (KNBS). Kenya Demographic and Health Survey 2008-2009. Calverton, Maryland: KNBS and ICF Macro; 2010. URL: http://dhsprogram.com/pubs/pdf/fr229/fr229.pdf [accessed 2016-03-27] [WebCite Cache ID 6gKNSkS2S]
15. Clark A, Sanderson C. Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data. Lancet 2009;373:1543-1549. [doi: 10.1016/S0140-6736(09)60317-2] [Medline: 19303633]
16. Gibson DG, Ochieng B, Kagucia EW, Obor D, Odhiambo F, O'Brien KL, et al. Individual level determinants for not receiving immunization, receiving immunization with delay, and being severely underimmunized among rural western Kenyan children. Vaccine 2015:6778-6785. [doi: 10.1016/j.vaccine.2015.10.021] [Medline: 26482146]
17. de TK, Skinner D, Nembaware V, Benjamin P. Investigation into the use of short message services to expand uptake of human immunodeficiency virus testing, and whether content and dosage have impact. Telemed J E Health 2012;18:18-23. [doi: 10.1089/tmj.2011.0058] [Medline: 22150712]
18. Lester RT, Ritvo P, Mills EJ, Kariri A, Karanja S, Chung MH, et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. Lancet 2010;376:1838-1845. [doi: 10.1016/S0140-6736(10)61997-6] [Medline: 21071074]
19. Mbuagbaw L, Thabane L, Ongolo-Zogo P, Lester RT, Mills EJ, Smieja M, et al. The Cameroon Mobile Phone SMS (CAMPS) trial: a randomized trial of text messaging versus usual care for adherence to antiretroviral therapy. PLoS One 2012;7:e46909 [FREE Full text] [doi: 10.1371/journal.pone.0046909] [Medline: 23236345]
20. Odeny TA, Bailey RC, Bukusi EA, Simoni JM, Tapia KA, Yuhas K, et al. Text messaging to improve attendance at post-operative clinic visits after adult male circumcision for HIV prevention: a randomized controlled trial. PLoS One 2012;7:e43832 [FREE Full text] [doi: 10.1371/journal.pone.0043832] [Medline: 22957034]

21. Pop-Eleches C, Thirumurthy H, Habyarimana JP, Zivin JG, Goldstein MP, de WD, et al. Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders. AIDS 2011;25:825-834 [FREE Full text] [doi: 10.1097/QAD.0b013e32834380c1] [Medline: 21252632]
22. Zurovac D, Sudoi RK, Akhwale WS, Ndiritu M, Hamer DH, Rowe AK, et al. The effect of mobile phone text-message reminders on Kenyan health workers' adherence to malaria treatment guidelines: a cluster randomised trial. Lancet 2011;378:795-803 [FREE Full text] [doi: 10.1016/S0140-6736(11)60783-6] [Medline: 21820166]
23. Banerjee AV, Duflo E, Glennerster R, Kothari D. Improving immunisation coverage in rural India: clustered randomised controlled evaluation of immunisation campaigns with and without incentives. BMJ 2010;340:c2220 [FREE Full text] [Medline: 20478960]
24. Chandir S, Khan AJ, Hussain H, Usman HR, Khowaja S, Halsey NA, et al. Effect of food coupon incentives on timely completion of DTP immunization series in children from a low-income area in Karachi, Pakistan: a longitudinal intervention study. Vaccine 2010;28:3473-3478. [doi: 10.1016/j.vaccine.2010.02.061] [Medline: 20199756]
25. Thornton RL. The demand for, and impact of, learning HIV status. Am Econ Rev 2008;98:1829-1863 [FREE Full text] [doi: 10.1257/aer.98.5.1829] [Medline: 21687831]
26. Kharbanda EO, Stockwell MS, Fox HW, Andres R, Lara M, Rickert VI. Text message reminders to promote human papillomavirus vaccination. Vaccine 2011;29:2537-2541. [doi: 10.1016/j.vaccine.2011.01.065] [Medline: 21300094]
27. Moniz MH, Hasley S, Meyn LA, Beigi RH. Improving influenza vaccination rates in pregnancy through text messaging: a randomized controlled trial. Obstet Gynecol 2013;121:734-740. [doi: 10.1097/AOG.0b013e31828642b1] [Medline: 23635672]
28. Stockwell MS, Kharbanda EO, Martinez RA, Vargas CY, Vawdrey DK, Camargo S. Effect of a text messaging intervention on influenza vaccination in an urban, low-income pediatric and adolescent population: a randomized controlled trial. JAMA 2012;307:1702-1708. [doi: 10.1001/jama.2012.502] [Medline: 22535855]
29. Stockwell M, Kharbanda E, Martinez R, Lara M, Vawdrey D, Natarajan K, et al. Text4Health: impact of text message reminder-recalls for pediatric and adolescent immunizations. Am J Public Health 2012;102:e15-e21. [doi: 10.2105/AJPH.2011.300331] [Medline: 22390457]
30. Bangure D, Chirundu D, Gombe V, Mandozana, G, Tshimanga M, Takundwa L. Effectiveness of short message services reminder on childhood immunization programme in Kadoma, Zimbabwe - a randomized controlled trial, 2013. BMC PUblic Health 2015;15:137. [doi: 10.1186/s12889-015-1470-6]
31. Haji A, Lowther S, Ngan'ga Z, Gura Z, Tabu C, Sandhu H, et al. Reducing routine vaccination dropout rates: evaluating two interventions in three Kenyan districts, 2014. BMC Public Health 2016;16:152. [doi: 10.1186/s12889-016-2823-5]
32. Wakadha H, Chandir S, Were EV, Rubin A, Obor D, Levine OS, et al. The feasibility of using mobile-phone based SMS reminders and conditional cash transfers to improve timely immunization in rural Kenya. Vaccine 2013;31:987-993 [FREE Full text] [doi: 10.1016/j.vaccine.2012.11.093] [Medline: 23246258]
33. Odhiambo FO, Laserson KF, Sewe M, Hamel MJ, Feikin DR, Adazu K, van Eijk Anna M, et al. Profile: the KEMRI/CDC Health and Demographic Surveillance System--Western Kenya. Int J Epidemiol 2012;41:977-987 [FREE Full text] [doi: 10.1093/ije/dys108] [Medline: 22933646]
34. Armah GE, Sow SO, Breiman RF, Dallas MJ, Tapia MD, Feikin DR, et al. Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in sub-Saharan Africa: a randomised, double-blind, placebo-controlled trial. Lancet 2010;376:606-614. [doi: 10.1016/S0140-6736(10)60889-6] [Medline: 20692030]
35. Phillips-Howard PA, Nahlen BL, Wannemuehler KA, Kolczak MS, ter Kuile Feiko O, Gimnig JE, et al. Impact of permethrin-treated bed nets on the incidence of sick child visits to peripheral health facilities. Am J Trop Med Hyg 2003;68(4 Suppl):38-43 [FREE Full text] [Medline: 12749484]
36. Sismanidis C, Moulton LH, Ayles H, Fielding K, Schaap A, Beyers N, et al. Restricted randomization of ZAMSTAR: a 2 x 2 factorial cluster randomized trial. Clin Trials 2008;5:316-327. [doi: 10.1177/1740774508094747] [Medline: 18697846]
37. Campbell MK, Piaggio G, Elbourne DR, Altman DG. Consort 2010 statement: extension to cluster randomised trials. BMJ 2012;345:e5661. [Medline: 22951546]
38. Hayes R, Moulton L. Cluster Randomised Trials: A Practical Approach (Interdisciplinary Statistics). New York: Chapman & Hall/CRC; 2009.
39. Amek N, Vounatsou P, Obonyo B, Hamel M, Odhiambo F, Slutsker L, et al. Using health and demographic surveillance system (HDSS) data to analyze geographical distribution of socio-economic status; an experience from KEMRI/CDC HDSS. Acta Trop 2015;144:24-30. [doi: 10.1016/j.actatropica.2015.01.006] [Medline: 25602533]
40. Hayes RJ, Bennett S. Simple sample size calculation for cluster-randomized trials. Int J Epidemiol 1999;28:319-326 [FREE Full text] [Medline: 10342698]
41. Gaarder MM, Glassman A, Todd JE. Conditional cash transfers and health: unpacking the causal chain. Journal of Development Effectiveness 2010;2:6-50. [doi: 10.1080/19439341003646188]
42. Garcia M, Moore C. The Cash Dividend: The Rise of Cash Transfer Programs in Sub-Saharan Africa (Directions in Development). Washington D.C: World Bank Publications; 2012.
43. Labrique A, Vasudevan L, Chang LW, Mehl G. H_pe for mHealth: more "y" or "o" on the horizon? Int J Med Inform 2013;82:467-469 [FREE Full text] [doi: 10.1016/j.ijmedinf.2012.11.016] [Medline: 23279850]

Abbreviations

CDC: Centers for Disease Control and Prevention
CI: community interviewer
ERC: ethical review committee
FIC: fully immunized child
GEE: general estimating equation
HDSS: health and demographic surveillance system
HFR: health facility recorder
KEPI: Kenyan Expanded Programme on Immunization
KES: Kenyan Shilling
M-SIMU: Mobile Solutions for Immunization
MCH: maternal and child health
SSC: scientific steering committee

Edited by G Eysenbach; submitted 25.10.15; peer-reviewed by S Muhula, J Kaewkungwal; comments to author 20.01.16; revised version received 22.01.16; accepted 22.01.16; published 17.05.16.

Please cite as:
Gibson DG, Kagucia EW, Ochieng B, Hariharan N, Obor D, Moulton LH, Winch PJ, Levine OS, Odhiambo F, O'Brien KL, Feikin DR
The Mobile Solutions for Immunization (M-SIMU) Trial: A Protocol for a Cluster Randomized Controlled Trial That Assesses the Impact of Mobile Phone Delivered Reminders and Travel Subsidies to Improve Childhood Immunization Coverage Rates and Timeliness in Western Kenya
JMIR Res Protoc 2016;5(2):e72
URL: http://www.researchprotocols.org/2016/2/e72/
doi:10.2196/resprot.5030
PMID:27189422

Protocol

Diagnosis of Basal Cell Carcinoma by Reflectance Confocal Microscopy: Study Design and Protocol of a Randomized Controlled Multicenter Trial

Malou Peppelman[1], PhD; Kim P Nguyen[1], MD; Hans A.C Alkemade[2], MD PhD; Birgitte Maessen-Visch[3], MD PhD; Jan C.M Hendriks[4], PhD; Piet E.J van Erp[1], PhD.; Eddy M.M Adang[4], PhD.; Marie-Jeanne P Gerritsen[1], MD, PhD

[1]Radboud University Medical Center, Department of Dermatology, Nijmegen, Netherlands

[2]Canisius Wilhelmina Hospital, Department of Dermatology, Nijmegen, Netherlands

[3]Rijnstate hospital, Department of Dermatology, Arnhem-Velp, Netherlands

[4]Radboud University Medical Center, Department for Health Evidence, Nijmegen, Netherlands

Corresponding Author:
Malou Peppelman, PhD
Radboud University Medical Center
Department of Dermatology
P.O. Box 9101
Nijmegen, 6500 HB
Netherlands
Phone: 31 362417240
Fax: 31 243635122
Email: malou.peppelman@radboudumc.nl

Abstract

Background: Skin cancer, including basal cell carcinoma (BCC), has become a major health care problem. The limitations of a punch biopsy (at present the gold standard) as diagnostic method together with the increasing incidence of skin cancer point out the need for more accurate, cost-effective, and patient friendly diagnostic tools. In vivo reflectance confocal microscopy (RCM) is a noninvasive imaging technique that has great potential for skin cancer diagnosis.

Objective: To investigate whether in vivo RCM can correctly identify the subtype of BCC and to determine the cost-effectiveness of RCM compared with punch biopsy (usual care). Study design: Randomized controlled multicenter trial.

Methods: On the basis of 80% power and an alpha of 0.05, 329 patients with lesions clinically suspicious for BCC will be included in this study. Patients will be randomized for RCM or for a punch biopsy (usual care). When a BCC is diagnosed, surgical excision will follow and a follow-up visit will be planned 3 months later. Several questionnaires will be filled in (EQ-5D, EQ-5D VAS, iMTA PCQ, and TSQM-9). We will perform statistical analysis, cost-effectiveness, and patient outcome analysis after data collection.

Results: This research started in January 2016 and is ethically approved. We expect to finish this study at the end of 2018.

Conclusions: In this study, we will investigate whether RCM is at least as good in identifying BCC subtypes as conventional pathological investigation of skin biopsies. Anticipating that RCM is found to be a cost-effective alternative, it saves on direct medical consumption like labor of the pathologist and other medical personnel as well as materials related to treatment failure with at least equal effectiveness.

Trial Registration: Clinicaltrials.gov NCT02623101; https://clinicaltrials.gov/ct2/show/NCT02623101 (Archived by WebCite at http://www.webcitation.org/6id54WQa2)

(JMIR Res Protoc 2016;5(2):e114) doi:10.2196/resprot.5757

KEYWORDS

basal cell carcinoma; reflectance confocal microscopy; diagnosis; cost effectiveness

Introduction

Skin Cancer

Skin cancer is a common type of cancer and its incidence is increasing rapidly in Western countries [1-3]. This cancer comprises two types: melanoma (MM) and nonmelanoma skin cancer (NMSC). NMSC is further divided into basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and its precursors actinic keratosis (AK) and Bowen disease. In the Netherlands, the registry of NMSC is poor. However, based on recent literature and guidelines, it is estimated that the incidence of malignant skin tumors and the premalignant AK is around 235,000 in 2015. This will have a major impact on our health care system. Moreover, it is predicted that numbers will rise at the rate of 4.5-8% per year, depending on the type of skin cancer. Currently, in case of suspicion of NMSC, the pathological examination of a punch biopsy is the gold standard, according to the Dutch guidelines. In case of clinical suspicion of AK, the diagnosis is made *à vue*, without pathological confirmation. Already in 2003 in the United States, skin cancer was found to be among the most costly of all cancers to treat. Therefore, it is evident that skin cancer places an enormous burden on health care systems with increasing costs [4]. In case of suspicion of skin cancer, it is important to diagnose and treat it in an early phase, preferably in a patient friendly manner. As BCC is the most common skin cancer (about 75% of all skin cancers), this study will focus on studying this skin cancer type. Clinically, BCC can vary in appearance but is often characterized by small, translucent, or pearly papules, with telangiectasias [5]. In the past, the diagnosis was mainly made clinically. However, noninvasive therapies have become available; therefore, determination of the BCC subtype has become more important. For this reason, pathological analysis of a punch biopsy is currently the gold standard to confirm the clinical diagnosis and determine the subtype of BCC. The following subtypes of BCC can be distinguished: superficial (sBCC), nodular (nBCC), aggressive BCC (micronodular (mnBCC), and infiltrative (iBCC)) [6]. It is experienced that there is a sample error in 29% of the cases with the conventional diagnostic procedure, resulting in an incorrect subtype diagnosis [7]. For this reason and because of the increasing incidence of skin cancer, more accurate, cost-efficient, and patient friendly diagnostic tools are desirable.

Reflectance Confocal Microscopy

Reflectance confocal microscopy (RCM) is a noninvasive imaging technique. It provides real-time images of cell and tissue structures and in vivo dynamics, without the need for ex vivo tissue samples. RCM visualizes human skin up to a depth of around 250 µm [8-12]. Refractive index differences between cells and surrounding tissue provide the contrast. The contrast of RCM imaging of the skin is mainly provided by melanin and keratin [10]. Most, but not all, tumors can be visualized. For thicker tumors, RCM may help to find the optimal localization to perform a punch biopsy, as superficial features in these tumors may help to spot these lesions [13]. Moreover, RCM can image the whole tumor. RCM features for NMSC have been described that showed a high correlation with conventional pathological features [13-15]. These features allow diagnosing AK, SCC, and BCC [13-15]. For both the BCC subtypes, nodular and micronodular BCC, the following RCM characteristics are described: tumor nests with peripheral palisading, branch-like structures, fibrotic septa, and increase of vascular diameter. The size and shape of the tumor nests allows further distinction between these BCCs. Solar elastosis and tumor nests connected with the basal cell layer characterize superficial BCC [14]. iBCCs are more challenging to visualize due to their histological complex appearance and deeper location [16].

Only few studies report data about diagnostic accuracy of RCM for primary BCC diagnosis [14,16-19]. These studies show a high sensitivity and specificity for RCM as diagnostic tool for BCC. Although these show the potential of RCM in BCC diagnosis, prospective large-scale studies are lacking. In addition to BCC diagnosis by RCM in general, no diagnostic accuracy data were reported on determination of BCC subtype by RCM. Such studies are required for implementation of RCM in the routine patient care and incorporation into the health insurance system. Implementation of RCM in the routine patient care settings has the advantage of making a diagnosis at the first consultation and therefore, the patient can be treated at short term. A second consultation for explaining the diagnosis and performing the treatment might be unnecessary. Therefore, time saved by using the RCM can be used for other new patients.

Objectives

The primary objective of this study is to investigate whether in vivo RCM can identify the subtype of BCC at least as correctly as a skin punch biopsy. We are hypothesizing that RCM imaging allows correct identification of the BCC subtype (nBCC, mnBCC, sBCC, iBCC, and mixed type BCC), and true and false positive results are equal or better as compared with conventional pathological investigation of skin biopsies (gold standard). It is postulated that RCM is more cost-effective and patient friendly compared with the current procedure. Therefore, the quality of life (Qol), costs, and quality adjusted life years (QALYs) will be evaluated as the secondary outcome measures. Overall, with the implementation of RCM in dermatology skin cancer care, it is aimed to contribute to cost-effective, noninvasive, patient friendly diagnostics.

Methods

Recruitment, Inclusion, and Study Design

Patients with lesions clinically suspicious (diagnosis *à vue*) for BCC, eligible for RCM, visiting the dermatological departments of the Radboud University Medical Center, Nijmegen, the Canisius Wilhelmina Hospital, Nijmegen, and the Rijnstate Hospital Arnhem-Velp, in The Netherlands will be asked to join this study.

In order to be eligible for participation in this study, a subject must meet all of the following criteria:

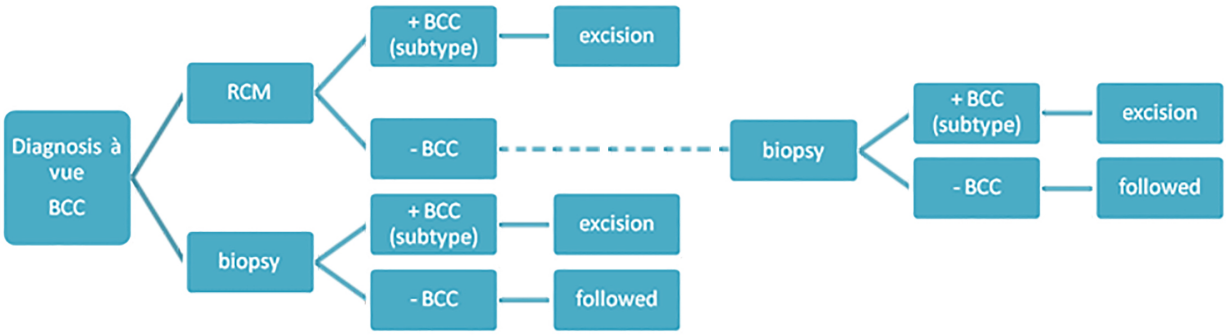
- Patients must be 18 years and above.
- Patients must be able to adhere to all requirements of the study.
- Patients must be willing to give written informed consent.
- There must be clinical diagnosis/clinical suspicion of basal cell carcinoma.

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- A patient participating in other investigational research currently or in the previous 28 days before the study
- Patient having a medical condition which excludes participating the research, according to the investigator
- Incapacitated subjects
- Subjects with lesion(s) on parts of the body which do not allow adequate imaging of the tumor with RCM

When a patient meets these criteria and gives informed consent, he or she is assigned to a randomization arm according to a computer-generated block randomization (Castor) (Figure 1).

Figure 1. Scheme of randomization. Two randomization arms are designed. After inclusion, a patient with a clinical diagnosis of BCC (diagnosis à vue) will be randomized over the two arms. One arm contains the standard procedure of a biopsypunch biopsy, the other arm contains the diagnostic tool to be investigated: RCM. A punch biopsy will also be obtained when there is no suspicion of a BCC using RCM.



Power Calculation

The primary outcome in this study is the percentage of correctly identified subtype of confirmed BCC after excision (gold standard in this study). We assume that this is 71% when a punch biopsy is used and 85% when RCM is used (based on an ongoing study). In this case, 148 patients are needed per group to obtain a power of 80% (Fisher's-exact, two-sided, alpha=0.05). We expect that 10% of the patients with a clinically suspected BCC will not have histopathologically confirmed BCC. Therefore, we will include approximately 329 patients with a clinical suspicion of BCC. In this multicenter randomized controlled trial (RCT), it is also possible to obtain empirical estimates of the (cost-) effectiveness in daily clinical practice, beyond the diagnostic value. The expected benefit of the experimental diagnostic tool is anticipated at €92 per patient. On the basis of a conservative choice of the SD of €100 and the CI of 95%, 146 patients per group are required. Counting a 10% possible dropouts, around 322 patients need to be included.

To answer both questions, in total 329 patients suspected with a clinical suspected BCC will be included in this study.

Outcome Measures

The primary outcome measure is defined as correct subtyping of the BCC after excision. The histopathological diagnosis of the excision specimen will be compared with either the diagnosis made by RCM or a punch biopsy. Secondary outcome measures are Qol, Cost, and QALYs.

Procedure

Patients will be assigned to either the RCM or the punch biopsy study arm (Figure 1). When a BCC is diagnosed using RCM or the gold standard (punch biopsy), surgical excision will follow according to standard care-time schedule at the center where the BCC is diagnosed with margins according to the guidelines (3 mm for sBCC and nBCC, 5 mm for aggressive BCC). In case of a BCC, a follow-up visit will be planned 3 months after surgery. If the diagnosis reveals the absence of a BCC, the patients will again be followed-up after 3 months. During visit 1 (diagnostic procedure) several questionnaires will be filled in (EQ-5D, EQ-5d VAS, iMTA PCQ, and TSQM-9). At the follow-up visit after treatment, the questions about satisfaction of the diagnostic procedure will be asked again. In order to establish the added monetary value of RCM, a contingent valuation method (CVM) was used. Patients that belong to the RCM arm and also had a punch biopsy, in which both diagnosis had the absence of a BCC, were interviewed according to the CVM.

RCM will be performed with the commercially available Vivascope 1500 (Caliber imaging & diagnostics, Rochester, NY, USA) according to a standardized protocol. Vivablocks of 4 × 4 mm will be made at the level of the stratum corneum, stratum spinosum, dermal epidermal junction, and dermis in order to find RCM features for BCC and the subtype. Vivastacks will be made in the areas of interest. Movies will be made to document vascularization. When indicated, the Vivascope 3000 handheld device will be used. The RCM user is working for 4 years with the device. If a punch biopsy needs to be obtained according to the randomization scheme, this will occur after local anesthesia (1% xylocaine/adrenaline) and the punch biopsy will have a diameter of 3 mm. The punch biopsy will be taken from the most clinically suspected area of the lesion.

Analysis

After data collection, analyses will be performed. The Fisher's-exacts test will be used to test the differences in the primary outcome between the two study arms (biopsy, RCM) for statistical significance. Multivariable logistic regression will be used to study possible differences between the subtypes and the effect of possible other variables. This will be done in order

to evaluate variables or sets of variables for its discriminative character that can be used to make protocols and guidelines for future Dutch RCM users.

Cost-Effectiveness Analysis

The cost analysis comprises two main parts. First, on patient level, volumes of care will be measured prospectively over the time path of the clinical trial using the iMCQ (a generic instrument for measuring medical costs [20]) complemented with procedure specific cost information like cost of RCM equipment and patient out-of-pocket expenses, such as over-the-counter drugs (for example pain related). Relevant, (missing) entries will be verified or completed by data from the medical records or inpatient treatment facility's administration system. Second, per modality (RCM or usual care) standard cost prices will be determined using the Dutch guideline [21] or else real/full cost prices via activity-based costing. Productivity losses will be estimated using a patient-based questionnaire [22]. The friction-cost method will be applied following the Dutch guidelines [21].

Patient Outcome Analysis

The effect analysis adheres to the design of a superiority/equivalent RCT and measures diagnostic performance and Qol at baseline, and at fixed points along the follow-up of the RCT. To measure the quality of the health status of the patients, a validated so-called health-related quality of life (HRQoL) instrument will be used, the EuroQol-5D-3L (EQ-5D) [23]. This HRQoL instrument will be completed by the patients and is available in a validated Dutch translation [24]. The EQ-5D is a generic HRQoL instrument comprising five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D index is obtained by applying predetermined weights to the five domains. This index gives a societal-based global quantification of the patient's health status on a scale ranging from 0 (death) to 1 (perfect health). Patients will also be asked to rate their overall HRQoL on a visual analogue scale (EQ-5D VAS) consisting of a line ranging from 0 (worst imaginable health status) to 100 (best imaginable). The patient outcome analysis will be complemented with a CVM questionnaire and measures of satisfaction and pain related to diagnosing subtype BCC.

Results

This investigator initiated multicenter RCT is conducted according to the principles of the Declaration of Helsinki (2013) and in accordance with the medical Research Involving Human Subjects Act (WMO). The study is funded by ZonMw, a Dutch organization that finances health science, and thereby stimulates the use of obtained knowledge to improve health care. The medical ethics committee (NL 54549.091.15) approved the study protocol in December 2015. The study will start in January 2016, and is expected to finish until the end of 2018. This trail had also been registered at ClinicalTrails.gov (nr: NCT02623101).

Discussion

Considering the increasing skin cancer problem, including BCC, and the disadvantages of the current diagnostic gold standard, histopathological diagnosis of a punch biopsy, indicates the need for cost- and time-efficient diagnostic tools with high accuracy for diagnosing skin cancers. These tools should be able to distinguish between skin cancer types and should be able to determine the correct BCC subtype, as different subtypes of BCCs are treated differently. Biopsies often result in sampling errors, as only a small part of the tumor is investigated resulting in potentially inappropriate chosen therapies. As a sample error may lead to treatment failures or recurrences, other subsequent treatments are needed. This will eventually lead to increasing costs. In addition, the conventional method is unfriendly for patients, as it is invasive, painful, and might result in scarring. Furthermore, the diagnosis cannot be made instantly.

To contribute to implementation of RCM as noninvasive skin cancer diagnostic tool, this study will investigate whether RCM is at least as good in identifying BCC subtypes as conventional histopathological investigation of skin biopsies. Hypothesizing that RCM is a cost-effective alternative to the present care, it saves on direct medical consumption like labor of the pathologist and other medical personnel as well as materials related to treatment failure with at least equal effectiveness.

Conflicts of Interest

None declared.

References

1. Flohil SC, de VE, Neumann H A Martino, Coebergh JW, Nijsten T. Incidence, prevalence and future trends of primary basal cell carcinoma in the Netherlands. Acta Derm Venereol 2011 Jan;91(1):24-30 [FREE Full text] [doi: 10.2340/00015555-1009] [Medline: 21264452]
2. Flohil SC, van der Leest Robert J T, Dowlatshahi EA, Hofman A, de VE, Nijsten T. Prevalence of actinic keratosis and its risk factors in the general population: the Rotterdam Study. J Invest Dermatol 2013 Aug;133(8):1971-1978 [FREE Full text] [doi: 10.1038/jid.2013.134] [Medline: 23510990]
3. Flohil SC, Seubring I, van Rossum Michelle M, Coebergh JW, de VE, Nijsten T. Trends in Basal cell carcinoma incidence rates: a 37-year Dutch observational study. J Invest Dermatol 2013 Apr;133(4):913-918 [FREE Full text] [doi: 10.1038/jid.2012.431] [Medline: 23190883]

4. Housman TS, Feldman SR, Williford PM, Fleischer AB, Goldman ND, Acostamadiedo JM, et al. Skin cancer is among the most costly of all cancers to treat for the Medicare population. J Am Acad Dermatol 2003 Mar;48(3):425-429. [doi: 10.1067/mjd.2003.186] [Medline: 12637924]
5. Madan V, Lear JT, Szeimies R. Non-melanoma skin cancer. Lancet 2010 Feb 20;375(9715):673-685. [doi: 10.1016/S0140-6736(09)61196-X] [Medline: 20171403]
6. Crowson AN. Basal cell carcinoma: biology, morphology and clinical implications. Mod Pathol 2006 Feb;19 Suppl 2:S127-S147 [FREE Full text] [doi: 10.1038/modpathol.3800512] [Medline: 16446711]
7. Wolberink E A W, Pasch MC, Zeiler M, van Erp P E J, Gerritsen M J P. High discordance between punch biopsy and excision in establishing basal cell carcinoma subtype: analysis of 500 cases. J Eur Acad Dermatol Venereol 2013 Aug;27(8):985-989. [doi: 10.1111/j.1468-3083.2012.04628.x] [Medline: 22759209]
8. Calzavara-Pinton P, Longo C, Venturini M, Sala R, Pellacani G. Reflectance confocal microscopy for in vivo skin imaging. Photochem Photobiol 2008;84(6):1421-1430. [doi: 10.1111/j.1751-1097.2008.00443.x] [Medline: 19067964]
9. Rajadhyaksha M, González S, Zavislan JM, Anderson RR, Webb RH. In vivo confocal scanning laser microscopy of human skin II: advances in instrumentation and comparison with histology. J Invest Dermatol 1999 Sep;113(3):293-303 [FREE Full text] [doi: 10.1046/j.1523-1747.1999.00690.x] [Medline: 10469324]
10. Rajadhyaksha M, Grossman M, Esterowitz D, Webb RH, Anderson RR. In vivo confocal scanning laser microscopy of human skin: melanin provides strong contrast. J Invest Dermatol 1995 Jun;104(6):946-952 [FREE Full text] [Medline: 7769264]
11. Peppelman M, Wolberink E A W, Gerritsen MP, van de Kerkhof P C M, van Erp P E J. Application of leukotriene B4 and reflectance confocal microscopy as a noninvasive in vivo model to study the dynamics of skin inflammation. Skin Res Technol 2015 May;21(2):232-240. [doi: 10.1111/srt.12181] [Medline: 25156913]
12. Wolberink Eshter A W, Peppelman M, van de Kerkhof Peter C M, van Erp Piet E J, Gerritsen MP. Establishing the dynamics of neutrophil accumulation in vivo by reflectance confocal microscopy. Exp Dermatol 2014 Mar;23(3):184-188. [doi: 10.1111/exd.12345] [Medline: 24521061]
13. Peppelman M, Nguyen KP, Hoogedoorn L, van Erp P E J, Gerritsen MP. Reflectance confocal microscopy: non-invasive distinction between actinic keratosis and squamous cell carcinoma. J Eur Acad Dermatol Venereol 2015 Jul;29(7):1302-1309. [doi: 10.1111/jdv.12806] [Medline: 25357235]
14. Peppelman M, Wolberink Esther A W, Blokx Willeke A M, van de Kerkhof Peter C M, van Erp Piet E J, Gerritsen MP. In vivo diagnosis of basal cell carcinoma subtype by reflectance confocal microscopy. Dermatology 2013;227(3):255-262. [doi: 10.1159/000354762] [Medline: 24158236]
15. Peppelman M, Wolberink Esther A W, Koopman Roland J J, van Erp Piet E J, Gerritsen MP. In vivo Reflectance Confocal Microscopy: A Useful Tool to Select the Location of a Punch Biopsy in a Large, Clinically Indistinctive Lesion. Case Rep Dermatol 2013 Jan;5(1):129-132 [FREE Full text] [doi: 10.1159/000351258] [Medline: 23687492]
16. Longo C, Lallas A, Kyrgidis A, Rabinovitz H, Moscarella E, Ciardo S, et al. Classifying distinct basal cell carcinoma subtype by means of dermatoscopy and reflectance confocal microscopy. J Am Acad Dermatol 2014 Oct;71(4):716-724.e1. [doi: 10.1016/j.jaad.2014.04.067] [Medline: 24928707]
17. Gerger A, Koller S, Weger W, Richtig E, Kerl H, Samonigg H, et al. Sensitivity and specificity of confocal laser-scanning microscopy for in vivo diagnosis of malignant skin tumors. Cancer 2006 Jul 1;107(1):193-200 [FREE Full text] [doi: 10.1002/cncr.21910] [Medline: 16615102]
18. Guitera P, Menzies SW, Longo C, Cesinaro AM, Scolyer RA, Pellacani G. In vivo confocal microscopy for diagnosis of melanoma and basal cell carcinoma using a two-step method: analysis of 710 consecutive clinically equivocal cases. J Invest Dermatol 2012 Oct;132(10):2386-2394 [FREE Full text] [doi: 10.1038/jid.2012.172] [Medline: 22718115]
19. Nori S, Rius-Díaz F, Cuevas J, Goldgeier M, Jaen P, Torres A, et al. Sensitivity and specificity of reflectance-mode confocal microscopy for in vivo diagnosis of basal cell carcinoma: a multicenter study. J Am Acad Dermatol 2004 Dec;51(6):923-930. [doi: 10.1016/j.jaad.2004.06.028] [Medline: 15583584]
20. Bouwmans C, Hakkaart-van Roijen L, Koopmanschap M, Krol M, Severens W, Brouwer W. ScienceOPEN. Rotterdam: iMTA, Erasmus Universiteit Rotterdam; 2013. Handleiding iMTA Medical Cost Questionnaire (iMCQ) URL: https://www.scienceopen.com/document?vid=349ba10f-11a5-4327-8cd2-bd45f82fc75b [accessed 2016-05-23] [WebCite Cache ID 6hiMh7wfc]
21. Tan SS, Bouwmans-Frijters CAM, Hakkaart-van Roijen L. Handleiding voor kostenonderzoek: methoden en referentieprijzen voor economische evaluaties in de gezondheidszorg. Tijds. gezondheids.wetenschappen 2012 Oct 11;90(6):367-372. [doi: 10.1007/s12508-012-0128-3]
22. Bouwmans C, Hakkaart-van Roijen L, Koopmanschap M, Krol M, Severens H, Brouwer W. Manual of the iMTA Productivity Cost Questionnaire (iPCQ). Rotterdam: iMTA, Erasmus University Rotterdam; 2013.
23. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997 Nov;35(11):1095-1108. [Medline: 9366889]
24. Lamers LM, Stalmeier P F M, McDonnell J, Krabbe P F M, van Busschbach J J. [Measuring the quality of life in economic evaluations: the Dutch EQ-5D tariff]. Ned Tijdschr Geneeskd 2005 Jul 9;149(28):1574-1578. [Medline: 16038162]

Edited by G Eysenbach; submitted 14.03.16; peer-reviewed by C Longo, D Kadouch; comments to author 03.04.16; revised version received 04.04.16; accepted 04.04.16; published 30.06.16.

Please cite as:
Peppelman M, Nguyen KP, Alkemade HA, Maessen-Visch B, Hendriks JC, van Erp PE, Adang EM, Gerritsen MJP
Diagnosis of Basal Cell Carcinoma by Reflectance Confocal Microscopy: Study Design and Protocol of a Randomized Controlled Multicenter Trial
JMIR Res Protoc 2016;5(2):e114
URL: http://www.researchprotocols.org/2016/2/e114/
doi:10.2196/resprot.5757
PMID:27363577

Protocol

Building a Tailored, Patient-Guided, Web-Based Self-Management Intervention 'ReumaUitgedaagd!' for Adults With a Rheumatic Disease: Results of a Usability Study and Design for a Randomized Control Trail

Judy W Ammerlaan[1], RN, MSc; Olga K Mulder[1], MSc; Nienke C de Boer-Nijhof[2], MA; Bertha Maat[2]; Aike A Kruize[1], MD, PhD; Jaap van Laar[1], MD, PhD; Harmieke van Os-Medendorp[3], RN, PhD; Rinie Geenen[4], PhD

[1]University Medical Center Utrecht, Department Rheumatology and Clinical Immunology, Utrecht, Netherlands

[2]Dutch Arthritis Foundation, Amsterdam, Netherlands

[3]University Medical Center Utrecht, Department Dermatology and Allergology, Utrecht, Netherlands

[4]Utrecht University, Department Clinical and Health Psychology, Utrecht, Netherlands

Corresponding Author:
Judy W Ammerlaan, RN, MSc
University Medical Center Utrecht
Department Rheumatology and Clinical Immunology
PO Box 85 500
Utrecht, 3508 GA
Netherlands
Phone: 31 887558660
Fax: 31 302518328
Email: j.ammerlaan@umcutrecht.nl

Abstract

Background: The chronic nature of rheumatic diseases imposes daily challenges upon those affected and causes patients to make daily decisions about the way they self-manage their illness. Although there is attention to self-management and evidence for the desirability of tailored interventions to support people with a rheumatic disease, interventions based on individual needs and preferences are scarce.

Objective: To provide a systematic and comprehensive description of the theoretical considerations for building a Web-based, expert, patient-guided, and tailored intervention for adult patients with a rheumatic disease. Also, to present the results of a usability study on the feasibility of this intervention, and its study design in order to measure the effectiveness.

Methods: To fit the intervention closely to the autonomy, needs, and preferences of the individual patient, a research team comprising patient representatives, health professionals, Web technicians, and communication experts was formed. The research team followed the new guidance by the Medical Research Council (MRC) for developing and evaluating complex interventions as a guide for the design of the intervention.

Results: Considerations from self-determination theory and a comprehensive assessment of preferences and needs in patients with a rheumatic disease guided the development of the Web-based intervention. The usability study showed that the intervention was useful, easy to use, and accepted and appreciated by the target group of patients. The planned randomized controlled trial is designed to be conducted among 120 adults with a rheumatic disease, who are assigned to the self-management intervention or a self-help control group. Both groups will be asked to formulate personal goals they want to achieve concerning their self-management. Progress toward the personal goal is the primary outcome measure of this study. Self-reported Web-based measures will be assessed before randomization at baseline, and 3 and 6 months after randomization. Also, feasibility and adherence to the Web-based self-management intervention as process outcomes will be evaluated.

Conclusion: By identifying the individual goals at the beginning of the intervention and customizing the intervention to the individual patient, we aim to improve the usefulness and effectiveness of the Web-based self-management intervention. If proven effective, ReumaUitgedaagd! Online will be implemented in the Netherlands.

(JMIR Res Protoc 2016;5(2):e113) doi:10.2196/resprot.5735

KEYWORDS

Web-based; self-management; tailored; intervention; pilot study; randomized controlled trial; personal goal; rheumatic diseases

Introduction

Background

Having a rheumatic disease often leads to symptoms of pain, fatigue, and physical constraints that are part of a reduced health-related quality of life [1]. The chronic nature of this disease imposes daily challenges upon those affected and causes patients to make daily decisions about the way they manage their illness [1-3]. The question is not "whether" patients self-manage their (chronic) illness, but "how" they do this [4]. The '(individual's) ability to manage the symptoms, treatment, physical, and psychosocial consequences and life style changes inherent in living with a chronic condition' has been defined as self-management [5]. Interventions to improve self-management commonly combine information-based and cognitive-behavioral strategies [6]. In the last decade, several interventions have been developed to improve self-management. For people with a rheumatic disease, the Arthritis Self-Management intervention (ASMP) of Stanford University is the most recognized and studied self-management intervention [7]. The ASMP intervention, based on the self-efficacy theory of Bandura [8] is led by expert patients and is designed to help people with arthritis gain confidence in their ability to control their symptoms and the impact of their condition on their lives [7,9,10]. For patients with rheumatoid arthritis and osteoarthritis, participating in an ASMP led to improved health behavior (cognitive symptom management, communication with physicians, dietary habit, exercises, and relaxation) and a decrease of depression. However, decreases in fatigue and anxiety were found not to be significant [6,7].

With the growing opportunities and use of the Internet, a Web-based self-management version of the ASMP intervention for patients with long-term conditions was developed in 2007 [11]. Evaluation of the effectiveness of this intervention after 12 months showed significant improvements on health status measures like distress, pain, and self-efficacy. In 2011, based on the ASMP intervention and the self-efficacy theory of Bandura and in cooperation with the Dutch Arthritis Foundation and young adults from the transition outpatient clinic of University Medical Center Utrecht, we developed a Web-based self-management intervention for young adults up to the age of 25 years [12]. The aim of that intervention was to enhance young adults' self-management in coping with their rheumatic disease.

With the expansion of the Web-based intervention in the Netherlands, older adults with rheumatic diseases also expressed their need for a Web-based self-management intervention. In order to meet this need, the Dutch Arthritis Foundation gave us a grant to develop a Web-based intervention for adults from the age of 25 years and older. The goal of this research protocol was to describe (1) the theoretical considerations that guided the development of this Web-based intervention for adult patients with rheumatic diseases, (2) the contents of the intervention, (3) the results of a pilot study to study the usability of the intervention, and (4) the study design in order to examine the effectiveness of the intervention.

Toward a Patient-Guided Intervention

As we inferred from our experiences with the development and research pertaining to the Web-based intervention for the young adult group, collaboration with the end-users in all phases of development of a Web-based self-management intervention is crucial and influences the actual use, adherence, and effectiveness [13]. Based on this notion and to fit the intervention closely to the autonomy, needs, and preferences of the patients, we formed a research team consisting of patient representatives of different ages, health professionals, Web technicians, and communication experts. The research team followed the new guidance for developing and evaluating complex interventions by the Medical Research Council (MRC) [14] as a guide for the design of the intervention. The guidance included the following phases: development, feasibility and piloting, and evaluation and implementation. During the development phase, the aims were to determine a theoretical foundation and to develop the structure and content of the first draft. To achieve these aims, we first screened the scientific literature for theoretical considerations and effectiveness of (Web-based) self-management interventions for people with a chronic or rheumatic disease. The search for qualitative and quantitative articles was conducted in Medline, the Cumulative Index to Nursing and Allied Health Literature, Web of science, PsycINFO, and Pubmed. We searched for studies published in English, which used the words: "self-management," "chronic disease," "rheumatic disease," "adults," "theoretical foundations/considerations," and "effectiveness" in different combinations. No publication year limit was used. Secondly, a focus group and concept mapping study was performed to assess preferences and needs of adult patients with a rheumatic disease regarding the structure and content of the future Web-based self-management intervention.

Theoretical Considerations

Although there is growing attention for interventions that are customized to individual patients with chronic diseases, the structure and contents are generally still protocol-based on group preferences [6,15]. And, disappointingly, to date there is no consistent (long-term) evidence of the efficacy of self-management interventions for patients with a chronic disease in general [6,16]. This might be due to various reasons, including diversity of interventions, insufficient theoretical foundation, and the heterogeneity of the patient populations [16]. Moreover, positive mean group outcomes may disguise that a substantial proportion of patients did not comply with or respond to the intervention [6,16]. A basic assumption about self-management is that when the intervention is customized to the individual needs and situation of the patient, the patient will be more motivated, adhere better, and benefit more and for a longer time [6,15,16]. Thereby, a change in behavior and long-term adherence to changed behavior is expected to be greater when a patient experiences a meaningful rationale for

change, values the change in behavior positively, and aligns it with other central values and lifestyle patterns [2,3,17]. Consistent with these assumptions is Self-determination Theory of Ryan and Deci [17], which emphasizes the importance of keeping goals of behavior change (like improvement of self-management) close to the autonomous motivation of people. In this theory, three basic needs determine motivation: autonomy, competence, and social relatedness [17]. Among these three, autonomy is considered as the most central need: if a behavior is autonomous, it is voluntary, originating from one's own values and self-determination. Competence refers to the necessity to experience that one is really able to achieve something, and is related to the construct of self-efficacy [10]. The third basic need, social relatedness, is the extent to which one finds support in one's environment, including support from a trainer or professional. High levels of autonomy, competence, and social relatedness enhance self-regulation.

Needs Assessment

An important part of the development phase consisted of a needs assessment, conducted by the combination of a focus group and concept mapping design (J.W. Ammerlaan, et al, unpublished data, 2016). Online focus group interviews among adult patients with rheumatic diseases in the Netherlands, a card sorting task, and hierarchical cluster analysis yielded an extensive overview of the individual preferences regarding structure and content. Patients preferred an intervention tailored to their needs, stage of life, and goals. Also, an expert patient as a trainer, the opportunity to be in contact and to share with others, and the ability to follow the intervention at one's own pace were preferred. With respect to needs for content of the intervention, hierarchical cluster analysis yielded 11 clusters involving increasing individual knowledge of treatment and consequences for daily life, skills including managing emotions, managing, the fluctuations of disease, and dealing with health professionals and social authorities. Self-regulating their own lives, including requesting support from their spouse, family, or coworkers, setting boundaries and the ability to communicate adequately, and dealing with pregnancy or intimacy issues and taking care of kids. Based on the data from this needs assessment and the theoretical considerations, the first draft of the Web-based self-management intervention (in Dutch: ReumaUitgedaagd! Online) was developed.

Methods

Design of the Web-Based Intervention

ReumaUitgedaagd! Online is a Web-based, password protected, tailored, self- management intervention for adults with a rheumatic disease, aimed at enhancing patients' self-management skills. The participants perform the intervention individually, are coached by a trainer, and have online contact with other participants on a discussion board. The role of the trainer is to support participants during the Web-based intervention in becoming a good self-manager and achieving their personal goals. The trainers are adults who also have a rheumatic disease. They are recruited through the website of the Dutch Arthritis Foundation and selected through assessments and interviews conducted by a professional coaching organization (Work21), in close cooperation with the Dutch Arthritis Foundation and the University Medical Center Utrecht. The selection process used questions about motivation, perceptions of self-management, the self-determination theory and strategies derived from the theoretical foundation, and goals of the Web-based intervention to identify those trainers who could adhere to the basic tenets of the intervention. Finally, the expert trainer was trained through a 3-day train-the-trainer (TTT) educational intervention. The TTT intervention consisted of following the intervention as a participant, knowledge of different themes, and teaching Web-based training skills. The trainers are given a volunteer contract and receive a stipend from the Dutch Arthritis Foundation. The basic needs of autonomy, competence, and social relatedness, derived from Self-Determination theory, are embedded in the intervention and combined with elements of skills training and modelling, based on the Self-efficacy theory [8]. Autonomy is taken into account by customizing the intervention to three individual needs and goals, which the participants choose at the beginning of the intervention. The participants choose thematic modules based on these individual needs and goals. For example: a woman who wants to learn more about coping with the consequences of her disease at work, may choose the 'Work' module, while a man who wants to increase his physical fitness may choose the 'Exercises' module. Competence is increased by making action plans, reflecting on one's own behavior by performing exercises, or sharing the output of exercises on the discussion board to receive feedback or support from other participants and the expert trainer. Social relatedness is achieved through the support of the expert trainer via individual chats and the message box, and also by sharing experiences and giving feedback and support with other participants.

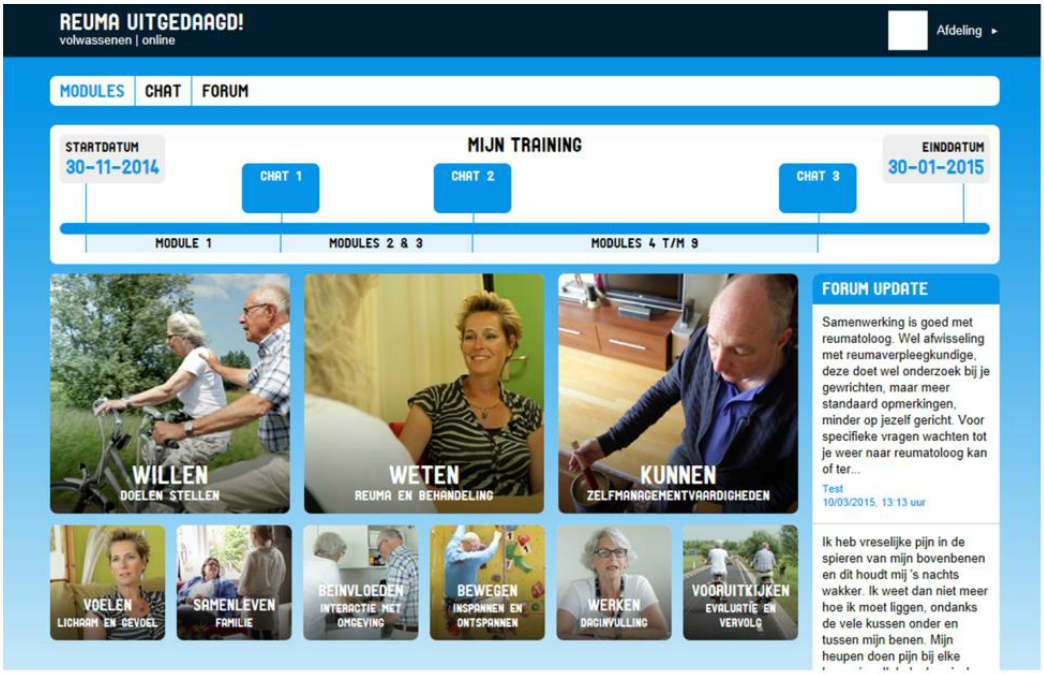
Content of the Web-Based Intervention

The Web-based self-management intervention consists of four components: nine thematic modules (willing, knowing, skills, feeling, living together, influence, exercise, work, and moving on), a chat application, a discussion board, and a message box.

Modules

Each module involves a specific theme. Both informative text about the theme and exercises are included. The information and the exercises are supported by short videos in which people with a rheumatic disease or a member of the multidisciplinary team tell about their experiences with arthritis. The content of the modules is described in Table 1. The participant performs the intervention individually and has 2 months to complete it. The total time investment for the participants is between 4 and 9 hours (approximately 30-60 minutes per module). The first three modules and the last module ('willing', 'knowing', 'skills', and 'moving on') are mandatory for all participants. The participant can choose other modules depending on his or hers personal goals. The nine modules are displayed in Figure 1.

Figure 1. Screen of the homepage, showing the nine modules of the online Reuma Uitgedaagd! (in Dutch).



Chat Sessions

The intervention includes three chat sessions between the participant with the trainer (after finishing module 1, after finishing module 3, and after finishing module 9). During the chat sessions, the trainer discusses the progress of the intervention and answers questions from participants. The duration of a chat session is approximately 15 to 30 minutes. The participant also has the ability to individually contact the trainer via a message box.

Discussion Board

The purpose of the discussion board is to exchange experiences between participants and trainers. In some exercises the participants put their output on the discussion board to start a discussion. For instance, they report how they tend to deal with being dispirited and whether or not they feel the strategy is proving to be successful.

'Look and Feel' of the Intervention

Based on the preferences of the research team, the design of the Web-based intervention was made attractive by using 'colorful, real-life pictures of people of different ages' to support information and exercises. Secondly, pictures of people, performing activities based on the content of the module, were used as pictograms to navigate. Thirdly, the videos to support the informative text of the modules were directed and produced by a professional company. Finally, a voice over was added to assist visually impaired participants.

Table 1. Content of the Nine Modules of the Web-Based Self-Management Intervention and Exercises

Module	Contents	Exercises
1. Willing (formulating personal goals)	Self-management	Awareness of self-management
	Priorities in life (getting to know yourself)	Evaluating self-management
	Setting and achieving personal goals	Life values (priorities in life)
		Formulating personal goals for the training
2. Knowing (disease-specific information and treatment)	A rheumatic disease: what does that mean?	Knowledge Quiz: what do you (already) know of your disease?
	Treatment possibilities	Gaining insight into treatment and treatment goals
	Getting control over one's disease and treatment	Working together with your physician and health professional
		Pain and fatigue diary
Additional	Medication	Practice and evaluation of consultation in the hospital
	A consultation in the hospital: how do you prepare yourself?	
3. Skills (self-management skills)	Being in charge:making choices	Evaluating your own behavior: making choices
	Problem solving	Circle of influence and engagement
	Communication	Feedback in your daily life
	To give and receive feedback	Saying no
	Setting boundaries	Recognizing your own coping scale
	Coping: dealing with consequences	
Additional		Self-assertiveness test
4. Feeling (body, mind, and emotions)	Having a rheumatic disease; what's next?	Loss of health; what does that mean to you?
	Consequences of having a rheumatic disease on your body, your mind, and socially	Feeling blue
	Pain, fatigue, and negative emotions	Evaluation of a situation to get insight into the influence of one's thoughts, behavior, and feelings
	Your own influence	Evaluation of the pain and fatigue diaries
Additional	Processing phases in the loss of health	Dealing with the loss of health
	Tips for handling pain	Relaxation exercises
	Tips for handling fatigue	To puzzle over: what can you do?
	To rack one's brain: what can one do about it?	
5. Living together (family and spouses)	Communicating with family and friends	Relationships
	Kids and stuff	Intimacy
		Sexuality
		Asking for help from your representatives or friends
Additional	Getting pregnant and having kids	Communicating with your partner
	Taking care of kids	
	Communicating with one's children	
6. Influence (interaction with your environment)	How to influence one's environment?	Explain your disease and consequences
	Dealing with lack of understanding (invalidation)	Asking for help: sharing experiences
	Asking for help	

Module	Contents	Exercises
7. Exercise (sport, exert, and relaxation)	Exercise and having a rheumatic disease	Your exercises
	Motion and physical activity	Exercise diary
	Pain and overload	Action plan
	Exertion and relaxation	Relaxation
Additional	Exercise and different rheumatic diseases	
8. Work (daily activities)	Suitable work	What's a suitable job for you?
	Dealing with invalidation at work	Who knows that you have a rheumatic disease at work?
	Dealing with fatigue and stress at work	Dealing with obstacles
	Rights and obligations	
	Going to school or university	
	To apply for a job	
Additional	Preparing for an interview with your colleagues or boss	Preparing for an interview with your colleagues or boss
	Being sick and getting back to work/school	
	Work adaptions	
9. Moving on (evaluation and looking forward)	Your personal goals	Self-management: reflection of your own knowledge and skills
	Action plan for the future	Action plan for the future
	Evaluation	Evaluating your own goals
Additional	An example of an action plan	

Usability Testing

Design

The first draft of the Web-based self-management intervention was tested in a quantitative pilot study, using the three concepts of the Technology Acceptance Model (TAM) [18]: perceived usefulness, perceived ease of use, and intention to use. According to TAM, the usability of a particular technical innovation can best be predicted by an individual's intention to use or re-use the innovation. This intention is determined by two components: (1) perceived ease of use, which can be defined as "the degree of ease, associated with the use of the applications," and (2) perceived usefulness, which can be defined as "the degree to which an individual believes that using applications will help him to attain gains or to increase personal performance." [18].

The participants of the pilot study were given 3-weeks' access to the Web-based self-management intervention to examine and apply the contents of the intervention. After 3 weeks, the participants completed a Web-based questionnaire on usability (based on the TAM).

Population

Adult patients with access to a computer with Internet, sufficient Internet skills, diagnosed with a rheumatic disease, and being able to read and write in Dutch were included. Participants were recruited through websites, Facebook, and Twitter accounts of the Dutch Arthritis Foundation [19] and ReumaUitgedaagd! [20]. All patients gave informed consent via the Internet.

Variables and Outcome Measures

Demographic variables like age and type of rheumatic disease and self-reported Internet-skills (measured on a 5-point Likert scale from very bad to very good) were collected to describe the group. Usability as primary outcome measure was operationalized using the three concepts of the TAM with 11 questions on a 5-point Likert scale (from totally disagree to totally agree) with the possibility to give additional comments. One question on 'overall satisfaction' was added, using a numeric rating system (NRS) from 0 (not satisfied) to 10 (most satisfied) (see Textbox 1).

Textbox 1. Questions to Measure the Three Concepts of the Technology Acceptance Model on Usability (All questions start with: "Now that you have seen the Web-based intervention…")

Perceived usefulness

- Did you perceive the content of the intervention to be useful?
- Did you perceive the content of the intervention as understandable?
- Did you perceive the exercises in the intervention to be useful?
- Did you perceive the content of the exercises as understandable?
- Did you perceive the intervention to be useful as a supplement to usual health care?
- Did you perceive the intervention to be useful in dealing with the consequences of having a rheumatic disease in daily life?

Perceived ease of use

- Did you perceive the Web-based self-management intervention to be easy to navigate?
- Could you easily find what you were looking for?

Intention to use

- Would you participate again, knowing now the content and structure?
- Would you recommend the Web-based self-management intervention to others (knowing now the content and structure)?

Overall satisfaction

- How do you rate your overall satisfaction with the intervention?
- How do you rate the look and feel of the intervention?

Results

Twenty-three respondents (22 women, mean age of 47 years) were given access to the Web-based intervention to test the usability. Most of them were diagnosed with inflammatory arthritis (16/23, 70%). Other diagnoses were osteoarthritis and fibromyalgia. Ninety-one percent (21/23) of participants rated their Internet-skills as 'very good'. Two participants rated their skills as average.

Ninety-one percent (21/23) of the participants indicated the content and exercises as easy to understand and useful (ie, agree/totally agree on the Likert-scale). The majority of the participants (21/23, 91%) indicated the intervention to be useful in dealing with the consequences of having a rheumatic disease in daily life. The navigation on the site itself was rated somewhat lower with 70% (16/ 23) of participants being critical about the menu with thematic modules on the homepage and finding their way on the website. The look and feel of the intervention was recognized by 78% (18/23) of participants as pleasant.

In terms of intention to use: 78% (18/23) would participate in the Web-based intervention themselves and 91% (21/23) would recommend it to others. The mean satisfaction score of the Web-based intervention was rated 7.9 (range 4-10) on a scale of 0 (not satisfied) to 10 (most satisfied).

Conclusion

Considering the three concepts, we concluded that the Web-based intervention was to be recognized as being useful and easy to use. Participants stated that they were likely to participate; now they were familiar with the content and structure. To improve the navigation and menu of the intervention, numbers were added to each module in order to indicate the sequence of the modules **.**

Study Design in Order to Measure the Effectiveness of the Newly Developed Web-Based Intervention

Design

To evaluate the Web-based self-management intervention, we have planned a randomized controlled trial with an intervention and a self-help control group and a 6-month follow-up period among adults in the Netherlands having a rheumatic disease. The control group will be put on a waiting list and will cross-over to the intervention after 6 months. Participants in the intervention group will be given access to the Web-based self-management intervention ReumaUitgedaagd! Both groups will receive usual care, based on the medical standard guidelines of the Dutch Association of Rheumatology [21], which also includes attention for self-management by the use of informational and educational materials that are normally used by patients to promote self-management. These materials are offered on the website of the Dutch Arthritis Foundation. Measuring the effectiveness means that we investigate whether there is an additional effect of the Web-based intervention in the intervention group on top of the care that is usually offered. The medical-ethical review board of the University Medical Center Utrecht in the Netherlands has approved the design and the procedures of this study.

Participants

Because we already have a Web-based self-management intervention for young adults (from 16-25 years), adults ≥26 years, having a rheumatic disease, diagnosed at least 2 years before inclusion by a rheumatologist or a General Practitioner,

are eligible for this study. In addition to having an Internet connection, patients need to have proficiency in the Dutch language and not having previously participated in a self-management intervention. Having a psychiatric disorder or being under (recent) treatment by a psychologist or psychiatrist are criteria for exclusion from this study. The participants will be recruited via the Internet through websites, Facebook, and Twitter accounts of the Dutch Arthritis Foundation [19] and ReumaUitgedaagd! [20]. After having signed consent forms, they receive information about the study and an information paper on goal setting with instruction and some examples of goals derived from the study on needs (J.W. Ammerlaan, et al, unpublished data 2016). After 1 week, a telephone call will be set up between the researcher and the participant to check the inclusion criteria and to answer any questions about the study. The participants will also be asked to think about three individual goals concerning their self-management they want to achieve. One week later, a second phone call will take place between the researcher and the participant to set the final three individual goals and to inform the participant about the randomization procedure. To warrant objectivity and standardization as much as possible, standardized scripts will be used for the two contacts. The telephone calls are conducted by an independent interviewer (OM) who is not involved in the care of patients with a rheumatic disease.

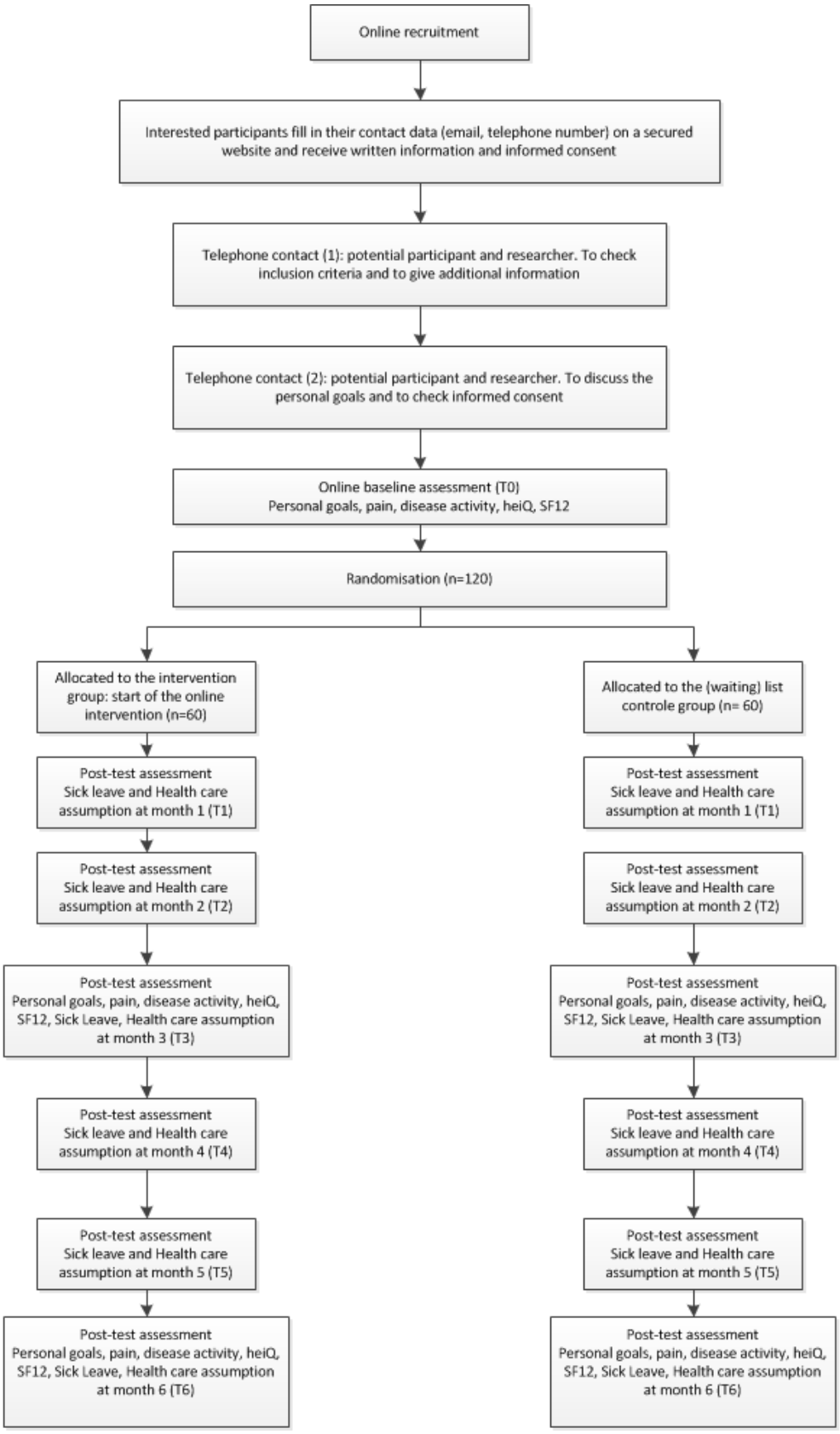
Randomization

Randomization will take place after informed consent and completion of the goal-setting procedure, using a computerized application of the University Medical Center Utrecht. This is an automated process with no interference from the investigators. We will use a stratified block randomization to decrease the likelihood of imbalance between three conditions (arthritis, osteoarthritis, and soft-tissue rheumatism). After randomization, the participants will be informed by the researcher if they are assigned to the intervention or control group. The participants of the intervention group will then start with the Web-based self-management intervention and be asked to work through the intervention within 2 months.

Outcome Measurements

In this study individual outcome measures, generic outcome measures, and process outcomes measures will be collected, most of them via the Internet with questionnaires, self-reported by the participants. Demographic variables including age, sex, disease duration, diagnosis, marital status, current treatment, education level, work, and comorbidity at baseline will be collected in order to characterize the group of participants. The timeframe for collecting the outcome measures is displayed in Figure 2.

Figure 2. Time frame and flow-chard study design.



Individual Outcomes: Goal Accomplishment

A crucial and novel aspect of this study is that the intervention is customized to the needs of the participant. This is one of the reasons why the change –progress toward– the main personal goal is chosen as the primary individual outcome measure. Studies show that on individual outcome measures the effect is larger than on generic outcome measures [22-24], which is not unexpected because many of the patients are already on a functional level of generic outcome measures; even more so,

given that patients with psychopathology are excluded. The three personal goals that the patient wants to accomplish are in a telephone interview with the researcher checked according to the following criteria: (1) the individual goals are aligned to the content and overall aim of the self-management intervention, (2) the goals focus on 'knowledge' and 'skills', and (3) the participant feels that each goal is achievable. In addition, the participant is asked to prioritize these goals (the first goal being the most important goal). Progress on the highest priority personal goal is the primary outcome of the study. Evaluations of the second and third personal goals are also conducted as (secondary) individual outcome measures.

The personal goals are measured with a Web-based NRS. The participant is asked to indicate with a score from 0 to 10 on the NRS to what extent he or she achieved this goal. The content of the primary goal can differ per person but the rate of change can be compared between subjects because they are measured on the same scale.

Generic Outcomes

The following generic outcome measures are assessed (all self-reports): pain, disease activity, self-management skills, quality of life, and sick leave.

Self-reported pain and disease activity will be scored by the participant on a Web-based NRS from 0 to 10. The higher the score, the more pain or disease activity.

Self-management will be measured with the Dutch translation of the Web-based Health Education Impact Questionnaire (heiQ) [25], which consists of 40 questions with scores ranging from 1 (not at all true) to 4 (exactly true) and are organized into a set of eight scales: health-directed behavior, positive and active engagement in life, emotional well-being, self-monitoring and insight, constructive attitudes and approaches, skills and technique acquisition, social integration and support, and health navigation. In a recent study of patients with a chronic disease, the heiQ scales showed good internal consistency, with Cronbach's alpha ranging from 0.70 to 0.89 on the eight independent scales, and high construct validity [26].

Quality of life will be assessed with the Web-based Medical Outcomes Study 12-item Short Form Health Survey (SF-12) [27], which includes eight questions on functional status, three questions on general well-being, and one question on general health. The psychometric properties of the SF-12 are good [27].

Sick leave is measured with three questions regarding (1) working in a paid job (yes/no/how many days a week), (2) sick leave during the past month, and (3) reasons for sick leave. Two measures of health care assumption are recorded as follows: self-reported visits to general practice, medical specialist, or physiotherapist, and whether or by whom support is offered to achieve the personal goals.

Process Outcomes

Feasibility is measured as a process outcome in the effectiveness study to evaluate the intervention in real-life in a larger group. Feasibility will be measured within the intervention group using the three concepts of the TAM [18,28] (see Textbox 1).

Use and adherence of the Web-based self-management intervention are digitally measured by Google Analytics within the intervention group. This was done by counting: (1) the number of starting and finishing participants within the time period, (2) the number of started and finished exercises, (3) the number of logins, (4) the number of messages that were put on the discussion board, (5) the number of contact moments with the expert trainers, and (6) the number of messages on the message box.

Power Calculation

To be able to compare our results with previous evaluations of self-management interventions, power calculation was based on the generic outcome parameters. In previous research, the generic measures of self-efficacy (which is close to our measurement of self-management skills) and functioning (which is part of our quality of life measurement), small to moderate effect-sizes (d) were found varying from 0.21 to 0.42 [11,29,30]. An effect-size d of 0.30 is similar to an effect-size f of 0.15 in repeated measures analysis of variance. In the current study, to be able to find a small to moderate difference (f=0.15) between the experimental and control groups using repeated measures analysis of variance, the total sample size needs to be N=90 (2 groups of n=45): G*Power3: f=0.15, 1-ß=.80, α=.05 two-tailed, r=.50, two groups, two repeated measures (baseline vs one post-therapy measurement) [31]. Taking a dropout rate of 25% into account, we decided to recruit 120 participants. The expectation of a small to moderate effect-size on these generic outcome measures may be explained because patients already have reasonable scores on self-management and quality of life at the start of the study. And there is little reason to expect that the intervention will affect other generic measures such as disease activity and sick leave.

As the crucial aspect of the current study is that the intervention is customized to the needs of the individual participant, the change on the main individual goal is chosen as primary outcome measure, and the change on the other two individual outcome measures (evaluation of the second and third personal goal) is considered important as well. Our sample size is large enough to examine differences in this primary outcome measure. Based on previous studies with individual outcome measures [22-24], we expect a moderate effect-size (d=0.5) for the control group and a large effect-size (d=1.2) for the intervention group resulting in a moderate to large (d=0.7, f=0.35) effect-size when comparing the intervention group and the control group using the three individual primary and secondary outcome measures. The calculated sample size is therefore considered to be safely chosen to test the main individual goal and both secondary individual outcome measures.

Statistical Analysis

Demographic and disease-specific outcomes will be descriptively presented per group, where possible, with means and standard deviations. The Consolidated Standards of Reporting Trials statement [32] will be used to report the results of this study. Quantitative data will be entered into a SPSS database. Effect analyses will be done according to intention to treat analysis by means of linear mixed-models for longitudinal measurements with random intercept. Fixed effects for group,

time, and group × time will be included in the model. Sick leave and health care use will be counted and differences between both groups will be analyzed using parametric tests or nonparametric tests, depending on the distribution of the data. Process outcomes, feasibility, use, and adherence will be analyzed with descriptive statistics.

Results

Patient inclusion and data collection will be completed in February 2017.

Discussion

Implications of the Intervention

A comprehensive assessment of the preferences and needs of patients with a rheumatic disease was used to build ReumaUitgedaagd! Online, guided by Self-Determination theory [17]. The usability study showed that the intervention was considered useful, easy to use, and accepted and appreciated by the target group of patients. These results predict that the intervention will be used to improve the use and effectiveness of this intervention, individual goals based on personal needs are identified at the beginning of the intervention and the intervention is customized to the individual patient. Because the intervention is personalized and guided by needs and preferences of patients, a low drop-out rate is expected.

According to the MRC framework [14], which was used by the research team to develop and evaluate the Web-based self-management intervention, this intervention can be defined as complex, taking into consideration the components, the required behaviors, and level of difficulty for both participants and trainer. The intervention is also flexible and customized to the individual participant. Although the MRC framework does not recommend active involvement of the users in the development or evaluation of the intervention, the knowledge and experiences of patient representatives were embedded in all phases of the framework. The aim of involving the users was to the use, acceptance, adherence, and effectiveness of the intervention [13,18]. Although we conducted a usability study in an earlier phase of the MRC model, we will measure additional process outcomes like feasibility, use, and adherence to gain knowledge of the working elements of the newly developed Web-based intervention.

Conclusion

Strong features of this Web-based intervention are that it is guided by needs and preferences of patients, that the precise contents of the interventions are customized to the individual patient, and that also the outcome measures fit the self-management goals that are really important to the individual patient. This makes the intervention an example of personalized, patient-centered care. If proven effective, ReumaUitgedaagd! Online will be implemented in the Netherlands.

Acknowledgments

All patients who participated in the study are gratefully acknowledged.

The usability study and the randomized controlled trial are supported by a grant from the Dutch Arthritis Foundation.

Conflicts of Interest

None declared.

References

1. Salaffi F, Carotti M, Gasparini S, Intorcia M, Grassi W. The health-related quality of life in rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis: a comparison with a selected sample of healthy people. Health Qual Life Outcomes 2009;7:25 [FREE Full text] [doi: 10.1186/1477-7525-7-25] [Medline: 19296831]
2. Kristiansen TM, Primdahl J, Antoft R, Hørslev-Petersen K. Everyday life with rheumatoid arthritis and implications for patient education and clinical practice: a focus group study. Musculoskeletal Care 2012;10:29-38. [doi: 10.1002/msc.224] [Medline: 22213280]
3. Hamnes B, Hauge MI, Kjeken I, Hagen KB. 'I have come here to learn how to cope with my illness, not to be cured': a qualitative study of patient expectations prior to a one-week self-management programme. Musculoskeletal Care 2011;9:200-210. [doi: 10.1002/msc.212] [Medline: 21774066]
4. Bodenheimer T, Lorig K, Holman H, Grumbach K. Patient self-management of chronic disease in primary care. JAMA 2002;288:2469-2475. [Medline: 12435261]
5. Barlow J, Wright C, Sheasby J, Turner A, Hainsworth J. Self-management approaches for people with chronic conditions: a review. Patient Educ Couns 2002;48:177-187. [Medline: 12401421]
6. Iversen MD, Hammond A, Betteridge N. Self-management of rheumatic diseases: state of the art and future perspectives. Ann Rheum Dis 2010;69:955-963. [doi: 10.1136/ard.2010.129270] [Medline: 20448289]
7. Lorig KR, Holman H. Self-management education: history, definition, outcomes, and mechanisms. Ann Behav Med 2003;26:1-7. [Medline: 12867348]
8. Bandura A. Self-efficacy: toward a unifying theory of behavioral change. Psychol Rev 1977;84:191-215. [Medline: 847061]

9. Marks R, Allegrante JP, Lorig K. A review and synthesis of research evidence for self-efficacy-enhancing interventions for reducing chronic disability: implications for health education practice (part II). Health Promot Pract 2005;6:148-156. [doi: 10.1177/1524839904266792] [Medline: 15855284]
10. Holloway A, Watson HE. Role of self-efficacy and behaviour change. Int J Nurs Pract 2002;8:106-115. [Medline: 11993577]
11. Lorig KR, Ritter PL, Laurent DD, Plant K. The internet-based arthritis self-management program: a one-year randomized trial for patients with arthritis or fibromyalgia. Arthritis Rheum 2008;59:1009-1017 [FREE Full text] [doi: 10.1002/art.23817] [Medline: 18576310]
12. Ammerlaan J, van OH, Scholtus L, de VA, Zwier M, Bijlsma H, et al. Feasibility of an online and a face-to-face version of a self-management program for young adults with a rheumatic disease: experiences of young adults and peer leaders. Pediatr Rheumatol Online J 2014;12:10 [FREE Full text] [doi: 10.1186/1546-0096-12-10] [Medline: 24666817]
13. van Gemert-Pijnen JE, Nijland N, van LM, Ossebaard HC, Kelders SM, Eysenbach G, et al. A holistic framework to improve the uptake and impact of eHealth technologies. J Med Internet Res 2011;13(4):e111 [FREE Full text] [doi: 10.2196/jmir.1672] [Medline: 22155738]
14. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. Int J Nurs Stud 2013;50:587-592. [doi: 10.1016/j.ijnurstu.2012.09.010] [Medline: 23159157]
15. Zangi HA, Ndosi M, Adams J, Andersen L, Bode C, Boström C, European League Against Rheumatism (EULAR). EULAR recommendations for patient education for people with inflammatory arthritis. Ann Rheum Dis 2015;74:954-962 [FREE Full text] [doi: 10.1136/annrheumdis-2014-206807] [Medline: 25735643]
16. Trappenburg J, Jonkman N, Jaarsma T, van Os-Medendorp H, Kort H, de Wit N, et al. Self-management: one size does not fit all. Patient Educ Couns 2013;92:134-137. [doi: 10.1016/j.pec.2013.02.009] [Medline: 23499381]
17. Ryan RM, Deci EL. Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. Am Psychol 2000;55:68-78. [Medline: 11392867]
18. Davis FD. Perceived usefulness, perceived ease of use and user acceptance of information technology. Management Information Systems Quarterly 1989;13:319-340.
19. Dutch Arthritis Foundation. 2016. URL: http://www.reumafonds.nl/ [accessed 2016-05-17] [WebCite Cache ID 6hZMLiphL]
20. Reuma Uitgedaagd!. 2016. URL: https://www.reuma-uitgedaagd.nl/ [accessed 2016-05-18] [WebCite Cache ID 6hbL1hLdM]
21. Dutch Association of Rheumatology. Richtlijnen, standpunten en zorgpaden. URL: http://www.nvr.nl/nvr-richtlijnen-en-standpunten [accessed 2016-05-17] [WebCite Cache ID 6hZMRxdAd]
22. Khan F, Pallant JF, Turner-Stokes L. Use of goal attainment scaling in inpatient rehabilitation for persons with multiple sclerosis. Arch Phys Med Rehabil 2008;89:652-659. [doi: 10.1016/j.apmr.2007.09.049] [Medline: 18373995]
23. Rushton PW, Miller WC. Goal attainment scaling in the rehabilitation of patients with lower-extremity amputations: a pilot study. Arch Phys Med Rehabil 2002;83:771-775. [Medline: 12048654]
24. Gordon JE, Powell C, Rockwood K. Goal attainment scaling as a measure of clinically important change in nursing-home patients. Age Ageing 1999;28:275-281 [FREE Full text] [Medline: 10475864]
25. Osborne RH, Elsworth GR, Whitfield K. The Health Education Impact Questionnaire (heiQ): an outcomes and evaluation measure for patient education and self-management interventions for people with chronic conditions. Patient Educ Couns 2007;66:192-201. [doi: 10.1016/j.pec.2006.12.002] [Medline: 17320338]
26. Kroon FP, van der Burg LR, Buchbinder R, Osborne RH, Johnston RV, Pitt V. Self-management education programmes for osteoarthritis. Cochrane Database Syst Rev 2014;1:CD008963. [doi: 10.1002/14651858.CD008963.pub2] [Medline: 24425500]
27. Gandhi SK, Salmon JW, Zhao SZ, Lambert BL, Gore PR, Conrad K. Psychometric evaluation of the 12-item short-form health survey (SF-12) in osteoarthritis and rheumatoid arthritis clinical trials. Clin Ther 2001;23:1080-1098. [Medline: 11519772]
28. Holden RJ, Karsh B. The technology acceptance model: its past and its future in health care. J Biomed Inform 2010;43:159-172 [FREE Full text] [doi: 10.1016/j.jbi.2009.07.002] [Medline: 19615467]
29. Lorig KR, Ritter PL, Dost A, Plant K, Laurent DD, McNeil I. The Expert Patients Programme online, a 1-year study of an Internet-based self-management programme for people with long-term conditions. Chronic Illn 2008;4:247-256. [doi: 10.1177/1742395308098886] [Medline: 19091933]
30. Ory MG, Smith ML, Ahn S, Jiang L, Lorig K, Whitelaw N. National study of chronic disease self-management: age comparison of outcome findings. Health Educ Behav 2014;41(Suppl):34S-42S. [doi: 10.1177/1090198114543008] [Medline: 25274709]
31. Faul F, Erdfelder E, Lang A, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39:175-191. [Medline: 17695343]
32. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, CONSORT. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. Int J Surg 2012;10:28-55 [FREE Full text] [doi: 10.1016/j.ijsu.2011.10.001] [Medline: 22036893]

Abbreviations

ASMP: arthritis self-management intervention
heiQ: health education impact questionnaire
MRC: medical research council
NRS: numeric rating scale
SF-12: short form health survey
TAM: technology acceptance model
TTT: train-the-trainer

Edited by G Eysenbach; submitted 09.03.16; peer-reviewed by J Wentzel; comments to author 28.03.16; accepted 10.04.16; published 23.06.16.

Please cite as:
Ammerlaan JW, Mulder OK, de Boer-Nijhof NC, Maat B, Kruize AA, van Laar J, van Os-Medendorp H, Geenen R
Building a Tailored, Patient-Guided, Web-Based Self-Management Intervention 'ReumaUitgedaagd!' for Adults With a Rheumatic Disease: Results of a Usability Study and Design for a Randomized Control Trail
JMIR Res Protoc 2016;5(2):e113
URL: http://www.researchprotocols.org/2016/2/e113/
doi:10.2196/resprot.5735
PMID:27339472

Original Paper

A Preliminary Exploration of Former Smokers Enrolled in an Internet Smoking Cessation Program

Sarah Cha[1], MSPH; Amy M Cohn[1,2], PhD; Hoda Elmasry[1], MPH; Amanda L Graham[1,2], PhD

[1]Schroeder Institute for Tobacco Research and Policy Studies at Truth Initiative, Washington, DC, United States

[2]Department of Oncology, Georgetown University Medical Center / Cancer Prevention and Control Program, Lombardi Comprehensive Cancer Center, Washington, DC, United States

Corresponding Author:
Sarah Cha, MSPH
Schroeder Institute for Tobacco Research and Policy Studies at Truth Initiative
900 G St NW, 4th Floor
Washington, DC, 20001
United States
Phone: 1 202 454 5946
Fax: 1 202 454 5785
Email: scha@truthinitiative.org

Abstract

Background: Internet interventions may have an important role to play in helping self-quitters maintain an initial period of abstinence. Little is known about the characteristics and utilization patterns of former smokers who use Internet cessation programs.

Objective: The overarching aim of this preliminary study was to establish the feasibility of a subsequent randomized trial of the effectiveness of Internet interventions in preventing relapse. Specifically, this study sought to determine the number of former smokers that register on a smoking cessation website, the characteristics of former smokers and their website utilization patterns, and potential predictors of sustained abstinence.

Methods: Participants were self-identified former smokers who registered on a free smoking cessation website. Recruitment occurred immediately following site registration. Participants completed Web-based baseline and 1-month follow-up assessments. Website utilization metrics were extracted at 1 month. Descriptive statistics were used to characterize the full sample. Baseline differences were examined between recent quitters (≤7 days of abstinence at enrollment) and more established quitters (8+ days of abstinence at enrollment) using chi-square tests and *t* tests. Univariate logistic regression examined demographic, smoking, psychosocial characteristics, and website utilization metrics as predictors of 1-month abstinence.

Results: During the 10-month study period, 1141 former smokers were recruited to participate: 494 accepted the invitation, 395 were eligible, 377 provided informed consent, and 221 completed the baseline and fully enrolled (56% of those eligible). At 1 month, 55.7% (123/221) of participants completed the follow-up survey. Mean age was 44.25 years (SD 12.78) and the sample was primarily female (174/221, 78.7%), white (196/221, 88.7%), and had at least some college education (177/221, 80.1%). Slightly more than half of participants (123/221, 55.7%) reported quitting more than a week prior to website registration and 43.9% (97/221) had quit within 7 days of registration. The website features most likely to be used were an interactive Quit Date tool (166/221, 75.1%) and the Community (134/221, 60.6%). Univariate regression models showed that recent quitters, those with higher motivation to remain abstinent, and those who used cessation medication in the past year were more likely to use the Community. Older age, longer duration of abstinence at registration, better health status, and health care provider advice to quit were associated with 1-month abstinence. Website utilization metrics did not predict abstinence, though odds ratios suggested higher utilization was associated with greater odds of abstinence.

Conclusions: This exploratory study demonstrated the feasibility of recruiting former smokers to a research study and documented the uptake of an Internet cessation intervention among this group of self-quitters. Results also showed higher levels of website utilization and greater likelihood of community use among smokers early in their quit attempt compared to those with a longer period of abstinence at enrollment. Important areas for future research include identifying former smokers who may be more susceptible to relapse and determining which components of an Internet intervention are most helpful to prevent relapse in the early and later stages of a quit attempt.

(JMIR Res Protoc 2016;5(2):e119) doi:10.2196/resprot.5542

KEYWORDS

smoking cessation; Internet; relapse prevention

Introduction

Identifying strategies to prevent relapse among the millions of smokers that attempt to quit each year remains a public health priority [1]. In 2012, 52.9% of smokers attempted to quit smoking, yet each year, only 5-7% of smokers are able to maintain abstinence for more than 6 months [2]. The majority of smokers relapse within several weeks after a quit attempt [3-6]. Despite decades of research on relapse prevention, a 2013 Cochrane systematic review of 63 studies found little support for the effectiveness of behavioral interventions delivered face-to-face or telephonically, or for pharmacological interventions [7]. As tobacco control policies continue to drive increased quit attempts [8], novel relapse prevention efforts are needed to increase the likelihood that these efforts translate into successful long-term cessation [9].

Internet interventions may be uniquely suited to provide relapse prevention approaches for smoking cessation as they are broad-reaching [10,11], cost-effective [12], and may appeal to individuals who would otherwise not seek cessation counseling. The Internet is a primary source of health information for a majority of adults [13] and is often the first place many people turn to when faced with a health-related question or concern [14]. A timely, on-demand intervention after a smoking lapse is a critical element of an effective relapse prevention approach [15] and one that other treatment modalities like face-to-face and telephonic interventions may be unable to provide. The 24/7 availability of Internet interventions and their ability to surmount geographic and other barriers to treatment use make them a powerful channel through which to address relapse at the time when support is most needed.

In addition, Internet interventions for smoking cessation commonly include social media and Web 2.0 applications that facilitate the exchange of information and support between and among users [16]. Real-time social support from current and former smokers may provide precisely the kind of encouragement, inspiration, and "road-tested" practical advice that former smokers need to prevent relapse [17]. High levels of social support have been associated with better cessation outcomes in a number of studies [18-20], and low levels of support have been conceptualized as a barrier to abstinence [21]. Few studies have examined the role of "offline" social support for relapse prevention [7], and only two studies to our knowledge have explored the impact of online social support through Internet cessation interventions. Schwarzer and Satow [22] found that recent quitters who posted the number of days they had been abstinent in an online bulletin board were less likely to relapse than those who did not post. In addition, posting more messages was associated with a greater likelihood of maintaining abstinence. The authors posited that making one's intentions to quit visible to an online community may strengthen an individual's commitment to quit and that active engagement naturally results in continued contact with others, being reminded of one's intention to quit, and potentially receiving praise. Selby et al [17] found that among individuals who posted within an online cessation community, the most common type of first posts were help-seeking messages from recent quitters who were struggling to remain abstinent. In this study, we were specifically interested in exploring whether use of an online community for smoking cessation was associated with lower rates of relapse among former smokers.

Internet interventions have shown promise for relapse prevention in mental health and addiction treatment [23,24], and several studies within smoking cessation suggest that there is demand for and utilization of online cessation resources among recent quitters. A study by Borland et al [25] sought to examine the impact of a Web-based intervention among current smokers and recent quitters (defined as quit for <4 days) but did not report outcomes by baseline smoking status. Interestingly, approximately 25% of participants screened for this smoking cessation study reported they had already quit smoking. Similarly, a 2006 study by Cobb and Graham [10] found that 24% of individuals searching for smoking cessation information on the Internet had quit smoking: 17% had quit within the previous 7 days, and 7% had quit more than 7 days prior. In an observational study of the Australian Web-based cessation program "QuitCoach," Balmford et al [26] found that return visits were most common among those who had just quit when they registered on the site and lowest among those not planning to quit.

These studies and others [11,27,28] suggest that Internet interventions may have an important role to play in helping those who have already quit to maintain an initial period of abstinence or to extend their abstinence. However, to date, few studies have documented the extent to which former smokers use Internet cessation programs or their effectiveness in preventing relapse. The goals of this preliminary study were to explore the feasibility of conducting a randomized trial to evaluate the effectiveness of Internet interventions in preventing relapse. Specifically, we sought to address the following questions: (1) Is it feasible to recruit former smokers to a research study, and what is the monthly recruitment volume?, (2) What are the characteristics of former smokers that register on an Internet smoking cessation website?, (3) How do former smokers utilize an Internet cessation program?, and (4) Are there baseline variables or website utilization metrics that predict a former smoker's ability to maintain abstinence?

Methods

Participants

Participants were individuals who registered on a free smoking cessation website and selected "former smoker" when asked about smoking status (options were "current smoker," "former smoker," or "looking for help for someone else"). The only other eligibility criteria were age 18 years or older and US residence, which were gathered during website registration. The study invitation was presented immediately following website registration. Eligibility screening, informed consent, and the baseline survey were administered online. Immediately

following the baseline survey, participants were directed back to the website where they were able to use the site as they desired; there were no additional interventions provided. At 1-month post-registration, participants were asked to complete an online survey to assess smoking status and other related variables. Participants received three email prompts for follow-up survey completion and were offered a US $20 incentive. The study protocol received human subjects protection approval from Copernicus Group Independent Review Board.

Intervention

BecomeAnEX is a free smoking cessation website developed and managed by Truth Initiative (formerly American Legacy Foundation) in partnership with the Mayo Clinic Nicotine Dependence Center [11,29]. Consistent with the 2008 Public Health Service Clinical Practice Guideline for Treating Tobacco Dependence [1], BecomeAnEX provides (1) problem-solving and skills training designed to enhance self-efficacy, (2) information and guidance in selecting and using FDA-approved smoking cessation pharmacotherapies, and (3) intra-treatment social support in the form of a large online community. BecomeAnEX guides and supports smokers through the process of planning and preparing to quit through the following interactive features: (1) a Quit Date tool that assists users in selecting a prospective quit date or documenting a retrospective quit date, (2) a Cigarette Tracker exercise to identify smoking triggers, (3) a Beat Your Smoking Triggers exercise (Separation exercise) to identify strategies to dissociate cigarettes from triggers, (4) a Build Your Support System exercise (Support exercise) to identify helpful supporters, (5) a Choose a Quit Smoking Aid exercise (Addiction exercise), in which users indicate their plans for pharmacotherapy use, and (6) Community, which is a large online network of thousands of current and former smokers who communicate through a variety of channels (eg, blog posts/replies, wall posts, private messages). In addition to these interactive features, the site contains static content to prepare for quit day, cope with slips, and prevent relapse; videos about addiction and medication; and a checklist (My Quit Plan) that displays whether each of the site's core components has been used and recommends next steps. The site can be browsed anonymously, but to save information or post content in the Community, visitors must register. To register on BecomeAnEX, individuals must agree to the site's Terms of Use and Privacy Policy. The Privacy Policy makes clear that (1) BecomeAnEX automatically collects information about its users and their use of the site, (2) information is used for research and quality improvement purposes only, and (3) personal information is kept confidential. BecomeAnEX has been promoted through a national multimedia campaign since 2008 [11], with more recent promotional activities focused on paid search advertising that targets current smokers.

Data Collection and Measures

Data sources for these analyses included (1) a Web-based survey administered at baseline, (2) a Web-based survey administered at 1-month post enrollment, and (3) 1-month website utilization metrics obtained via automated tracking software. Demographic variables included age, gender, race, education, employment, and marital status.

Abstinence-related questions asked when participants decided to quit smoking, their quit date and confidence about the accuracy of that date, and the date of their last puff of a cigarette. These questions were used to calculate the number of days they had been abstinent when they registered on BecomeAnEX. The Abstinence Related Motivational Engagement Short Form (ARME) [30] was administered to assess motivation to remain abstinent. This scale consists of 5 Likert items (1=completely disagree to 7=completely agree): (1) I try to anticipate and prepare for any challenges to being smoke-free (vigilance), (2) The thought of being a nonsmoker still excites me (excitement), (3) At this time, I am still very excited by the idea of being smoke-free (excitement), (4) I spend a great deal of time thinking about becoming or staying smoke-free (cognitive effort), and (5) I am carefully watching out for things that might put me at risk for smoking (vigilance). The short form has demonstrated adequate reliability (alpha=.82) and has been correlated with length of abstinence [31].

Smoking history questions asked about the number of quit attempts made in the past year, and the use of behavioral (books/pamphlets, individual/group counseling, telephone quitline, Web-based interventions), pharmacologic (nicotine patches, gum, lozenges, nasal spray and inhaler, Zyban, Chantix), and alternative (e-cigarettes, switching to chew or snuff, switching brand or cutting back, acupuncture, hypnosis, herbal/laser/other alternative methods) quit methods during the past year. Reports of using "willpower/cold turkey" or "prayer" were coded as unassisted quit attempts.

Health history items included current health status (excellent, very good, good, fair, poor; [32]), history of an illness caused or made worse by smoking (yes/no), and whether the participant had received advice to quit smoking from a health care provider in the past year (yes/no).

Psychosocial measures assessed "offline" social support as potential influences on online Community use. They included the Appraisal and Belonging subscales of the 12-item Interpersonal Support Evaluation List [33], which is a general measure of perceived social support. The Appraisal subscale measures the perceived availability of someone to talk to about one's problems, and the Belonging subscale measures the perceived availability of people one can do things with. Each subscale contains four statements that participants indicate are definitely true, probably true, probably false, or definitely false. One item from the UCLA Loneliness Scale [34] was administered, which asked how often the participants felt that there were people they can turn to (1=Never, 4=Always).

Internet and social media use were assessed with items that asked about frequency and duration of Internet use [35] and frequency of communication with other people via the Internet (eg, via blogs, instant messaging, forums) [36].

Website utilization data were obtained via Adobe Analytics software [37], a customizable Web analytics tool that is used to monitor, report on, and optimize use of the BecomeAnEX website. General utilization metrics examined in this study included number of return visits following website registration, total number of minutes spent on the site, and the number of pages viewed. Data were also extracted on the use of the six

interactive features described above. Because website utilization typically shows a steep attrition curve [38-43], we focused on utilization metrics during the first month following site registration.

Smoking abstinence at 1-month post enrollment was measured as 7-day and 30-day point prevalence abstinence.

Statistical Analyses

Descriptive statistics were examined to characterize former smokers on sociodemographic variables, smoking history, health status, and psychosocial measures. We also examined baseline differences between recent quitters (≤7 days of abstinence at enrollment) and more established quitters (8+ days of abstinence at enrollment) using chi-square tests and *t* tests. Our decision to use 7 days as a cut-point was largely an empirical one. Relapse is most common within the first week after a quit attempt, and prior analyses have shown that the largest proportion of Internet cessation treatment users that self-identify as former smokers report quitting within the past 7 days [3,10,44]. Previous studies of relapse prevention interventions have varied widely in terms of abstinence-related inclusion criteria [45]. Our intent was to determine if there were distinguishing characteristics based on length of abstinence at program enrollment that might suggest that a subsequent effectiveness study should focus specifically on recent quitters.

Website utilization patterns were examined using descriptive statistics. The full sample was characterized, and comparisons between recent quitters and more established quitters were explored. Means and standard deviations were computed for general website utilization variables and compared using two-sample *t* tests. Given that general website utilization data were positively skewed, the median and interquartile range are also reported and differences examined using the Wilcoxon Mann Whitney test.

To identify characteristics of participants who used the Community, univariate logistic regression models examined baseline demographic, smoking history, and psychosocial variables. To identify predictors of 1-month abstinence, univariate logistic regression models examined the association between 30-day abstinence and baseline characteristics (demographic, smoking history, psychosocial measures), website utilization metrics (return visits, time on site, Community use), and other treatment utilization (behavioral interventions, medication use, alternative methods). Statistical significance for all analyses was set to an alpha of .05. Analyses were performed using SPSS version 21 and SAS software version 9.3.

Results

Recruitment and Follow-Up Results

Between November 15, 2012, and September 17, 2013, a total of 1141 consecutive registered users who identified as former smokers were recruited to participate in the study: 494 accepted the invitation, 395 were eligible, 377 provided informed consent, and 221 completed the baseline survey and fully enrolled (56% of those eligible). This represents an available pool of approximately 114 former smokers per month from which to recruit and a recruitment rate of approximately 22 participants per month. At 1-month post registration, 55.7% (123/221) of participants completed the follow-up survey. Survey non-respondents were more likely to have a high school degree or less (OR 2.68, 95% CI 1.35-5.30) and to be black/African American (OR 4.26, CI 1.14-15.97). One-month follow-up attrition was significantly correlated with website utilization. Specifically, those with fewer site visits, time on site, and number of page views were also more likely to be lost to follow-up (all ORs 1.76, $P<.04$).

Baseline Characteristics of Former Smokers

Table 1 shows the demographic, smoking history, and psychosocial characteristics of the full sample of former smokers. Mean age was 44.25 years (SD 12.78), and the sample was primarily female (174/221, 78.7%), white (196/221, 88.7%), college educated (177/221, 80.1% reporting some college or more), employed full or part-time (149/221, 67.4%), and married or living with a partner (135/221, 61.1%). Two thirds (148/221, 67.0%) reported having an illness either caused or made worse by smoking, and 69.7% (154/221) had been advised to quit by a health care provider in the past year. The average score for ARME was high (mean 29.51, SD 5.69), with the two "excitement" items ("thought of being nonsmoker still excites me," "I am still very excited by the idea of being smoke-free") yielding the highest mean values (mean 6.1, SD 1.5 for both items).

Table 1. Baseline characteristics of former smokers by number of days quit at enrollment.

	All former smokers, N=221	Days quit at enrollment		
		≤7 days, n=97	8+ days, n=123	*P* value[a]
Demographic characteristics				
Age, years, mean (SD)	44.25 (12.78)	40.39 (11.82)	47.33 (12.76)	<.001
Gender, female, n (%)	174 (78.7)	74 (76.3)	99 (80.5)	.45
Race, white, n (%)	196 (88.7)	85 (87.6)	110 (89.4)	.76
Ethnicity, Hispanic, n (%)	12 (5.4)	6 (6.2)	6 (4.9)	.67
Education, some college or more, n (%)	177 (80.1)	76 (78.4)	100 (81.3)	.59
Employment, full-time or part-time, n (%)	149 (67.4)	67 (69.1)	82 (66.7)	.70
Marital status, married/partner, n (%)	135 (61.1)	54 (55.7)	81 (65.9)	.12
Smoking history				
ARME, range (5-35), mean (SD)	29.51 (5.69)	30.46 (4.89)	28.75 (6.18)	.03
# quit attempts past year, mean (SD)[b]	2.29 (2.90)	2.21 (2.73)	2.34 (3.04)	.74
Quit methods, #quit attempt past year ≥1, n (%)	N=182	N=74	N=107	
Unassisted	131 (72.0)	51 (68.9)	79 (73.8)	.47
Behavioral interventions	58 (31.9)	22 (29.7)	36 (33.6)	.58
Medications	135 (74.2)	56 (75.7)	78 (72.9)	.68
Alternative methods	81 (46.6)	34 (46.6)	46 (46.0)	.94
Health status, n (%)				
Self-reported health status, fair or poor	50 (22.6)	18 (18.6)	31 (25.2)	.24
History of smoking-related illness	148 (67.0)	61 (62.9)	86 (69.9)	.27
Health care provider advice to quit past year	154 (69.7)	66 (68.0)	87 (70.7)	.72
Psychosocial variables				
ISEL[c] Appraisal subscale, range (1-12), mean (SD)	7.63 (2.03)	7.82 (1.85)	7.48 (2.16)	.21
ISEL Belonging subscale, range (1-12), mean (SD)	7.02 (1.39)	7.12 (1.26)	6.95 (1.49)	.36
Loneliness, never or rarely, n (%)	19 (8.6)	10 (10.3)	9 (7.3)	.43
Internet use, n (%)				
How long used Internet, 5 years	208 (94.1)	91 (93.8)	116 (94.3)	.80
How often use Internet, several times/day	176 (79.6)	81 (83.5)	94 (76.4)	.34
Use of Internet to blog/chat/instant message				.74
Several times/day	80 (36.2)	38 (39.2)	42 (34.1)	
Once a day	42 (19.0)	18 (18.6)	24 (19.5)	
Less than daily	99 (44.8)	41 (42.3)	57 (46.3)	

[a]Former smokers who had quit within the past 7 days at enrollment compared to former smokers who had quit 8 days or more at enrollment. One respondent who did not provide valid date-based responses was excluded from comparison but included in all former smokers column.

[b]Quit attempts were restricted to ≤20 attempts, removing 1 outlier.

[c]ISEL=Interpersonal Support Evaluation Scale.

Table 2. One-month website utilization metrics of former smokers by days quit at enrollment.

	All former smokers, N=221	Days quit at enrollment		
		≤7 days, n=97	8+ days, n=123	*P* value[a]
General website utilization				
No. return visits, mean (SD)	6.61 (17.79)	8.79 (21.46)	4.93 (14.19)	.13
No. return visits, median (IQR)	2.00 (1.00-4.00)	3.00 (2.00-6.00)	2.00 (1.00-3.00)	.01
Time on site (minutes), mean (SD)	115.69 (433.42)	159.60 (549.90)	81.93 (313.10)	.22
Time on site (minutes), median (IQR)	28.27 (14.50-56.40)	42.33 (18.30-75.90)	25.37 (11.90-39.50)	.02
No. page views, mean (SD)	82.00 (228.33)	110.70 (279.90)	59.98 (176.60)	.12
No. page views, median (IQR)	32.00 (11.00-58.00)	39.00 (18.00-88.00)	26.00 (9.00-45.00)	.05
Feature utilization, n (%)				
Set a Quit Date	166 (75.1)	85 (87.6)	81 (65.9)	<.001
Visited Community	134 (60.6)	68 (70.1)	66 (53.7)	.01
Choose a quit smoking aid	63 (28.5)	34 (35.1)	29 (23.6)	.06
Separation exercise	62 (28.1)	33 (34.0)	29 (23.6)	.09
Addiction videos	102 (46.2)	52 (53.6)	50 (40.7)	.06
Support exercise	38 (17.2)	20 (20.6)	18 (14.6)	.24
Cigarette tracker	34 (15.4)	13 (13.4)	20 (16.3)	.56
Community utilization, n (%)				
Viewed user profiles	36 (16.3)	20 (20.6)	16 (13.0)	.13
Read blog posts	29 (13.1)	19 (19.6)	10 (8.1)	.01
Wrote blog posts	19 (8.6)	13 (13.4)	6 (4.9)	.03
Wrote on user message board	13 (5.9)	10 (10.3)	3 (2.4)	.01
Sent private messages	11 (5.0)	8 (8.3)	3 (2.4)	.05

[a]Recent quitters (≤7 days abstinence at enrollment) compared to more established quitters (8+ days abstinence at enrollment). One respondent who did not provide valid date-based responses was excluded from comparison but included in all former smokers column.

Table 3. Univariate logistic regression model of odds of 30-day abstinence at 1 month among former smokers.

Variable	Group	Abstinent, n=83	Smoking, n=40	Crude OR	95% CI	*P* value
Demographic variables						
Age (5-year increments)				1.23	1.05-1.40	.01
Gender						
	Female (ref)	66	30	—	—	
	Male	17	10	0.77	0.32-1.89	.57
Education						
	HS or less (ref)	9	7	—	—	
	Some college or more	74	33	1.74	0.60-5.08	.31
Race						
	White (ref)	74	36	—	—	
	Non-white	9	4	1.10	0.32-3.80	.89
Ethnicity						
	Non-Hispanic (ref)	79	37	—	—	
	Hispanic or Latino	4	3	0.62	0.13-2.93	.55
Employment status						
	Not employed (ref)	22	14	—	—	
	Employed	61	26	1.49	0.66-3.36	.33
Marital status						
	No partner (ref)	29	19	—	—	
	Partner	54	21	1.69	0.78-3.63	.18
Smoking variables						
Consider self former smoker						
	Within past week (ref)	33	29	—	—	
	More than a week ago	42	8	4.61	1.87-11.41	<.001
Days quit at enrollment						
	8+ days (ref)	55	10	—	—	
	≤7 days	28	30	0.17	0.07-0.40	<.001
ARME				1.01	0.94-1.09	.70
Past year quit methods						
Unassisted						
	No (ref)	17	9	—	—	
	Yes	56	21	1.41	0.55-3.65	.48
Behavioral						
	No (ref)	47	21	—	—	
	Yes	26	9	1.29	0.52-3.23	.59
Medication						
	No (ref)	16	9	—	—	
	Yes	57	21	1.53	0.59-3.98	.39
Alternative methods						
	No (ref)	39	14	—	—	
	Yes	28	16	0.63	0.26-1.49	.29

Variable	Group	Abstinent, n=83	Smoking, n=40	Crude OR	95% CI	*P* value
Health status						
Health						
	Fair/poor (ref)	13	13	—	—	
	Excel/very good/ good	70	27	2.59	1.07-6.30	.04
Illness from smoking						
	No (ref)	24	16	—	—	
	Yes	59	24	1.64	0.74-3.61	.22
Health care provider advice to quit						
	No (ref)	19	16	—	—	
	Yes	64	24	2.25	1.00-5.07	.05
Communicate via Internet						
	Less than daily (ref)	62	37	—	—	
	Daily or more often	68	54	0.80	0.38-1.70	.56
Past month quit methods at follow-up						
Unassisted						
	No (ref)	21	13	—	—	
	Yes	62	27	1.42	0.62-3.25	.40
Behavioral interventions						
	No (ref)	47	25	—	—	
	Yes	36	15	1.28	0.60-2.77	.54
Medication						
	No (ref)	45	21	—	—	
	Yes	38	19	0.93	0.44-1.99	.86
Alternative methods						
	No (ref)	51	24	—	—	
	Yes	32	16	0.94	0.44-2.04	.88
1 month website utilization						
2+ return visits						
	No (ref)	14	12	—	—	
	Yes	69	28	2.11	0.87-5.13	.10
30+ minutes on site						
	No (ref)	37	20	—	—	
	Yes	46	20	1.24	0.58-2.65	.57
2+ community visits						
	No (ref)	29	19	—	—	
	Yes	54	21	1.69	0.78-3.63	.18

Slightly more than half of participants (123/221, 55.7%) were “more established quitters” (days abstinent at registration: mean 358.8, SD 1504.9, range 9713) and 43.9% (97/221) of the sample were “recent quitters” (days abstinent at registration: mean 3.1, SD 2.0, range 7). One respondent did not provide valid date-based quitting-related responses and the length of their quit at registration is unknown. Recent quitters were younger (mean 40.39, SD 11.82 vs mean 47.33, SD 12.76, *P*<.001) and had higher scores on the ARME (mean 30.46, SD 4.89 vs mean 28.75, SD 6.18, *P*=.03) than more established quitters. No other baseline differences were observed.

One-Month Website Utilization Patterns and Predictors of Community Use

Website utilization metrics are presented in Table 2. During the first month after registration, participants made an average of

6.61 return visits to the site (SD 17.79; median 2.00), spent 115.69 minutes on the site (SD 433.42; median 28.27), and viewed 82.00 pages (SD 228.33; median 32.00). The most commonly used features were Set a Quit Date (75.1%) and Community (60.6%). There were significant differences between recent quitters and more established quitters across a number of utilization metrics. Recent quitters made more return visits (median 3.00, interquartile range (IQR) 2.00-6.00 vs median 2.00, IQR 1.00-3.00, *P*=.01), spent more time on the site (median 42.33, IQR 18.30-75.90 vs median 25.37, IQR 11.90-39.50, *P*=.02), and viewed more pages (median 39.00, IQR 18.00-88.00 vs median 26.00, IQR 9.00-45.00, *P*=.05), compared to more established quitters. Recent quitters were also more likely than more established quitters to set a quit date on the site (87.6% vs 65.9%, *P*<.001), to visit the Community (70.1% vs 53.7%, *P*=.01), and to engage in the Community both passively (read blog posts: 19.6% vs 8.1%, *P*=0.01) and actively (wrote a blog post: 13.4% vs 4.9%, *P*=.03; wrote on message boards: 10.3% vs 2.4%, *P*=.01; sent private messages: 8.3% vs 2.4%, *P*=.05).

Predictors of Abstinence

Univariate regression analyses showed that several baseline characteristics were predictive of 1-month abstinence (see Table 3). Older age (OR 1.23, CI 1.05-1.40), self-identification as a more established quitter (OR 4.61, CI 1.87-11.41), better health status (OR 2.59, CI 1.07-6.30), and being advised by a health care provider to quit in the past year (OR 2.25, CI 1.00-5.07) were associated with increased abstinence, whereas 7 or fewer days of abstinence at registration was associated with lower odds of 1-month sustained abstinence (OR 0.17, CI 0.07-0.40). General website utilization metrics (number of return visits, time on site) and community use did not emerge as significant predictors of abstinence, though odds ratios suggested that higher levels of utilization were associated with increased abstinence.

Discussion

Principal Findings

This study is one of the first to characterize a sample of former smokers that registered on an evidence-based Internet smoking cessation program, document their website utilization patterns, and explore the factors that predicted maintenance of an initial period of abstinence. Over the 10-month study period, 1141 former smokers registered on the site. This is noteworthy given that all promotional efforts describe the site as a smoking cessation intervention for current smokers. Promotional efforts that specifically appeal to recent quitters may attract an even larger audience, as our data demonstrate that an online cessation program is of interest to recent quitters looking for information and support. The study enrollment rate is comparable to several recent large-scale Internet cessation trials [25,46] and demonstrates the feasibility of recruiting former smokers to participate in research.

In general, this was a sample of very recent quitters, nearly half of whom had quit within the past week and who were very motivated to maintain this initial period of abstinence. Two-thirds reported having an illness caused or made worse by smoking and having been advised by a health care provider to quit smoking. Participants had made multiple quit attempts in the past year, and the majority had used medication and alternative quit methods during these quit attempts. These characteristics paint a picture of middle-aged smokers who had experienced multiple failed quit attempts using other treatment strategies but who were still engaged in the process of quitting. That the sample was largely female is consistent with reports that women are more likely than men to seek health care information online [13].

Self-identified former smokers were not a homogeneous group when it came to website utilization patterns. Recent quitters (ie, those who had quit in the last week) returned to the site more often, viewed more pages, and spent more time on the site than more established quitters (ie, those who had quit more than a week ago). They were also more likely to use the quit date feature and to participate in the Community both actively and passively. These differences may signal the more precarious nature of their abstinence and the need for different type of guidance and support than those who are more established in their quit. It is noteworthy that of all the website features examined, the most consistent patterns of differences emerged in use of the online Community. Additional research to understand the nature of the posts that former smokers make in blogs and on message boards may help inform more tailored treatment strategies specifically designed for recent quitters versus more established quitters.

Approximately a third of participants who completed the follow-up survey indicated that they had returned to smoking at 1 month. Older age, longer duration of abstinence at enrollment, better health status, and having received advice from a health care provider to quit smoking were predictive of abstinence. These findings suggest that it may be possible to identify former smokers at higher risk for relapse using baseline characteristics, which is consistent with previous research [47]. More intensive or directed intervention for former smokers at greater risk of relapse—potentially leveraging the constant availability of online community support—may be a fruitful line of inquiry for future research.

Limitations

This study has several limitations. First, the wide confidence intervals in several of the univariate analyses point to small cell counts for several variables. This was a feasibility study primarily designed to determine the available pool of participants for a subsequent trial and to characterize this understudied group of website users. Future research with a larger sample is needed to confirm some of the preliminary associations we have identified. Second, given the exploratory nature of the study, we did not control for the number of statistical analyses conducted so as not to miss important potential relationships. This approach may have increased the likelihood of Type I error. Third, as this was an exploratory study, univariate logistic regression results are unadjusted and the associations noted in the results section may not persist if appropriate adjustments are made. Fourth, assessing abstinence at 1-month post registration provides only an early peek at the potential effectiveness of an Internet intervention in preventing relapse. Studies with a longer-term follow-up are needed to

assess the extent to which the early signals of intervention effect are sustained over time. Finally, slightly more than half the sample was reached for follow-up. Although this degree of attrition is common in Internet-based studies [48], it may have resulted in an overestimate of the proportion of participants who were abstinent in responder-only analyses and may limit the generalizability of these findings. However, our use of automated tracking data ensured that we captured the full extent of website utilization during the study period.

Conclusion

Our findings suggest that the Internet may be a promising delivery channel for relapse prevention intervention and highlight several important areas for future studies. Additional research should focus on identifying recent quitters who may be more susceptible to relapse and determining which specific aspects of a Web-based intervention are most helpful to recent quitters in preventing relapse. Optimizing Internet interventions to help recent quitters maintain an initial period of abstinence may yield significant benefits for reducing the prevalence of smoking.

Acknowledgments

This study was supported by funds from Truth Initiative and by grants from the National Cancer Institute (Graham, R01 CA155489 and R01 CA192345; Cohn, R03 CA175870).

Conflicts of Interest

All authors are employees of Truth Initiative, a nonprofit public health foundation that runs BecomeAnEX.org.

References

1. Fiore MC, Jaén CR, Baker TB, et al. Treating Tobacco Use and Dependence Update. Clinical Practice Guideline. Rockville, MD: Department of Health and Human Services. Public Health Service; 2008.
2. Centers for Disease Control and Prevention (CDC). Quitting smoking among adults--United States, 2001-2010. MMWR Morb Mortal Wkly Rep 2011 Nov 11;60(44):1513-1519 [FREE Full text] [Medline: 22071589]
3. Hughes JR, Keely J, Naud S. Shape of the relapse curve and long-term abstinence among untreated smokers. Addiction 2004 Jan;99(1):29-38 [FREE Full text] [Medline: 14678060]
4. Piasecki TM, Fiore MC, McCarthy DE, Baker TB. Have we lost our way? The need for dynamic formulations of smoking relapse proneness. Addiction 2002 Sep;97(9):1093-1108. [Medline: 12199822]
5. Westman EC, Behm FM, Simel DL, Rose JE. Smoking behavior on the first day of a quit attempt predicts long-term abstinence. Arch Intern Med 1997 Feb 10;157(3):335-340. [Medline: 9040302]
6. Zhou X, Nonnemaker J, Sherrill B, Gilsenan AW, Coste F, West R. Attempts to quit smoking and relapse: factors associated with success or failure from the ATTEMPT cohort study. Addict Behav 2009 Apr;34(4):365-373. [doi: 10.1016/j.addbeh.2008.11.013] [Medline: 19097706]
7. Hajek P, Stead LF, West R, Jarvis M, Hartmann-Boyce J, Lancaster T. Relapse prevention interventions for smoking cessation. Cochrane Database Syst Rev 2013;8:CD003999. [doi: 10.1002/14651858.CD003999.pub4] [Medline: 23963584]
8. Guide to Community Preventive Services. Reducing tobacco use and secondhand smoke exposure: Smoke-free policies. 2012. URL: http://www.thecommunityguide.org/tobacco/smokefreepolicies.html [accessed 2015-11-02] [WebCite Cache ID 6ckPGOk2e]
9. Borland R, Partos TR, Yong H, Cummings KM, Hyland A. How much unsuccessful quitting activity is going on among adult smokers? Data from the International Tobacco Control Four Country cohort survey. Addiction 2012 Mar;107(3):673-682 [FREE Full text] [doi: 10.1111/j.1360-0443.2011.03685.x] [Medline: 21992709]
10. Cobb NK, Graham AL. Characterizing Internet searchers of smoking cessation information. J Med Internet Res 2006;8(3):e17 [FREE Full text] [doi: 10.2196/jmir.8.3.e17] [Medline: 17032633]
11. McCausland K, Curry L, Mushro A. Promoting a Web-Based Smoking Cessation Intervention: Implications for Practice. Cases in Public Health Communication & Marketing. 2011. p. 3-26 URL: http://publichealth.gwu.edu/departments/pch/phcm/casesjournal/volume5summer/peer-reviewed/V5_Case1PR.pdf [WebCite Cache ID 6hwar3GoV]
12. Graham A, Chang Y, Fang Y. Cost-effectiveness of internet and telephone treatment for smoking cessation: an economic evaluation of The iQUITT Study. Tob Control 2013;22(6):e11. [Medline: 23010696]
13. Fox S, Duggan M. Health Online. 2013. URL: http://www.pewinternet.org/2013/01/15/health-online-2013/ [accessed 2015-02-11] [WebCite Cache ID 6ckPOXmXf]
14. Pew Internet & American Life Project. Health fact sheet. 2015. URL: http://www.pewinternet.org/fact-sheets/health-fact-sheet/ [accessed 2015-11-02] [WebCite Cache ID 6ckPic792]
15. Brandon TH, Vidrine JI, Litvin EB. Relapse and relapse prevention. Annu Rev Clin Psychol 2007;3:257-284. [doi: 10.1146/annurev.clinpsy.3.022806.091455] [Medline: 17716056]
16. North American Quitline Consortium. Web-Based Services. 2015. URL: http://map.naquitline.org/reports/web/ [accessed 2015-11-02] [WebCite Cache ID 6ckPkp7ca]

17. Selby P, van Mierlo T, Voci SC, Parent D, Cunningham JA. Online social and professional support for smokers trying to quit: an exploration of first time posts from 2562 members. J Med Internet Res 2010;12(3):e34 [FREE Full text] [doi: 10.2196/jmir.1340] [Medline: 20719739]
18. Cohen S, Lichtenstein E. Partner behaviors that support quitting smoking. J Consult Clin Psychol 1990 Jun;58(3):304-309. [Medline: 2365893]
19. Coppotelli HC, Orleans CT. Partner support and other determinants of smoking cessation maintenance among women. J Consult Clin Psychol 1985 Aug;53(4):455-460. [Medline: 4031200]
20. Mermelstein R, Cohen S, Lichtenstein E, Baer JS, Kamarck T. Social support and smoking cessation and maintenance. J Consult Clin Psychol 1986 Aug;54(4):447-453. [Medline: 3745596]
21. Mermelstein R, Lichtenstein E, McIntyre K. Partner support and relapse in smoking-cessation programs. J Consult Clin Psychol 1983 Jun;51(3):465-466. [Medline: 6863711]
22. Schwarzer R, Satow L. Online intervention engagement predicts smoking cessation. Prev Med 2012 Sep;55(3):233-236. [doi: 10.1016/j.ypmed.2012.07.006] [Medline: 22813919]
23. Fichter MM, Quadflieg N, Nisslmüller K, Lindner S, Osen B, Huber T, et al. Does internet-based prevention reduce the risk of relapse for anorexia nervosa? Behav Res Ther 2012 Mar;50(3):180-190. [doi: 10.1016/j.brat.2011.12.003] [Medline: 22317754]
24. Holländare F, Anthony SA, Randestad M, Tillfors M, Carlbring P, Andersson G, et al. Two-year outcome of internet-based relapse prevention for partially remitted depression. Behav Res Ther 2013 Nov;51(11):719-722. [doi: 10.1016/j.brat.2013.08.002] [Medline: 24021360]
25. Borland R, Balmford J, Swift E. Effects of Encouraging Rapid Implementation and/or Structured Planning of Quit Attempts on Smoking Cessation Outcomes: a Randomized Controlled Trial. Ann Behav Med 2015 Oct;49(5):732-742. [doi: 10.1007/s12160-015-9706-3] [Medline: 25877340]
26. Balmford J, Borland R, Benda P. Patterns of use of an automated interactive personalized coaching program for smoking cessation. J Med Internet Res 2008;10(5):e54 [FREE Full text] [doi: 10.2196/jmir.1016] [Medline: 19097975]
27. Burri M, Baujard V, Etter J. A qualitative analysis of an internet discussion forum for recent ex-smokers. Nicotine Tob Res 2006 Dec;8 Suppl 1:S13-S19. [Medline: 17491166]
28. Hung WT, Dunlop SM, Perez D, Cotter T. Use and perceived helpfulness of smoking cessation methods: results from a population survey of recent quitters. BMC Public Health 2011;11:592 [FREE Full text] [doi: 10.1186/1471-2458-11-592] [Medline: 21791111]
29. Richardson A, Graham AL, Cobb N, Xiao H, Mushro A, Abrams D, et al. Engagement promotes abstinence in a web-based cessation intervention: cohort study. J Med Internet Res 2013;15(1):e14 [FREE Full text] [doi: 10.2196/jmir.2277] [Medline: 23353649]
30. Simmons VN, Heckman BW, Ditre JW, Brandon TH. A measure of smoking abstinence-related motivational engagement: development and initial validation. Nicotine Tob Res 2010 Apr;12(4):432-437 [FREE Full text] [doi: 10.1093/ntr/ntq020] [Medline: 20190004]
31. Simmons VN, Cruz LM, Brandon TH, Quinn GP. Translation and adaptation of smoking relapse-prevention materials for pregnant and postpartum Hispanic women. J Health Commun 2011 Jan;16(1):90-107. [doi: 10.1080/10810730.2010.529492] [Medline: 21120739]
32. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992 Jun;30(6):473-483. [Medline: 1593914]
33. Cohen S, Hoberman HM. Positive Events and Social Supports as Buffers of Life Change Stress. J Appl Social Pyschol 1983 Apr 19;13(2):99-125 [FREE Full text] [doi: 10.1111/j.1559-1816.1983.tb02325.x] [Medline: 24843434]
34. Russell DW. UCLA Loneliness Scale (Version 3): reliability, validity, and factor structure. J Pers Assess 1996 Feb;66(1):20-40. [doi: 10.1207/s15327752jpa6601_2] [Medline: 8576833]
35. Smith A. Home Broadband. 2010. URL: http://www.pewinternet.org/2010/08/11/home-broadband-2010/ [accessed 2015-11-02] [WebCite Cache ID 6ckPn1h78]
36. Hampton K, Goulet L, Rainie L, Purcell K. Social networking sites and our lives. 2011. URL: http://www.pewinternet.org/files/old-media/Files/Reports/2011/PIP%20-%20Social%20networking%20sites%20and%20our%20lives.pdf [accessed 2015-11-02] [WebCite Cache ID 6ckPojlOX]
37. Adobe Systems Incorporated. Adobe Analytics. 2015. URL: http://www.adobe.com/marketing-cloud/web-analytics/marketing-analytics-capabilities.html [accessed 2016-01-19] [WebCite Cache ID 6eek67iz7]
38. Eysenbach G. The law of attrition. J Med Internet Res 2005;7(1):e11 [FREE Full text] [doi: 10.2196/jmir.7.1.e11] [Medline: 15829473]
39. Brouwer W, Kroeze W, Crutzen R, de NJ, de Vries NK, Brug J, et al. Which intervention characteristics are related to more exposure to internet-delivered healthy lifestyle promotion interventions? A systematic review. J Med Internet Res 2011;13(1):e2 [FREE Full text] [doi: 10.2196/jmir.1639] [Medline: 21212045]
40. McClure JB, Shortreed SM, Bogart A, Derry H, Riggs K, St JJ, et al. The effect of program design on engagement with an internet-based smoking intervention: randomized factorial trial. J Med Internet Res 2013;15(3):e69 [FREE Full text] [doi: 10.2196/jmir.2508] [Medline: 23529377]

41. Donkin L, Christensen H, Naismith SL, Neal B, Hickie IB, Glozier N. A systematic review of the impact of adherence on the effectiveness of e-therapies. J Med Internet Res 2011;13(3):e52 [FREE Full text] [doi: 10.2196/jmir.1772] [Medline: 21821503]
42. Crutzen R, de NJ, Brouwer W, Oenema A, Brug J, de Vries NK. Strategies to facilitate exposure to internet-delivered health behavior change interventions aimed at adolescents or young adults: a systematic review. Health Educ Behav 2011 Feb;38(1):49-62. [doi: 10.1177/1090198110372878] [Medline: 21189422]
43. Kelders S, Kok R, Ossebaard H, van GJ. Persuasive system design does matter: a systematic review of adherence to web-based interventions. J Med Internet Res 2012;14(6):a.
44. Graham AL, Bock BC, Cobb NK, Niaura R, Abrams DB. Characteristics of smokers reached and recruited to an internet smoking cessation trial: a case of denominators. Nicotine Tob Res 2006 Dec;8 Suppl 1:S43-S48 [FREE Full text] [Medline: 17491170]
45. Agboola S, McNeill A, Coleman T, Leonardi BJ. A systematic review of the effectiveness of smoking relapse prevention interventions for abstinent smokers. Addiction 2010 Aug;105(8):1362-1380. [doi: 10.1111/j.1360-0443.2010.02996.x] [Medline: 20653619]
46. Mason D, Gilbert H, Sutton S. Effectiveness of web-based tailored smoking cessation advice reports (iQuit): a randomized trial. Addiction 2012 Dec;107(12):2183-2190. [doi: 10.1111/j.1360-0443.2012.03972.x] [Medline: 22690882]
47. Brandon TH, Meade CD, Herzog TA, Chirikos TN, Webb MS, Cantor AB. Efficacy and cost-effectiveness of a minimal intervention to prevent smoking relapse: dismantling the effects of amount of content versus contact. J Consult Clin Psychol 2004 Oct;72(5):797-808. [doi: 10.1037/0022-006X.72.5.797] [Medline: 15482038]
48. Mathieu E, McGeechan K, Barratt A, Herbert R. Internet-based randomized controlled trials: a systematic review. J Am Med Inform Assoc 2013 May 1;20(3):568-576 [FREE Full text] [doi: 10.1136/amiajnl-2012-001175] [Medline: 23065196]

Abbreviations

ARME: Abstinence Related Motivational Engagement
ISEL: Interpersonal Support Evaluation Scale

Edited by G Eysenbach; submitted 19.01.16; peer-reviewed by E Bloom, K McGeechan; comments to author 18.02.16; revised version received 11.04.16; accepted 21.04.16; published 14.06.16.

Please cite as:
Cha S, Cohn AM, Elmasry H, Graham AL
A Preliminary Exploration of Former Smokers Enrolled in an Internet Smoking Cessation Program
JMIR Res Protoc 2016;5(2):e119
URL: http://www.researchprotocols.org/2016/2/e119/
doi:10.2196/resprot.5542
PMID:27302500

Original Paper

Measuring Health Information Dissemination and Identifying Target Interest Communities on Twitter: Methods Development and Case Study of the @SafetyMD Network

Venk Kandadai[1*], MPH; Haodong Yang[2*], MS; Ling Jiang[2*], MS; Christopher C Yang[2*], PhD; Linda Fleisher[1*], MPH, PhD; Flaura Koplin Winston[1,3*], MD, PhD

[1]Center for Injury Research and Prevention, Children's Hospital of Philadelphia, Philadelphia, PA, United States

[2]College of Computing and Informatics, Drexel University, Philadelphia, PA, United States

[3]Perelman School of Medicine, Department of Pediatrics, University of Pennsylvania, Philadelphia, PA, United States

[*]all authors contributed equally

Corresponding Author:
Christopher C Yang, PhD
College of Computing and Informatics
Drexel University
3401 Market Street
Philadelphia, PA,
United States
Phone: 1 215 895 1631
Fax: 1 215 895 2492
Email: chris.yang@drexel.edu

Abstract

Background: Little is known about the ability of individual stakeholder groups to achieve health information dissemination goals through Twitter.

Objective: This study aimed to develop and apply methods for the systematic evaluation and optimization of health information dissemination by stakeholders through Twitter.

Methods: Tweet content from 1790 followers of @SafetyMD (July-November 2012) was examined. User emphasis, a new indicator of Twitter information dissemination, was defined and applied to retweets across two levels of retweeters originating from @SafetyMD. User interest clusters were identified based on principal component analysis (PCA) and hierarchical cluster analysis (HCA) of a random sample of 170 followers.

Results: User emphasis of keywords remained across levels but decreased by 9.5 percentage points. PCA and HCA identified 12 statistically unique clusters of followers within the @SafetyMD Twitter network.

Conclusions: This study is one of the first to develop methods for use by stakeholders to evaluate and optimize their use of Twitter to disseminate health information. Our new methods provide preliminary evidence that individual stakeholders can evaluate the effectiveness of health information dissemination and create content-specific clusters for more specific targeted messaging.

(JMIR Res Protoc 2016;5(2):e50) doi:10.2196/resprot.4203

KEYWORDS

Twitter; health information; dissemination; health communication; digital health

Introduction

The Centers for Disease Control and Prevention (CDC) uses Twitter as its sole microblogging platform, actively encouraging its use to reach stakeholders with relevant health information [1] and to provide a framework for health information dissemination best practices [2]. Web 2.0 and social media platforms like Twitter provide an opportunity to bridge the gap between innovation and dissemination by leveraging the viral spread of information across large networks of potential stakeholders. However, little is known about the ability of

individual stakeholder groups to achieve their health information dissemination goals through Twitter.

Twitter allows for easy communication and spread of information through networks. Methods to determine the effectiveness of this communication are well documented and widely accessible through an application programming interface (API). Twitter information spread begins when a user posts a short message (currently limited to 140 characters) referred to as a tweet. Users (the stakeholders to which the CDC refers), including influential users, can spread health information through Twitter by encouraging others to follow their tweets. In addition to receiving the information, followers can spread the information to their followers through retweeting (ie, echoing a message by another user). This is the benefit of social media networks: important information can be spread rapidly by sending a message on Twitter to a large and active following base.

An analysis of data from the Health Information and National Trends Survey (HINTS) revealed 23% of Internet users actively engaged in social networking sites [3], and a 2013 study showed 74% of online adults use social networking sites, suggesting a more than 2-fold growth of social network users in the past 5 years [4]. In particular, 35% of Internet users who use Twitter are young adults (aged 18-29 years) or elderly (65 years and older), and nearly 30% are from racial and ethnic minority populations [5]. This is the second potential benefit of Twitter: special groups that might be difficult to reach through other channels can be reached on Twitter, where they are already actively engaged.

There is little information, however, about the effectiveness of Twitter in spreading health information disseminated by credible, nongovernmental individual or group stakeholders. Such individuals and groups are usually part of a network of professionals with whom they work closely, and the network is a crucial channel to spread credible materials in the field. Exploring the effectiveness of the information dissemination in such networks is significant for enhancing the promotion of valuable news and findings. So far, few techniques are available for optimizing dissemination of credible health information by linking user interests with content. In an effort to develop tools to improve this dissemination, the authors report on a methodology examining a case study of an existing Twitter network, @SafetyMD. This study aimed to develop and apply methods of (1) measuring the continued emphasis of health information themes as they spread through two levels of followers of @SafetyMD and (2) identifying targeted interest groups among the followers of @SafetyMD. The goal of this study was to advance methodology for the systematic evaluation and optimization of health information dissemination by stakeholders through Twitter.

Methods

The @SafetyMD Network

The Center for Injury Research and Prevention (CIRP) at the Children's Hospital of Philadelphia has a research-to-action-to-impact outreach strategy that relies on a large network of child and adolescent professionals interested in injury prevention and treatment. Outreach professionals within the center work closely with scientists and engineers to translate evidence into credible messages and materials delivered mostly on the Web. One of the channels for disseminating this information is the official CIRP Twitter handle, @SafetyMD, launched in 2011 and led by the center's scientific director.

Content for @SafetyMD tweets and retweets is based on empirical research conducted within CIRP, new science from the injury research community at large, news, policy decisions, and advances in injury prevention strategies developed by industry. Followers of @SafetyMD include fellow physicians, nonprofit organizations, corporations, journalists, policymakers, and other influencers (eg, users from governmental or corporate entities) as well as researchers, entrepreneurs, and the general community. At the time of this analysis, @SafetyMD had 1790 followers (now 2550), and 458 tweets had been composed with an original-tweet-to-retweet ratio of 18 to 1 (indicating an emphasis on original content versus aggregated content). Given the purpose of the @SafetyMD handle, the relative diversity of its followers (in comparison to similarly sized research groups), and its level of activity, the authors concluded that @SafetyMD represented a typical academic/public health nongovernmental research entity that the CDC referred to in its Twitter strategy for disseminating health information. As such, @SafetyMD provided a convenient and generalizable platform to pilot test methods for measuring health information dissemination on Twitter. See Figure 1 for a screen shot of @SafetyMD's current Twitter page.

Figure 1. The @SafetyMD Twitter Page. Note: Screen shot was taken on February 16, 2014 (after this analysis had been conducted).

Data Extraction and Organization of the @SafetyMD Network

This protocol was exempt from review by the Children's Hospital of Philadelphia's Institutional Review Board. Based on Twitter protocols [6], we used the representational state transfer (REST) API version 1.0 provided by Twitter to acquire data. Specifically, we used the Status method to collect tweets posted by @SafetyMD and the Search method to collect retweets with keywords "RT *@username*."

Between July and November 2012, available profile information (eg, handle name, total number of followers, number followed by, total number of original tweets, user-provided Twitter profile descriptions, and tweet/retweet text content) was obtained from the 1790 @SafetyMD followers. Using the REST API's *GET statuses/user_timeline* method, a custom PHP-crawler program was developed to interface with the API, extract JavaScript Object Notation (JSON) data from followers, and store this data in a MySQL database for accessible tabular data formats. The resulting database included tweets from @SafetyMD's network: those who follow @SafetyMD, those who retweet @SafetyMD, and those who retweet content from followers of @SafetyMD. Text content from @SafetyMD tweets was queried to identify the most frequent repeated words after the content was processed to remove stop words such as "a," "and," and "or." [7]. In order to pilot test and evaluate the methodology, we extracted important keywords from the tweets to investigate how key information disseminated through the network. We employed term frequency, commonly used in information retrieval to measure a terms' significance in the corpus, to identify as keywords terms repeated at least 10 times.

Objective 1: Dissemination

This objective aimed to develop and apply methods for measuring the continued emphasis of health information themes as they spread through two levels of followers of @SafetyMD. A measure of user emphasis was defined as the proportion of total words in retweets that contained @SafetyMD keywords. As a baseline, we also measured the proportion of @SafetyMD keywords in the cumulative words of all @SafetyMD tweets. For this analysis, the @SafetyMD network was limited to those that were active retweeters and organized into three levels. In order to isolate mutually exclusive Twitter users, we defined Level 0 as @SafetyMD (n=458 original tweets), Level 1 as users who retweeted content from @SafetyMD (n=112 users, n=252 retweets), and Level 2 as those users who retweeted content from Level 1 and not directly from Level 0 (n=2356 users, n=4508 retweets).

Objective 2: Targeted Interest Communities

In order to develop more targeted dissemination strategies, this objective examined whether @SafetyMD followers clustered into content-relevant groups. To pilot test this approach, a 10.00% random sample of @SafetyMD followers (n=179) was chosen and further limited to those who retweeted keywords from @SafetyMD (final sample analyzed n=170). For this sample, each user's 50 most recent tweets (inclusive of original tweets, retweets from @SafetyMD, and retweets from others) were selected for content analysis, and available user profile information was extracted and linked to the content analysis. The range of each user's 50 most recent tweets was set at 0 to 128 days from data extraction (this does not factor in each Twitter user's account lifetime, which could fall within the 0-128 day range).

Unique words were identified from the sample of 8500 tweets by a custom-written Java program that removed handle names,

URLs, punctuation symbols, and stop words. Words that included the hashtag symbol "#" as a prefix were kept because they represented a grouping of similar messages and topics on Twitter. This process yielded 1027 unique words. A word importance metric was created by computing the term frequency-inverse document frequency (TF-IDF) value using a Weka (Waikato Environment for Knowledge Analysis) filter class [8] for each word in each of the 8500 individual tweets. This processing generated a large matrix (170 followers × 1027 unique words) that required further data reduction through a 2-step process.

First, principal component analysis (PCA) [9] was conducted to explain the variance-covariance structure of linear combinations of TF-IDF values. After excluding components with eigenvalues less than 1, a second step involved hierarchical cluster analysis (HCA) [10] on the components to further segment the sample of @SafetyMD followers. Similarity was calculated based on affinities among the components extracted from PCA. See Figure 2 for the formula calculating the minimal distance.

In this analysis, x_{ij}= the TF-IDF value of term *j* in follower *i*. After calculating the distance between the new cluster and other clusters, HCA combined any two closest clusters recursively until the algorithm merged all the variables into one final cluster. The furthest neighbor (complete linkage) cluster method was used [10]. As an additional exploratory step, common interests from followers from each cluster were obtained by reading available Twitter profile descriptions and extracting common words and themes.

Statistical Analysis

Descriptive statistics, including frequencies and proportions, were computed as appropriate. A scree plot and tabulated eigenvalues from the PCA and a dendrogram from the HCA were generated to identify unique clusters. All aggregate analyses were performed using R version 3.0.1 and SPSS version 19 (IBM Corp).

Figure 2. Formula calculating minimal distance.

$$Similarity(i,j) = \frac{x_{i1}x_{j1} + x_{i2}x_{j2} + \cdots + x_{ip}x_{jp}}{\sqrt{x_{i1}^2 + x_{i2}^2 + \cdots + x_{ip}^2}\sqrt{x_{j1}^2 + x_{j2}^2 + \cdots + x_{jp}^2}}$$

Results

Description of the @SafetyMD Network and Keywords

@SafetyMD had 1790 followers by the end of the 5-month study period and had composed 458 original tweets and retweets. The 1790 followers had a cumulative following base of 10,866,958 followers. The 458 @SafetyMD tweets and retweets contained 6538 words, and the stop word filter removed 2560 words (39.16%) of these words. A total of 31 keywords (words repeated at least 10 times) were generated from @SafetyMD's 458 tweets, and these keywords were repeated 785 times (Table 1).

Dissemination Across the Network

Of the 6538 words from the 458 tweets generated by @SafetyMD (Level 0), the keywords reflected a user emphasis, or proportion of @SafetyMD words in tweets that were keywords, of 12.01%. Within each subsequent level, the user emphasis remained and decreased: Level 1 contained 6.10% of @SafetyMD's keywords among its 3711 retweeted words; Level 2, 2.50% of 60,795 retweeted words. All 31 keywords were represented in each level at least once.

The results depicted a possible dilution effect when retweeting from one level to the subsequent level. The @SafetyMD dissemination strategy aimed to use the viral nature of Twitter to spread evidence-based injury prevention information. While there was evidence of dissemination, only 2.50% of the content reached a second stage of spread. The change in keywords throughout the diffusion process demonstrated how users at different levels in the constructed retweet network could serve as a proxy filter. They pass on the core information posted by @SafetyMD while shifting the focus by disseminating other types of information such as social events and social behavior.

Targeted Interest Communities

The random sample was selected of 170 @SafetyMD followers who had composed 1,073,770 tweets and had a combined following base of 2,066,980 users. The 50 most recent tweets from these followers had a total word count of 35,602. Of these words, 9.60% were keywords, and all 31 @SafetyMD keywords were represented at least once among the 8500 tweets. PCA revealed 129 unique components from the data. Figure 3 depicts the scree plot generated from the 170×1027 matrix.

In an attempt to further classify the 170 followers, HCA generated 12 unique clusters from the 129 components (the dendrogram could not be presented due to its extremely large size but is available upon request). Table 2 reveals that the clusters shared common interests based on available Twitter profile descriptions provided by the users.

Nearly 60.0% of the followers were grouped in cluster 2 with common interests shared around driving education/safety and pediatric health and the words "drive," "new," "help," "driver," and "safe" had the five largest TF-IDF values. Although the HCA algorithm was able to differentiate clusters 5, 7, and 8, common interests from available Twitter profile descriptions were not available and could not be determined.

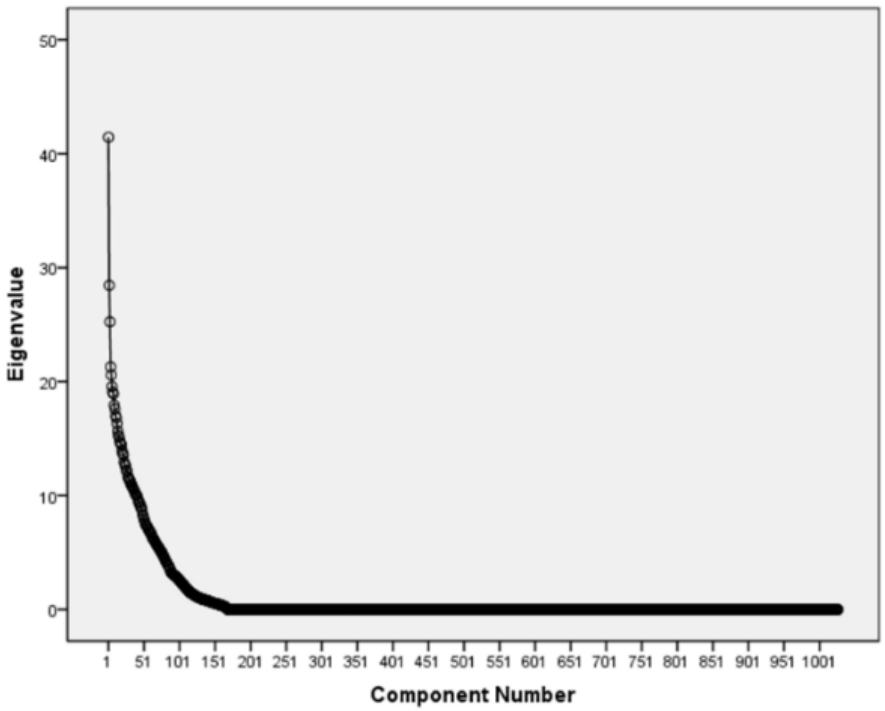
Table 1. @SafetyMD keywords.

Rank	Keyword	Frequency
1	#teendriving2012	112
2	teen	73
3	safety	51
4	driving	47
5	#safety2012	40
6	teens	32
7	driver	29
8	drivers	25
9	research	23
9	Safe	23
11	#roadsafety	21
12	#AMIA2012	20
12	#CelebrateMyDrive	20
12	CHOP	20
12	parents	20
16	crash	19
16	crashes	19
16	risk	19
19	chat	17
19	injury	17
21	car	16
22	study	15
23	drive	14
24	child	13
24	concussion	13
24	seat	13
27	#OHSU10X10	12
27	children	12
29	kids	10
29	passenger	10
29	positive	10

Table 2. Distribution of common interests across the 170 @SafetyMD followers grouped into 12 clusters.

Cluster	Followers, n	Common interests
1	5	Physician blogger, medical journalist
2	101	Driving school, drive training, driving safety, injury prevention, child health, pediatric physician
3	15	Moms, reporters, business owners
4	5	Spread of health-related information through social network
5	4	Could not be determined
6	8	Health research and health services, especially for driving safety
7	5	Could not be determined
8	6	Could not be determined
9	6	Physicians and medical research, especially child injury prevention
10	7	Medical education, driving education and training
11	4	Pediatricians and moms
12	4	Healthcare professionals, road safety professionals

Figure 3. Scree plot of extracted components and their corresponding eigenvalues. Components with Eigenvalues <1 were excluded revealing 129 components.



Discussion

Principal Findings

As a popular microblogging platform, Twitter enables users to disseminate information to a large audience. Users can be selective in deciding whether to retweet a tweet, and this is a natural filtering process. Only those who consider the information as valuable and credible would pass along the message and make it accessible to peers with common interests. Although the information could be diluted throughout the information dissemination process, Twitter makes it easy and fast for information to reach more relevant people than the original author's immediate network. This study is one of the first to develop methods for use by stakeholders to evaluate and optimize their use of Twitter for disseminating health information. Our newly developed methods provide preliminary evidence that individual stakeholders can evaluate the effectiveness of health information dissemination and create content-specific clusters for more specific targeted messaging through Twitter's direct messaging function.

As an indicator of dissemination, the new metric *user emphasis* was defined representing the proportion of Twitter content that included keywords used by the stakeholder. The case study network, @SafetyMD, demonstrated a persistent but decreasing user emphasis of original @SafetyMD content (keywords) as the information spread through two levels of followers via

retweeting. By Level 2 (the followers of @SafetyMD's followers), user emphasis indicated that the use of @SafetyMD keywords had persisted but dropped by 9.5 percentage points. A second method created follower clusters based on content tweeted. The data reduction methods were able to differentiate 12 unique clusters of followers of @SafetyMD.

While multiple studies have conducted health information content analyses across Twitter networks [11-17], few have developed systematic methods to measure health information spread and leverage an existing Twitter network in order to differentiate interest groups. In a particular study utilizing NodeXL methods, Smith and colleagues [18] were able to identify clusters of content and proximal-based groups based on hashtags or selected words. In a study outside of the health sector examining the dissemination of anti-Islamic extremism on a popular Twitter handle, Blanquart and Cook [19] concluded that message dilution was a common phenomenon without the use of hashtags and embedded URLs in original tweets to magnify the messages. Our methods extend those reported previously by examining health information dissemination through a specific Twitter user network, identifying metrics for health information dissemination and leveraging an existing organization's Twitter strategy to effectively reach targeted groups.

More than 10 years ago, Berwick [20] argued that health care leaders lag in translating successful scientific innovations into practice and provided 7 recommendations to accelerate the diffusion of innovations. More recently, Glasgow and colleagues [21] suggested that traditional implementation and dissemination strategies recommended by Berwick (such as getting packaged or messaged information to influencers via traditional networking and partnership) yield labor-intensive and cost-inefficient results. Kreuter and Bernhardt [22] extend these ideas and recommend that health care entities establish systematic evaluation measures to successfully disseminate evidence-based public health programs. The authors stress the need for more pragmatic methodologies for efficient dissemination of health care innovations. Our methods directly respond to this recommendation by providing tools for stakeholders to conduct systematic evaluation on their social media interventions.

Given the wide popularity of Twitter (nearly 232 million active users worldwide [23]), the CDC endorses its use as an opportunity to reach new audiences and bridge dissemination gaps [1]. However, health messages on Twitter can be lost in the large volume of content (more than 5000 tweets composed each second and nearly 300 billion cumulative tweets [23]). Our research supports the potential for Twitter to disseminate health information; however, Twitter communication strategies may need to be optimized.

Limitations

Our results are not without limitations. The newly proposed indicator, user emphasis, only takes into consideration retweets across levels of followers within an existing network and does not account for original status updates that may reference @SafetyMD keywords. In addition, user emphasis may change over time based on new followers and the content that is shared. Also, the current calculation of user emphasis was limited to retweets resulting in a potential conservative estimate because it did not consider other ways that followers interacted with @SafetyMD (eg, through mentions and conversations). The list of the 31 @SafetyMD keywords was generated directly from @SafetyMD tweets and was not further compared to common words used in the broader health information environment. Therefore, we were not able to classify these keywords as original @SafetyMD content versus content influenced by the general health information environment on Twitter.

Our random selection of 170 @SafetyMD followers and their 50 most recent tweets may not necessarily represent content that best describes their information interests or needs, which might change over time. In particular, the range of recent tweet content was within 0 to 128 days of data extraction and may not have taken into account a user's most current Twitter behavior. Future studies should examine a larger sample and the evaluation should be rolling over time to look at trends in interests. Also, the user-provided Twitter profile description might not have been current or complete (as it is part of the registration process and limited in length). Future studies might consider use of surveys to evaluate user interests.

It is clear from the HCA that the overwhelming majority of users were grouped in cluster 2; less than 10% were spread among the remaining 11 clusters. In addition, the common interests of many of the clusters are quite similar to each other, which may imply that available Twitter profile information is not a reliable and valid tool to describe mathematically unique groups on Twitter (given the inconsistency of available profile information). Future studies are needed to validate the relative uniqueness of these clusters and describe the clusters generated from this method using rigorous methodologies that may not involve using available profile information. Finally, these methods will only be useful as long as Twitter continues to share the data.

Conclusions

This study aimed to develop and test a set of methods to (1) measure health information spread across an existing Twitter network and (2) leverage an existing Twitter network to identify target interest groups in an effort to provide tools for organizations that use Twitter to communicate health information. The results from @SafetyMD case study provide preliminary evidence of systematic yet simple tools that can be used to effectively leverage an existing Twitter network used to promote credible health information.

Acknowledgments

This project was funded by a grant to Flaura Winston from the Pennsylvania Department of Health. The Department specifically disclaims responsibility for any analyses, interpretations, or conclusions. The authors thank Twitter and their well-documented API and the followers of @SafetyMD. We also acknowledge the outreach professionals at CIRP at the Children's Hospital of Philadelphia for the review of this article and their efforts in translating research into action for child injury prevention.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-reviewed final report to funding agency (Pennsylvania Department of Health).

[PDF File (Adobe PDF File), 931KB - resprot_v5i2e50_app1.pdf]

References

1. Social media at CDC: Twitter. Atlanta GA: Centers for Disease Control and Prevention URL: http://www.cdc.gov/socialmedia/tools/twitter.html [accessed 2015-01-05] [WebCite Cache ID 6VMEhtb9w]
2. Twitter guidelines and best practices. Atlanta GA: Centers for Disease Control and Prevention URL: http://www.cdc.gov/socialmedia/tools/guidelines/twitter.html [accessed 2015-01-05] [WebCite Cache ID 6VMEjovIR]
3. Chou WS, Hunt YM, Beckjord EB, Moser RP, Hesse BW. Social media use in the United States: implications for health communication. J Med Internet Res 2009;11(4):e48 [FREE Full text] [doi: 10.2196/jmir.1249] [Medline: 19945947]
4. Social Networking Fact Sheet. Washington DC: Pew Internet and American Life Project URL: http://www.pewinternet.org/fact-sheets/social-networking-fact-sheet [accessed 2015-01-05] [WebCite Cache ID 6VMElY90S]
5. Brenner J, Smith A. 72% of online adults are social networking site users. Washington DC: Pew Internet and American Life Project URL: http://www.pewinternet.org/2013/08/05/72-of-online-adults-are-social-networking-site-users [accessed 2015-01-05] [WebCite Cache ID 6VMEnATpt]
6. Twitter Developers. Twitter Developers Web site URL: https://dev.twitter.com/ [accessed 2015-01-05] [WebCite Cache ID 6VMEpusaQ]
7. Scott JG. Social Network Analysis: a Handbook. London UK: SAGE Publications; 2000.
8. Frank E, Holmes G, Pfahringer B, Reutemann P, Witten IH. The WEKA data mining software: An update. SIGKDD Explorations 2009;11(1):10-18.
9. Jolliffe IT. Principal Component Analysis. New York NY: Springer; 2002.
10. Knoke D, Yang S. Social Network Analysis (Quantitative Applications in the Social Sciences). London UK: Sage Publications, Inc; 2007.
11. Shive M, Bhatt M, Cantino A, Kvedar J, Jethwani K. Perspectives on acne: what Twitter can teach health care providers. JAMA Dermatol 2013 May;149(5):621-622. [doi: 10.1001/jamadermatol.2013.248] [Medline: 23677100]
12. Scanfeld D, Scanfeld V, Larson EL. Dissemination of health information through social networks: Twitter and antibiotics. Am J Infect Control 2010 Apr;38(3):182-188 [FREE Full text] [doi: 10.1016/j.ajic.2009.11.004] [Medline: 20347636]
13. Myslín M, Zhu S, Chapman W, Conway M. Using Twitter to examine smoking behavior and perceptions of emerging tobacco products. J Med Internet Res 2013;15(8):e174 [FREE Full text] [doi: 10.2196/jmir.2534] [Medline: 23989137]
14. Lee JY, Sundar SS. To tweet or to retweet? That is the question for health professionals on Twitter. Health Commun 2013;28(5):509-524. [doi: 10.1080/10410236.2012.700391] [Medline: 22873787]
15. Heaivilin N, Gerbert B, Page JE, Gibbs JL. Public health surveillance of dental pain via Twitter. J Dent Res 2011 Sep;90(9):1047-1051 [FREE Full text] [doi: 10.1177/0022034511415273] [Medline: 21768306]
16. Harshavardhan A, Gandhe A, Lazarus R, Yu SH, Liu B. Predicting flu trends using Twitter data. Computer Communications Workshops 2011:702-707. [doi: 10.1109/INFCOMW.2011.5928903]
17. Neiger BL, Thackeray R, Burton SH, Thackeray CR, Reese JH. Use of Twitter among local health departments: an analysis of information sharing, engagement, and action. J Med Internet Res 2013;15(8):e177 [FREE Full text] [doi: 10.2196/jmir.2775] [Medline: 23958635]
18. Smith MA, Rainie L, Shneiderman B, Himelboim I. Mapping Twitter topic networks: From polarized crowds to community clusters. Washington DC: Pew Internet and American Life Project URL: http://www.pewinternet.org/2014/02/20/mapping-twitter-topic-networks-from-polarized-crowds-to-community-clusters/ [accessed 2015-01-05] [WebCite Cache ID 6VMErjTEN]
19. Blanquart G, Cook DM. Twitter influence and cumulative perceptions of extremist support: A case study of Geert Wilders. 2013 Presented at: Proceedings of the 4th Australian Counter Terrorism Conference; 2013; Perth, Australia p. 1-11.
20. Berwick DM. Disseminating innovations in health care. JAMA 2003 Apr 16;289(15):1969-1975. [doi: 10.1001/jama.289.15.1969] [Medline: 12697800]

21. Glasgow RE, Phillips SM, Sanchez MA. Implementation science approaches for integrating eHealth research into practice and policy. Int J Med Inform 2014 Jul;83(7):e1-e11. [doi: 10.1016/j.ijmedinf.2013.07.002] [Medline: 23910896]
22. Kreuter MW, Bernhardt JM. Reframing the dissemination challenge: a marketing and distribution perspective. Am J Public Health 2009 Dec;99(12):2123-2127. [doi: 10.2105/AJPH.2008.155218] [Medline: 19833993]
23. Ahmad I. 30+ of the most amazing Twitter statistics.: Social Media Today URL: http://www.socialmediatoday.com/content/30-most-amazing-twitter-statistics-infographic [accessed 2015-01-05] [WebCite Cache ID 6VMEtNG21]

Abbreviations

API: application program interface
CDC: Centers for Disease Control and Prevention
CIRP: Center for Injury Research and Prevention
HCA: hierarchical cluster analysis
HINTS: Health Information and National Trends Survey
PCA: principal component analysis
TF-IDF: term frequency-inverse document frequency

Edited by G Eysenbach; submitted 05.01.15; peer-reviewed by J Lee; comments to author 08.04.15; revised version received 11.12.15; accepted 04.01.16; published 05.05.16.

Please cite as:
Kandadai V, Yang H, Jiang L, Yang CC, Fleisher L, Winston FK
Measuring Health Information Dissemination and Identifying Target Interest Communities on Twitter: Methods Development and Case Study of the @SafetyMD Network
JMIR Res Protoc 2016;5(2):e50
URL: http://www.researchprotocols.org/2016/2/e50/
doi:10.2196/resprot.4203
PMID:27151100

Original Paper

Determination of the Role of CBP- and p300-Mediated Wnt Signaling on Colonic Cells

Michael Bordonaro[1], PhD; Darina Lazarova Lazarova[1], PhD

The Commonwealth Medical College, Scranton, PA, United States

Corresponding Author:
Michael Bordonaro, PhD
The Commonwealth Medical College
525 Pine Street
Scranton, PA, 18509
United States
Phone: 1 570 504 9646
Fax: 1 570 504 9636
Email: mbordonaro@tcmedc.org

Abstract

Background: The Wnt signaling pathway, mediated through active beta-catenin, is responsible for initiating the majority of cases of human colorectal cancer (CRC), and we have previously shown that hyperactivation of this pathway by histone deacetylase inhibitors (HDACis), such as butyrate, can induce the death of CRC cells. An important cellular switch that mediates the effects of Wnt-signaling activation is variation in the association between beta-catenin and the transcriptional coactivators cAMP response element binding (CREB) binding protein (CBP) and p300. Association of CBP with beta-catenin is thought to activate a set of genes linked to cell proliferation, while the p300-mediated Wnt genetic program is believed to promote cell differentiation. Small molecule agents have been discovered that modulate CBP/p300 Wnt transcriptional programs by altering the association of CBP and p300 to beta-catenin. ICG-001 and ICG-427 inhibit CBP- and p300-mediated Wnt activity, respectively, while IQ-1 prevents the shift from CBP-mediated to a p300-mediated Wnt activity.

Objective: Aim 1 of this proposal is designed to determine the role of CBP- and p300-mediated Wnt signaling in the response of CRC cells to HDACis. Aim 2 is to determine the role of CBP and p300 in the maintenance of high- and low-Wnt fractions in CRC cell line. Aim 3 will compare the effects of CBP- and p300-mediated Wnt activity on CRC initiation and progression.

Methods: In Aim 1, cells will be cotreated with HDACis and ICG-001, ICG-427, or IQ-1 and the levels of Wnt activity, apoptosis, proliferation, differentiation, and CBP- or p300-beta-catenin binding measured. Aim 2 of this proposal may mirror similar heterogeneity observed in human tumors and which may be of clinical significance. Aim 3 will use CRC cell line model systems of initiation and progression: the normal colon cell lines CCD-841CoN, the adenoma line LT97, the primary colon carcinoma cell line SW480, and the lymph node metastasis cell line SW620. Cells will be treated with HDACis and the small molecule agents, and assayed as described above.

Results: We will also attempt to use changes in CBP- and p300-mediated Wnt signaling to shift colonic cells between cell type, modifying CBP- and p300-mediated gene expression in the LT97 adenoma line to shift the adenoma phenotype to more characteristic of the CCD-841CoN normal cells, or the SW480 carcinoma cells. We will use microarray analyses to determine the patterns of gene expression responsible for these CBP- or p300-mediated changes in colonic neoplastic phenotype.

Conclusions: The findings generated from this study will lead to future, more in-depth projects to further dissect the action of CBP/p300 Wnt–mediated transcriptional programs in colonic neoplasia, with an emphasis on methods to modulate these genetic programs for chemopreventive effect.

(JMIR Res Protoc 2016;5(2):e66) doi:10.2196/resprot.5495

KEYWORDS

Wnt; butyrate; beta-catenin; CBP; p300; histone acetylation; colorectal cancer

Introduction

Colorectal cancers (CRCs) are amenable to a high degree of prevention [1-12] through diet; however, CRC remains the second leading cause of cancer mortality in the United States. Two large clinical studies convincingly demonstrated a relationship between fiber intake and reduced risk of CRC [10-12]. The protective action of dietary fiber against colon cancer has been attributed to the fermentation of fiber by anaerobic bacteria in the colon, producing butyrate [13], an inhibitor of histone deacetylases (HDACi) that is present in the colonic lumen at high concentrations [14] and has the potential to produce cell cycle arrest, differentiation, and/or apoptosis of CRC cells [15-18].

In addition to butyrate, other HDACis have emerged as promising anticancer agents due to their ability to preferentially induce growth arrest, differentiation, and apoptosis in malignant cells [19,20]. Thus, several HDACis are currently in clinical trial and, recently, the US Food and Drug Administration (FDA) approved the HDACi vorinostat, suberoylanilide hydroxamic acid (SAHA), for the treatment of cutaneous T-cell lymphoma. Considering the increasing clinical evaluations of HDACis, knowledge of how these agents express their antineoplastic properties is important. Initially, the major activity of HDACis was believed to involve net histone acetylation, leading to modified chromatin assembly and altered gene expression [19,20]. Thus, the HDACis sodium butyrate (NaB) and trichostatin A (TSA), which induce apoptosis in SW620 CRC cells in vitro, hyperactivate Wnt transcriptional activity in these cells [21].

Wnt signaling is induced by the binding of Wnt ligands to their cell surface receptors, resulting in inhibition of glycogen synthase kinase-3 beta (GSK-3beta) activity [22,23]. When active, GSK-3beta, in complex with adenomatous polyposis coli (APC) and Axin, promotes the phosphorylation and degradation of beta-catenin [24-26]; however, when GSK-3beta activity is inhibited, dephosphorylated beta-catenin accumulates and interacts with transcription factor/lymphoid enhancer-binding factor (Tcf/Lef) DNA binding proteins [27-32]. Beta-catenin-Tcf (BCT) transcriptional complexes are detected by their ability to drive transcription from Tcf/Lef site-containing promoter constructs [29,30]. It has been established that constitutively activated Wnt signaling, due to mutations in the APC [29-31] and beta-catenin [30] genes, promotes cell proliferation and tumorigenesis in the colon. Thus, the finding that the HDACis NaB and TSA induce programmed cell death, as well as hyperactivate Wnt signaling in SW620 CRC cells [21], seems to be a paradox. This initial observation was subsequently confirmed in a more comprehensive study, which established a linear relationship between the induction of Wnt transcriptional activity and the levels of apoptosis and the inhibition of clonal growth in 10 human CRC cell lines treated with NaB [1]. In addition to butyrate, other structurally unrelated HDACis, including TSA, vorinostat, and MS275 also hyperactivate Wnt activity in CRC cells at concentrations that result in apoptotic levels similar to those induced by a physiologically relevant concentration (5 mM) of NaB [2]. The causative relationship between induction of Wnt activity and apoptosis was analyzed in NaB-treated CRC cells expressing dominant negative Tcf4 (DN-Tcf4), an amino terminally truncated form of Tcf4, which does not bind beta-catenin and which inhibits the activity of endogenous BCT complexes. DN-Tcf4 suppressed the induction of Wnt transcriptional activity by NaB and resulted in reduced levels of apoptosis [1].

While the majority of published studies associate the activation of Wnt signaling with proliferation and tumorigenesis, several in vivo studies [33-36] support the relationship between upregulated Wnt activity and high levels of apoptosis in CRC cells exposed to NaB [1] including: (1) homozygous mutation in the Drosophila homolog of *APC* results in neuronal cell apoptosis in the Drosophila retina [33], (2) expression of stabile, amino-terminally truncated beta-catenin results in 3- to 4-fold higher apoptotic levels in the intestinal villi of transgenic mice [34], (3) conditional targeting of *Apc*, the mouse version of *APC*, in murine neural crest cells results in massive apoptosis of cephalic and cardiac neural crest cells at 11.5 days post coitum [35], and (4) expression of constitutively active beta-catenin in 129/Sv cells of chimeric mice results in apoptosis of these cells [36]. These findings contrast with the reports that decreased Wnt activity, produced by expression of wild-type APC in *APC*-/- CRC cells, induces apoptosis [37,38], probably by downregulation of survivin [39], and that increased levels of beta-catenin protect cells from suspension-induced apoptosis [40]. These contradictory findings can be reconciled by the fact that different levels of Wnt activity are achieved in different experimental systems. Thus, Wong et al [39] proposed that cells exposed to high levels of Wnt activity undergo apoptosis; whereas, cells exposed to moderate levels of Wnt activity maintain a proliferative state, and cells exposed to low levels of Wnt activity undergo differentiation (terminal differentiation followed by apoptosis). The “just right hypothesis” for CRC formation is based upon a similar concept: APC mutations that result in moderate levels of Wnt signaling are optimal for tumor formation and growth; whereas, APC mutations that lead to relatively high levels of Wnt signaling are not selected, most probably due to apoptosis of cells with such mutations [41].

Based upon published studies by others [33-36], as well as by our findings [1,2,21], we postulate that both relatively high and relatively low levels of Wnt transcriptional activity lead to CRC cell apoptosis. Therefore, Wnt activity can be viewed and analyzed as a gradient, within which absence of detectable Wnt signaling (such as in cells at the top of the colonic crypt) results in terminal differentiation and apoptosis, relatively low levels of signaling (such as in the stem cell compartment of the colonic crypt) lead to controlled self-renewal, moderate levels of signaling (such as in CRC cells) promote proliferation, and relatively high levels of Wnt activity (such as in CRC cells treated with HDACis) lead to enhanced apoptosis (Figure 1). Because of mutation, most CRC and/or CRC precursor cells exhibit aberrant Wnt signaling [29-31]. Therefore, these cells undergo apoptosis with relatively high levels of Wnt activity at the right end of the Wnt signaling continuum; whereas, normal colonic cells undergo apoptosis predominantly through regulatory mechanisms that likely lead to terminal differentiation and are associated with the downregulation of Wnt activity (Figure 1).

Based upon our findings in vitro [1,2,21], we propose that high levels of dietary butyrate in the colonic lumen have a "surveillance" function, whereby butyrate drives premalignant and malignant cells with constitutively activated aberrant Wnt signaling into apoptosis through the hyperinduction of Wnt transcriptional activity. The constitutive activation of Wnt signaling makes cells particularly vulnerable to the apoptosis inducing effects of butyrate.

We have established that the hyperactivation of Wnt signaling activity in NaB-treated CRC cells results from increased levels of Ser-37/Thr-41-dephosphorylated (active) beta-catenin, augmented formation of BCT complexes, as well as enhanced BCT complex-DNA binding [1,2]. The HDACis TSA, SAHA, and MS-275 hyperinduce Wnt activity in CRC cells via the same mechanisms [2]. The increased dephosphorylation of beta-catenin [42-44] in the presence of HDACis is triggered at the plasma membrane level. Thus, we demonstrated that Dkk-1 and sFRP2, Wnt-signaling antagonists, which interfere with Wnt ligand-receptor interactions at the cell membrane [45-55], inhibit the upregulation of active beta-catenin and the hyperactivation of Wnt transcriptional activity by the HDACis NaB, TSA, SAHA, and MS-275 in CRC cells [2]. Consistent with this, other groups have provided evidence for autocrine Wnt signaling in CRC cells [52,53].

Results from our in vitro studies [1,2] suggest that the chemopreventive action of HDACis may differ depending upon the levels of Wnt signaling induced in different cancer subtypes. Thus, we have identified two classes of CRC cell lines: those that respond to butyrate treatment with a high-fold induction of Wnt activity and apoptosis (HWA), and those that exhibit a low-fold induction of Wnt activity and apoptosis (LWA) [1]. If such differences exist in vivo, colorectal adenomas, CRCs, and other Wnt signaling-positive neoplasms can be divided into HWA and LWA groups that differ in their response to HDACis, including butyrate derived from dietary fiber. In addition to differences in Wnt activity between different CRC cell lines (ie, HWA vs LWA), variation in basal and HDACi-induced levels of Wnt activity exist between cells of the same CRC cell line. Applying novel flow cytometry-based methodology, we distinguished between cells with high Wnt activity from cells with low or no Wnt activity within individual CRC cell lines [1]. In these experiments, transfections with enhanced green fluorescent protein (EGFP)-expressing vectors under the transcriptional control of a Wnt-sensitive promoter allowed us to evaluate the number of cells with Wnt activity in the cellular population before and after NaB treatment. In both HWA and LWA cell lines, NaB induced Wnt activity in cells with no detectable Wnt activity; therefore, the fraction of Wnt-positive/high-Wnt cells increases in cell lines exposed to NaB. However, HWA cell lines exhibited a larger fold increase in Wnt-positive cells than LWA cell lines. Thus, treatment of HWA cell lines with NaB resulted in more efficient induction of Wnt in an additional number of cells. Based upon our data, the difference between HWA and LWA cell lines in the upregulation of Wnt activity by HDACis derives from (1) HWA cell lines exhibit a greater increase in the Wnt positive cell fraction than do LWA cells, and (2) the levels of Wnt activity per cell are higher in HWA cells than in LWA cells. Further, we have shown that the low-Wnt fraction of a CRC cell population represents cells more resistant to the proapoptotic effects of NaB [1,2]. The greater the fraction of high-Wnt activity cells, the greater the apoptotic response to HDACis. The heterogeneity observed in the levels of Wnt signaling in different CRC cells in vitro may be analogous to the presence of significant heterogeneity in CRC tumors in vivo. It is plausible that the sensitivity of colorectal neoplasms to HDACis depends upon the relative fraction of HDACi-sensitive cells with high levels of Wnt activity. Therefore, the ability to modulate Wnt signaling within populations of neoplastic cells, possibly through Wnt cofactor activity, may lead to enhanced chemopreventive and therapeutic efficacy of HDACis.

An important transcriptional control point that influences the levels and outcomes of Wnt-signaling activation is the association between beta-catenin and the transcriptional coactivators cAMP response element binding (CREB) binding protein (CBP) and p300 [3-6]. Both CBP and p300 are histone acetyl transferase (HAT) proteins known to influence Wnt activity [3-6,56-59]. The interaction between CBP/p300 and Wnt signaling is complex; these cofactors can either up- or downregulate [56-59] Wnt activity. Both CBP and p300 [56-59] bind to Tcf, and this association possibly also mediates the effects of these proteins on Wnt activity. In addition, acetylation of beta-catenin by p300 enhances formation of BCT complexes, and this may be one mechanism by which HAT factors stimulate Wnt signaling [60]. Knockdown of CBP and p300 levels with small-interfering RNA (siRNA) upregulated Wnt activity in the SW480 CRC cell line, suggesting a repressive function for these factors [58]. However, overexpression of p300 or CBP in SW480 cells could not reverse this activation of Wnt activity and actually further upregulated Wnt signaling [58]. This paradoxical finding is possibly due to a dual role for CBP and p300 in both up and downregulating Wnt activity in a context dependent fashion [58].

Interactions between CBP/p300 and Wnt signaling are optimally dissected using inhibitors known to be specific for CBP-Wnt and p300-Wnt transcriptional programs, the small molecule inhibitors ICG-001, ICG-427, and IQ-1. ICG-001 binds to CBP but not to p300, despite the significant homology between these two proteins [3]. SSW480 CRC cells exhibit significant association of CBP with beta-catenin, but minimal beta-catenin-p300 binding. Treatment of SW480 cells with ICG-001, resulting in ICG-001-CBP binding, downregulates the association between beta-catenin and CBP and upregulates the association between beta-catenin and p300 [3]. This transition from CBP to p300 as the predominant binding partner to beta-catenin results in downregulated TOPFlash Wnt reporter activity and decreased steady-state RNA and protein levels for the Wnt target genes survivin and cyclin D1 [3]. This effect of ICG-001 on CBP-mediated Wnt activity was specific to CBP's role in Wnt signaling, as ICG-001 did not influence other CBP reporters, including AP-1 and CRE [3]. ICG-001 resulted in cancer cell-specific physiological effects; caspase levels, indicative of apoptotic status, were enhanced in SW480 and HCT-116 CRC cells treated with ICG-001, but unchanged in ICG-001-treated CCD-841CoN normal colonic cells [3]. Further, ICG-001 preferentially reduced cell growth and viability in the

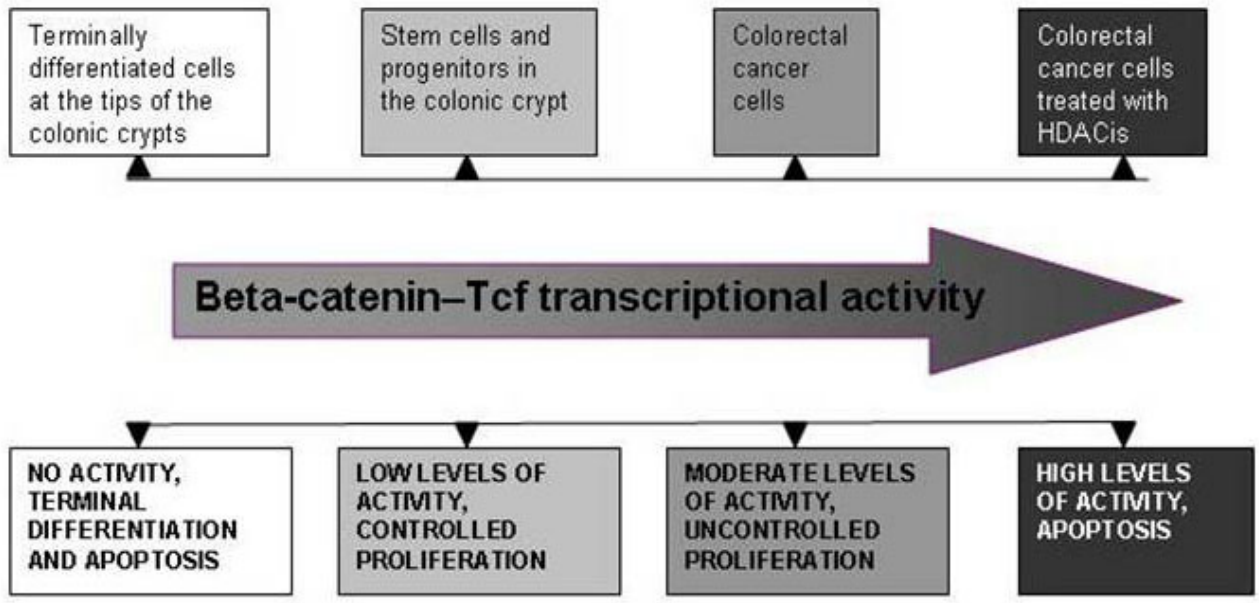
cancer cell lines, and a water soluble version of ICG-001 reduced the formation of intestinal neoplasms in the Min mouse model of *APC* mutation initiated CRC, demonstrating preliminary in vivo efficacy of these agents [3]. Thus, the data suggest that ICG-001, by switching beta-catenin binding from CBP to p300, downregulates CBP-dependent Wnt signaling, resulting in enhanced CRC apoptosis. In the context of the Wnt signaling continuum, one proposed action of ICG-001 is stimulation of apoptosis by downregulation of Wnt activity below the levels required for maintained proliferation. Alternatively, downregulation of CBP-mediated Wnt activity stimulates p300-mediated Wnt signaling, resulting in the activation of genes promoting terminal differentiation and apoptosis. Further, it is known that Wnt signaling is important for maintaining the pluripotency of embryonic stem cells (ESCs) [6 and references therein]. Another small molecule, IQ-1, maintained Wnt-dependent ESC pluripotency by blocking the transition from CBP-mediated Wnt activity to p300-mediated Wnt activity [6]. The tools available to modulate CBP/p300 Wnt activity also include the small molecule ICG-427, which selectively inhibits p300-beta-catenin association [4].

One factor that must be considered is the CBP/p300 status of colonic neoplastic cells, which has been associated with microsatellite instability (MSI) phenotypes [61]. While most CRCs are microsatellite stable (MSS) and exhibit chromosome instability, approximately 10% to 15% of CRCs are of the MSI type. With respect to human CRC cell lines, HCT-116, SW48, Lovo, LS174T, and DLD-1 are MSI, while the primary CRC/lymph node metastasis paired cell lines SW480/SW620, derived from the same patient, are commonly used representatives of the more prevalent MSS type. Mutation in p300 and CBP, leading to truncated, unexpressed, and/or nonfunctional proteins is often observed in MSI CRCs and CRC cell lines. HCT-116 cells express p300 truncated distal to the HAT domain; however, HCT-116 cells exhibit both p300 and CBP activity. DLD-1 CRC cells, despite being of the MSI phenotype, express at least normal-sized p300 and CBP proteins. Therefore, HCT-116 and DLD-1 CRC cells represent MSI lines that exhibit CBP and p300 activity; consistent with this, treatment with ICG-001-stimulated apoptosis in HCT-116, but not normal, colonic cells [3].

With respect to mechanism(s) by which HDACis may modulate CBP/p300-mediated Wnt activity, we hypothesize that HDACis (1) result in the hyperacetylation of specific proteins that enhance CBP/p300-Wnt complex formation and activity, (2) alter gene expression and the target genes modulate CBP/p300-mediated Wnt activity, (3) result in a more open chromatin configuration, allowing enhanced access of CBP/p300-Wnt complexes to target DNA promoter/enhance regions, and/or (4) hyperacetylation of histone and nonhistone proteins resulting from HDACi inhibition complements the acetylation induced by the HAT proteins CBP and p300. Thus, treatment with HDACis can enhance either CBP- or p300-mediated Wnt activity. Whether HDACis activate the CBP or p300 pathways would be dependent upon which of those two pathways are most active in the cells at the time of HDACi treatment; thus, in this scenario, the small molecule inhibitors shift the cells toward either CBP-Wnt or p300-Wnt signaling, reinforcing whichever of the two pathways is activated in the cells. There are many possible mechanisms by which HDACis both generally upregulate Wnt activity and apoptosis as well as more specifically influencing CBP/p300-mediated Wnt activity; these mechanisms of action will be explored in a separate study building upon the findings of the current proposal. The specific aims of the current proposal are specifically focused upon using the small molecule inhibitors ICG-001, ICG-427, and IQ-1 to evaluate the requirement for CBP-Wnt and p300-Wnt interactions with respect to the induction of Wnt activity and of apoptosis by HDACis, and tumorigenic progression represented by a cell culture model of colonic neoplasia.

In summary, CBP- and p300-mediated Wnt signaling likely influences the (1) differential response of CRC cell lines to HDACis, (2) maintenance of low- and high-Wnt fractions within single CRC cell lines, which may be representative of in vivo tumor heterogeneity, and (3) progression of colonic neoplasia from normal cells to metastatic carcinoma. In the current proposal, we will use in vitro models of CRC to explore the role of CBP/p300-mediated Wnt activity in these phenomena. The findings will lead to future projects to explore potential chemopreventive and therapeutic approaches based upon the modulation of CBP/p300-mediated Wnt activity. For example, it may be possible to modulate CBP- versus p300-mediated Wnt signaling to make colonic neoplasms more sensitive to the proapoptotic action of HDACis. Thus, pharmacological interventions based upon the small molecule inhibitors ICG-001, ICG-427, and/or IQ-1 can be used with butyrate derived from high fiber diets (chemoprevention) or therapeutic application of vorinostat (treatment and/or chemoprevention) to enhance the antineoplastic properties of these HDACis. If, for example, it is discovered that CBP-mediated Wnt activity promotes CRC cell proliferation and inhibits the apoptotic pathway induced by HDACis, then cotreatment with HDACis and a pharmacological agent similar in action to ICG-001 (CBP-Wnt inhibitor) will have greater antineoplastic efficacy than application of HDACis alone. Further, if, for example, p300-mediated Wnt signaling is shown to mediate the proapoptotic effects of HDAC-induced Wnt hyperactivation, then suppression of CBP-mediated Wnt activity with ICG-001 will enhance the p300-mediated pathway [3]. On the other hand, if findings from the current proposal demonstrate that CBP-mediated Wnt activity is responsible for the enhanced apoptosis promoted by HDACi-induced apoptosis, then pharmacological agents similar to ICG-427 and IQ-1 would be appropriately used in conjunction with HDACis for maximal therapeutic effect. These treatments may be suitable for suppressing tumor initiation (chemoprevention) and/or inhibiting tumor progression (therapeutics). Therefore, future in vivo studies should be directed toward evaluating combinatory treatments of HDACis with modulators of CBP/p300 signaling in mouse models of CRC to determine whether tumor/size incidence is reduced compared with treatment with each class of agent in isolation. If successful, these in vivo studies would lead to the formulation of CBP/p300 Wnt-modulating agents suitable for human use in clinical trials.

Figure 1. Wnt activity viewed as a gradient. Absence of detectable Wnt signaling, such as in cells at the top of the colonic crypt, results in terminal differentiation, and apoptosis; relatively low levels of signaling, such as in the stem cell compartment of the colonic crypt, lead to controlled self-renewal; moderate levels of signaling, such as in CRC cells, promote proliferation; and relatively high levels of Wnt activity, such as in CRC cells treated with HDACis, lead to enhanced apoptosis. Reproduced from Bordonaro et al [42].



Methods

Aim 1. Determination of the Role of CBP and p300 in the Response of CRC Cells to Histone Deacetylase Inhibitors (HDACis)

We hypothesize that the effects of HDACis on Wnt signaling and cell fate are mediated by changes in the association of CBP and p300 with beta-catenin, and by modulation of BCT complex formation and Wnt activity. To investigate this hypothesis, we will first investigate the effects of CBP- and p300-mediated Wnt activity in the HWA HCT-116, and DLD-1 CRC cell lines, which respond to HDACis with a high-fold induction of Wnt activity and apoptosis (HCT-116 cells, 21.8-fold induction Wnt, 2.5-fold induction apoptosis; DLD-1 cells, 15.4 Wnt, 3.5 apoptosis), the LWA HT29 cell line, which exhibit a low-fold increase in Wnt activity and apoptosis after HDACi treatment (1.4-fold Wnt, 1.5-fold apoptosis), and SW620 cells, which exhibit a moderate-fold increase in Wnt activity and apoptosis after HDACi treatment. Although there are no clear divisions between HWA and LWA cell groups, based upon findings with 10 CRC cell lines, HWA is defined as a 10-fold or greater increase in Wnt activity and a 2-fold or greater increase in apoptosis; LWA is defined as a 1- to 4-fold increase in Wnt activity and a 1- to 1.5-fold increase in apoptosis, and a moderate fold increase in Wnt activity and apoptosis is between 5- and 10-fold for Wnt activity and 1.5- and 2-fold for apoptosis [1,2]. In general, the highest induction of apoptosis is observed in those CRC cells that respond to HDACis with a 15-fold or greater increase in Wnt activity, and a linear relationship exists between induction of Wnt activity and apoptosis [1,2]. Therefore, we hypothesize that modulation of CBP/p300-mediated Wnt activity can enhance the ability of HDACis to upregulate Wnt activity, resulting in higher levels of apoptosis. Although HCT-116 cells are of the MSI phenotype and express a truncated form of p300 [60], this cell lines is characterized by CBP and p300 HAT activity and has been successfully used to evaluate the effects of ICG-001 on cell apoptosis [61,63,63].

The reported effects of CBP and p300 on Wnt activity are most likely mediated through changes in the association of these HAT proteins with Wnt signaling factors, particularly beta-catenin [3-6]. CBP [59] and p300 [62] may associate with Tcf factors and that this may also influence Wnt activity; in addition, p300 HAT activity has been reported to enhance BCT complex formation through increased acetylation of beta-catenin [59]. Therefore, we will first determine whether treatment with HDACis alters the association of CBP and p300 with beta-catenin through coimmunoprecipitation assays, which will be performed essentially as described [1-3]. Initial HDACi treatment will be with 5 mM sodium butyrate or 10 µM vorinostat for 24 hours, which efficiently upregulates Wnt activity and apoptosis in CRC cells [1,2]. If necessary, we will adjust the concentration of HDACis and exposure time to these agents for these and subsequent experiments. Subsequently, we will also use coimmunoprecipitation to determine the effects of HDACis on the association between CBP or p300 and Tcf1 and Tcf4, and between Tcf factors and beta-catenin.

To determine how CBP- or p300-mediated modulation of Wnt activity specifically influences the effects of HDACis on Wnt activity and cell physiology, CRC cells will be cotreated with HDACis and with ICG-001, ICG-427, or IQ-1 for 24 hours, or with each of the small molecule inhibitors alone. In addition, experiments will be conducted with the combination of ICG-001 and IQ-1. ICG-001 and ICG-427 inhibit CBP- and p300-mediated Wnt activity [3-5], respectively, while IQ-1 prevents the shift from CBP-mediated to p300-mediated Wnt activity [6]. Therefore, the combination of ICG-001 and IQ-1 is specifically designed to knockdown CBP-mediated Wnt activity

in the absence of any concomitant upregulation of p300-mediated Wnt activity. Thus, treatment with ICG-001 alone is expected to specifically inhibit CBP-mediated Wnt activity, with the possibility of an upregulation of p300-mediated Wnt activity. Cotreatment with ICG-001 and IQ-1 is expected to suppress CBP-mediated Wnt activity without increasing p300-mediated Wnt activity. Therefore, for all three aims of this proposal, comparison of the effects of ICG-001 alone to that of combinatorial treatment with ICG-001 and IQ-1 will allow us to distinguish cellular effects specifically due to downregulated CBP-mediated Wnt activity alone (combinatorial treatment of ICG-001 and IQ-1) to effects due to downregulation of CBP-mediated Wnt activity coupled to a relative increase in p300 Wnt activity (ICG-001 alone). Dependent upon cellular context, it is also possible that ICG-001 alone will inhibit CBP-mediated Wnt activity without increasing p300-mediated Wnt activity; thus, an increase in p300-beta catenin associated will not be assumed after ICG-001 treatment, but carefully assayed by coimmunoprecipitation experiments. In summary, the three small molecule inhibitors, used alone and in combination, are effective tools to dissect the relationships between CBP- and/or p300- mediated Wnt activity, cell physiology, and effects of HDACis.

The appropriate levels of the small molecule effectors will be determined empirically. After treatment with these combinations of agents, coimmunoprecipitation assays, performed as described [1-3], will be used to determine CBP/p300 binding to beta-catenin, Tcf1, and Tcf4, as well as the association between beta-catenin and Tcf1 and Tcf4. Measurements of Wnt transcriptional activity in CRC cells treated with these agents will be performed with the Wnt reporter TOP/FOP luciferase reporter system that has wild-type (TOP) or mutant (FOP) Tcf binding sites upstream of a minimal c-fos promoter [29,30]. The ratio of luciferase expression driven by the wild-type TOP promoter to that driven by the mutant FOP promoter specifically assays the contribution of Wnt activity to the expression of luciferase [1,2,21,29,30]. Wnt-driven luciferase expression will be measured using the dual luciferase assay system. For these transfections, we will use Geneporter or Lipofectamine 2000 as described [1,2]; alternatively, for higher transfection efficiencies, the Nucleofector system will be used. We will measure the expression of the Wnt target genes survivin, cyclinD1, and c-myc, which are important mediators of decisions of cell proliferation and apoptosis. ICG-001 has been shown to downregulate the expression of survivin and cyclin D1 in CRC cells [3]; all three genes are downregulated by butyrate [64-66].

Further, expression of the receptor tyrosine kinases EphB2 and EphB4, which binds to EphrinB2, is controlled by CBP- and p300-mediated Wnt signaling, and these differences of expression influence cell physiology [67]. EphB4 is usually absent in normal colonic cells but tends to be expressed in CRC; expression level correlates to more advanced neoplasia [67 and references therein]. On the other hand, EphB2 is expressed by normal colonic progenitor cells and tends to be downregulated in CRC [67 and references therein]. CBP-mediated Wnt signaling, which promotes colonic cell proliferation while inhibiting differentiation [3-5], activates EphB4 expression while inhibiting levels of EphB2 [67]; this is consistent with a possible role for CBP-mediated Wnt signaling in promoting colonic neoplasia [3-5]. Knockdown of EphB4 expression suppresses tumor growth and metastases [67], which is consistent with the observed antitumorigenic activity of the CBP-Wnt inhibitor ICG-001 [3-5]. Thus, expression of EphB2 and EphB4 will be measured in the colonic cell lines exposed to the small molecule inhibitors and HDACis. For all proteins (survivin, cyclinD1, c-myc, EphB2, and EphB4), Western blotting using commercially available antibodies will be used to determine changes in expression levels.

Aspects of CRC cell physiology that may be modulated by CBP/p300-mediated Wnt signaling will be determined. For example, it has been reported that inhibition of CBP-mediated Wnt activity stimulates apoptosis in CRC cells [3]. Further, given our data showing that hyperactivation of Wnt activity by HDACis at least partially mediates the effects of those agents on CRC apoptosis [1,2], it is important to understand the specific roles of CBP- versus p300-mediated Wnt activity in HDACi-induced CRC cell apoptosis. Cells will be treated as described above, and cell proliferation will be assayed by the CellTiter cell viability/proliferation assays. In selected experiments, growth potential will also be assayed by clonogenic assays, performed as previously described [1]. Apoptotic analyses will be performed using the Vybrant Apoptosis Assay Kit #2 or the Annexin V-PE Apoptosis Detection Kit I, as previously described [12,24]. Alternatively, the Caspase-Glo luciferase system will be used to quantitate early (caspase 9 activity) and late (caspase 3 activity) apoptotic events. In addition, the extent of CRC cell differentiation will be measured by alkaline phosphatase activity, essentially as described [68].

Our hypothesis is that the effects of HDACis on promoting apoptosis of CRC cells by the hyperactivation of Wnt signaling is dependent upon the specific induction of either CBP- or p300-mediated Wnt signaling, and that by specifically blocking CBP- or p300-mediated Wnt signaling with the appropriate small molecule inhibitor, we will also suppress the induction of apoptosis by the HDACis. To the extent that induction of Wnt activity by HDACis influences other aspects of colonic cell physiology (eg, cell proliferation or differentiation), these phenomena would be specifically dependent upon CBP- or p300-mediated Wnt signaling as well. These findings, particularly, with respect to apoptosis, will have significant chemopreventive and/or therapeutic significance, because modulation of CBP/p300-mediated Wnt signaling may evolve into therapeutic approaches to induce CRC cell apoptosis, either alone or in conjunction with stimulation of excessive Wnt activity by HDACis.

We will also cotreat selected CRC cell lines with combinations of the small molecule agents (ICG-001 and IQ-1, as well as ICG-001 and ICG-427) in the presence and absence of butyrate. For selected experiments, we will use vorinostat, to compare the findings with that obtained with butyrate. As described above, the ICG-001 and IQ-1 combination will inhibit CBP-mediated Wnt activity while simultaneously preventing the cells from switching to p300-mediated signaling. For all three aims, this will be an important control to distinguish effects of diminished CBP-mediated Wnt activity from that of lower

CBP– and higher p300–mediated Wnt signaling. The combination of ICG-001 and ICG-427 will simultaneously block both CBP- and p300-mediated Wnt activity. These combinations will measure the extent that signaling from both CBP and p300 pathways is required for endogenous and butyrate-stimulated Wnt activity in CRC cells. These data will be confirmed by knockdown of CBP and p300 with siRNA. The objective of these latter experiments is to determine the extent that basal and HDACi-induced Wnt activity is mediated through CBP and p300, and evaluate if significant levels of CBP/p300-independent Wnt activity occur in these cell lines. If we demonstrate that significant Wnt signaling occurs even in the absence of CBP and p300 activity, we will ascertain whether CBP- or p300-mediated Wnt signaling is required for the proapoptotic action of the HDACi butyrate in CRC cells. The combinatorial treatments will be repeated, and apoptosis measured as described above.

HDACis also influence the levels of, and activity of, p300 and CBP. For example, in Hela cells, butyrate induces the degradation of p300 through the 26S proteosome pathway [69]; in addition, butyrate can activate p300 HAT activity [69] in intestinal epithelial cells [69-71]. However, it is uncertain whether HAT activity is required to mediate the action of CBP/p300 on Wnt activity [56-59]. If HAT activity is in fact required to mediate the effects of CBP and p300 on Wnt activity, the ability of HDACis to enhance net acetylation may synergize with HAT factors to achieve these effects. Thus, HDACis may have secondary effects on HAT factors that need to be determined in order to properly interpret the findings of this proposal. Butyrate may enhance p300 degradation in Hela cells; therefore, we will ascertain the levels of CBP and p300 in the HDACi-treated CRC cell lines, using Western blot analyses and the appropriate antibodies for CBP and p300. The role of HAT activity in the modulation of Wnt activity by CBP and p300 has not yet been fully determined; however, given the possibility that changes in HAT activity induced by HDACis may influence CBP- and p300-mediated Wnt signaling, we will determine the effects of HDACis on CBP- and p300-specific HAT activity. CRC cells will be treated with HDACis, or left untreated, and CBP or p300 will be immutnoprecipitated from cell lysates with the appropriate antibodies. We will then use colorimetric or fluorescent HAT assays to determine changes of CBP and p300 HAT activity from the lysates of HDACi-treated CRC cells. These HAT assays will confirm that the MSI phenotype cell lines HCT-116 and DLD-1 express functional CBP and p300, as reported [60-63 and refs therein]. In addition, it has been reported that HDACis increase p300 autoacetylation which enhances the association of that p300 with other factors [72].

Therefore, using an anti-acetyl-CBP/p300 antibody, we will ascertain the effects of HDACi treatment on CBP/p300 autoacetylation in our cell lines. This will determine if there is a correlation between HAT factor autoacetylation and the ability of these factors to mediate the effects of HDACis on Wnt activity [3-6].t p300/CBP-associated factor (PCAF) activity may mediate some of the effects of CBP/p300 Wnt activity through stabilization of beta-catenin and upregulation of Wnt activity. The steady-state levels of beta-catenin and Tcf4 in the CRC cells will be evaluated by Western blot analyses subsequent to treatment with the small molecular inhibitors and the HDACis. If the small molecular inhibitors modulate levels of beta-catenin, association of PCAF with beta-catenin will be measured through coimmunoprecipitation assay. If the any of the small molecule inhibitors alters the association of PCAF with beta-catenin, siRNA-mediated knockout of PCAF will be used to determine whether CBP/p300-mediated Wnt signaling is at least partially mediated through PCAF association with beta-catenin. If so, it is expected that repression of PCAF expression and activity will repress levels of Wnt activity controlled by the action of CBP and p300. If PCAF is related to CBP/p300-mediated Wnt activity, we hypothesize that PCAF will be associated with CBP-mediated Wnt activity, because previous findings suggest that higher levels of Wnt activity in CRC cells is more dependent on CBP, compared with p300, action [3]. Thus, knockdown of PCAF would be expected to inhibit CBP-mediated Wnt activity and enhance the repression of that activity by the small molecule inhibitor ICG-001.

Interpretation of Results

For Aim 1, we expect to find that cells with higher levels of Wnt activity, and higher levels of induction of Wnt activity by HDACis, will exhibit a greater proportion of CBP-beta-catenin complexes compared with p300-beta-catenin complexes. If this expected result is observed, the major findings of Aim 1 would be correlated as follows. The greater increase in Wnt activity (measured by luciferase reporter assays) and apoptosis (measured by the Annexin V-PE Apoptosis Detection Kit I or the Caspase-Glo luciferase system) achieved in HWA cells treated with HDACis will be associated with a greater degree of CBP-beta-catenin complex formation (measured by co-immunoprecipitation) compared with LWA cells. Conversely, the weaker response of LWA cells to HDACis is expected to be correlated to a relatively higher association of p300 to beta-catenin compared to CBP-beta-catenin complexes. ICG-001, which interferes with the association of CBP and beta-catenin would therefore be expected to strongly suppress the marked upregulation of Wnt activity and apoptosis observed in HDACi-treated HWA cells; it is expected that ICG-001 and HDACi cotreatment would result in the following set of results: inhibition of CBP-beta-catenin complex formation, increased p300-beta-catenin complex formation, lower levels of Wnt signaling, and lower levels of apoptosis.

The weak induction of Wnt signaling and apoptosis by HDACis in LWA cells would be relatively unaffected by ICG-001, because the LWA cells are expected to have minimal CBP Wnt activity even in the absence of ICG-001. However, treatment of HWA cells with HDACis and ICG-427/IQ-1, which inhibit p300 signaling and potentiate CBP- mediated Wnt activity, would be expected to enhance the induction of Wnt activity and apoptosis by HDACis; this would be correlated with an increase in CBP-beta-catenin complexes and a decrease in p300-beta-catenin complexes. It is possible that inhibition of p300-mediated Wnt activity by ICG-427/IQ-1 may enhance the sensitivity of LWA cells to HDACis by increasing CBP-beta-catenin complex formation and action. SW620 cells, which exhibit a phenotype midway between that of HWA and LWA cells, would also be expected to exhibit moderate

upregulation of CBP-beta-catenin complex formation and activity after exposure to HDACis, and would be also expected to exhibit a moderate response to the small molecule inhibitors. These expected results would be generally consistent with our preliminary data, which showed that expression of a dominant negative form of p300 significantly enhanced Wnt activity in SW620 CRC cells, possibly by shifting Wnt complexes to CBP-mediated activity. Increased Wnt activity can be reasonably expected to be associated with enhanced levels of BCT complexes, and we have found that HDACis can enhance BCT complex formation in some CRC cell lines [1,2]. We also expect that the inhibition of CBP-mediated Wnt activity will suppress the hyperactivation of Wnt activity in CRC cells treated with HDACis.

However, the interactions between HDACis and the CBP and p300 signaling pathways are likely to be complex because (1) HDACis such as butyrate stimulate CRC cell differentiation and apoptosis, which is more consistent with the p300 Wnt pathway, (2) CBP-mediated Wnt activity is likely to be correlated with higher expression of survivin, cyclinD1, and EphB4 [3,67], which is expected to favor proliferation and suppress apoptosis, while paradoxically (3) the hyperactivation of Wnt activity induced by HDACis is more likely associated with CBP-mediated Wnt activity, because blockade of CBP-Wnt signaling by ICG-001 reduces overall Wnt activity in CRC cells [3]. Therefore, the relationship between CBP/p300 signaling and the induction of Wnt activity by HDACis cannot be accurately predicted and will be determined empirically. For example, if p300- mediated Wnt activity, and not CBP-mediated activity, is responsible for the marked upregulation of Wnt activity and apoptosis in HDACi-treated HWA cells, then the expected correlations described above would be reversed. Thus, for example, treatment of HWA CRC cells with HDACis would upregulate p300-beta-catenin complex formation, Wnt activity and apoptosis, and possibly downregulate levels of survivin, cyclinD1, and EphB4, which require CBP activity for expression. If the effects of HDACis on CRC cells are dependent on p300-mediated Wnt signaling, then it is reasonable to expect the induction of Wnt activity and apoptosis by HDACis would be suppressed by ICG-427 and potentiated by ICG-001.

Aim 2. Determination of the Role of CBP and p300 in the Maintenance of High Wnt and Low Wnt Fractions in CRC Cell Lines

The existence of high- and low-Wnt fractions in CRC cells in culture is a stable and reproducible phenomenon [1], which may be related to the known heterogeneity of in vivo tumors with respect to distribution of nuclear beta-catenin and, hence, of Wnt activity, likely of clinical significance [54,55]. It is important to distinguish high and low Wnt fractions within CRC cells (Aim 2) from the existence of HWA and LWA cell lines (Aim 1). The distinction between HWA and LWA cell lines, studied in Aim 1, evaluates the relative response of the total cell population to HDACis, with respect to induction of Wnt activity and apoptosis. In contrast, high- and low-Wnt fractions, studied in Aim 2, evaluate the different subpopulations that exist within each cell line. Thus, for example, Aim 1 is focused on evaluating the role of CBP/p300-mediated Wnt activity in the response of HWA HCT-116 cells compared with LWA HT-29 cells; Aim 2 focuses upon the role of CBP/p300-mediated Wnt signaling in maintaining the existence of separate high- and low-Wnt fractions within the HCT-116 cell population. Our hypothesis is that high- and low-Wnt cell fractions within single CRC cell lines in vitro are characterized by distinctive profiles of relative CBP- or p300-mediated Wnt activity, and that disruption of CBP/p300-mediated Wnt activity by the small molecule inhibitors ICG-001, ICG-427, or IQ-1 will significantly alter the distribution of high- and low-Wnt fractions characteristic of defined CRC cell lines.

Flow cytometry will be used to separate HCT-116 cells into their constituent high- and low-Wnt fractions in the presence or absence of butyrate [1]. This cell line exhibits a marked upregulation of the proportion of high-Wnt activity cells after exposure to the HDACi butyrate [1]. The green fluorescent protein vectors EGFP-TOP and EGFP-FOP, with wild- and mutant-type Wnt-responsive promoters will be transfected into the cells. Transfections will be performed with 20 µg of EGFP-TOP or EGFP-FOP (10-cm dishes). In some cases, to confirm that the sorted fractions do in fact differ in levels of Wnt activity, cells will be cotransfected with 4 µg of the Wnt reporter vectors LEF-OT or LEF-OF and 0.8 ng of pRLnull, a fraction of the sorted cells will be lysed in passive lysis buffer, and luciferase expression measured as described above. Six hours after transfection, cells will be harvested by scraping and transferred to 15-cm dishes. Twenty-four hours after transfection, cells will be treated with 5 mM NaB or 10 µM vorinostat, or left untreated, and collected 24 hours later for analyses.

Flow cytometric sorting of HCT-116 cells into high (“Wnt positive”) and low (“Wnt negative”) Wnt fractions based upon Wnt-specific GFP expression will be performed essentially as described [1,2]. Cells will be harvested, their density will be adjusted to 5×10^6 cells per milliliter of alpha-minimal essential medium (αMEM), and samples analyzed by flow cytometry based upon fluorescence. Representative plots of relative cell numbers (counts) versus fluorescence in EGFP-TOP and EGFP-FOP transfected HCT-116 cells will be overlaid. The relative levels of CBP-beta-catenin and p300-beta-catenin complexes in each of the cell fractions will be ascertained through coimmunoprecipitation; the association of CBP and p300 with Tcf1 and Tcf4, as well as the formation of BCT complexes, will be similarly ascertained. Subsequently, the original mixed-cell populations will be cotreated with the HDACis and ICG-001, ICG-427, and/or IQ-1 (eg, ICG-001 and IQ-1 together), or with each of the small molecule inhibitors alone, followed by separation by flow sorting to determine if the proportion of cells in each fraction is altered when the CBP- or p300-mediated Wnt activity is repressed. The association of CBP and p300 with beta-catenin, Tcf1, and Tcf4, as well as the formation of BCT complexes, will be determined by coimmunoprecipitation assays in these cotreated cells. Levels of Wnt activity in the cell fractions will be ascertained using the OT/OF reporter system; we will calculate the Wnt fraction metrics described shown in Table 1 (Preliminary Studies) to determine if modulation of CBP or p300 activity alters Wnt activity per cell and/or the fraction of cells exhibiting Wnt

activity [1,2]. Levels of cell proliferation, apoptosis, and differentiation in the fractions will be measured as described above.

In Table 1. T/F measures total Wnt activity in the cell population, determined by transfection with TOPFlash or FOPFlash luciferase reporter. To determine the percent Wnt positive cells (%W), cells were transfected with EGFP-TOP or EGFP- FOP vectors, and processed by flow cytometry as described in to obtain overlay plots of relative cell numbers versus fluorescence in EGFP-TOP and EGFP-FOP transfected cells. Cells with Wnt activity are those defined by high fluorescence present only in EGFP-TOP and not in EGFP- FOP samples. T/F/W is the T/F ratio divided by the percent Wnt positive cells, which provides a relative determination of Wnt activity on a per Wnt positive cell percentage basis. No NaB represents measurements of untreated cells, while NaB represents measurements after 24-hour exposure to 5 mM NaB. ΔT/F is the fold-upregulation of total Wnt activity after treatment with NaB (NaB/No NaB), Δ%W is the fold-upregulation of the percent Wnt positive cells after NaB treatment, and ΔT/F/W is the fold increase in the T/F/W ratio resulting from exposure to NaB.

Table 1. Upregulation of Wnt activity in NaB-treated CRC cells occurs by both an increase in the percent cells with Wnt activity and the levels of Wnt activity per cell.

	No NaB			NaB			NaB/No NaB		
Cell line	T/F	% W	T/F/W	T/F	%W	T/F/W	ΔT/F	Δ%W	ΔT/F/W
HCT-116	4.8	9.8	0.49	104.6	46.0	2.3	21.8	4.7	4.7
DLD-1	6.2	10.0	0.62	95.5	20.5	4.7	15.4	2.1	7.6
LS174T	14.5	19.8	0.73	193.6	40.4	4.8	13.3	2.0	6.6
LoVo	5.7	11.7	0.49	17.9	16.5	1.1	3.2	1.4	2.2
SW48	14.7	26.4	0.56	32.7	34.6	0.95	2.2	1.3	1.7

Interpretation of Results

We expect that CBP-mediated Wnt activity will be associated with the high-Wnt fraction in untreated cells, and p300-mediated Wnt activity with the low-Wnt fraction. If so, the correlated findings will be similar to that described in Aim 1; the high-Wnt fraction of the cell population will be associated with higher levels of CBP-beta-catenin complexes, Wnt activity, and sensitivity to HDACis. However, as explained in Aim 1, it is possible that the induction of apoptosis through hyperactivated Wnt activity may occur through either CBP- or p300- mediated Wnt signaling, which needs to be determined empirically. Therefore, it is difficult to predict which of the two Wnt coactivators will be predominantly involved in changes in the proportion of high and low Wnt fractions induced by HDACis. This will be determined empirically, through the experiments outlined in Aim 2. Discovery of an association between CBP- or p300-mediated Wnt activity and the maintenance of high- and low-Wnt fractions in CRC cells in vitro would suggest the possibility of modulating CBP- and/or p300-mediated Wnt activity in vivo, to either repress Wnt signaling and proliferation at the invasive front of CRC tumors, which constitutes a high Wnt fraction component of the neoplasm, or in conjunction with HDACis, hyperactivate Wnt signaling in the high-Wnt activity fraction at the tumor's invasive front, in order to target these potentially metastatic cells [57,58] for apoptosis [1,2]. Therefore, understanding the roles of CBP- and p300-mediated Wnt signaling in intra-CRC heterogeneity, particularly, heterogeneity of Wnt activity, is expected to lead to therapeutic approaches targeting the more invasive and metastatic components of CRCs.

Aim 3. In Vitro Determination of the Role of CBP and p300 Wnt Modulation in the Progression of Colonic Neoplasia In Vitro

Aim 1 of the current proposal focuses upon the role of CBP- and p300-mediated Wnt activity for the upregulation of Wnt signaling and apoptosis in CRC cells treated with HDACis; the major objective of Aim 2 is to determine the role of CBP/p300-mediated Wnt signaling in the maintenance, and response to HDACis, of high- and low-Wnt fractions within CRC cell populations. Thus, after determining the activity of CBP- and p300-mediated Wnt activity, and response to HDACis, between (Aim 1) and within (Aim 2) established carcinoma cell lines, Aim 3 extends these findings to evaluate CBP- and p300-mediated Wnt activity across four colonic cell lines ranging from normal to metastatic and thus representing an in vitro model of tumorigenic progression, and as a mechanism by which the tumorigenic phenotype of colonic cells can be modulated by altering the relative levels of CBP- versus p300-mediated Wnt signaling.

Therefore, to contrast and compare the effects of CBP- and p300-mediated Wnt activity on colonic neoplastic progression (normal cells to adenoma to carcinoma to metastasis), we will use, as an in vitro model system, the normal colon cell line CCD-841CoN, the adenoma line LT97 [7,8], as well as the primary colon carcinoma cell line SW480 and the lymph node metastasis cell line SW620, which was derived from the same patient as SW480 cells. The LT97 cell line is of especial use for these experiments; the LT97 human adenoma cell line was isolated from a microadenoma [7], the earliest possible neoplasm that can be surgically isolated, from a human patient with hereditary familial adenomatous polyposis (FAP). Therefore, as expected, LT97 cells are characterized by the presence of C-terminus truncated APC protein and a lack of full-length, wild-type protein [7,8]. While we expect LT97 cells to exhibit

both endogenous Wnt activity as well as significant upregulation of this activity by HDACis, a recent study has suggested that early APC mutant adenomas may not exhibit nuclear beta-catenin and Wnt signaling, which occurs later in later adenomas and in progression to carcinoma [73]. Thus, the level of Wnt signaling in LT97 cells has not been formally documented, and this determination, which is important in and of itself, with be a component of Aim 3.

Unlike colon carcinoma cells, LT97 cells are incapable of growing in soft agar [3]; the LT97 line exhibits an early premalignant phenotype, quite distinct from that of the typical carcinoma cell lines used as in vitro models of CRC. Thus, LT97 cells are a unique model of the early stages of APC mutation-initiated human colonic tumorigenesis [7]. Based upon both our findings on the effects of HDACis on CRC cells and on the literature, we believe that butyrate, and hence, dietary fiber, would be more effective in suppressing CRC during the earlier stages of tumorigenesis. Consistent with this, it has been shown that the LT97 cells are more sensitive to the growth-suppressing effects of butyrate than are CRC HT-29 cells [8]. Likewise, the nonmetastatic SW480 cell line [74] exhibits greater sensitivity to the effects of butyrate on Wnt activity and apoptosis than the metastatic cell line SW620, derived from the same patient [1,2]. This suggests that early-stage neoplastic colonic cells are more sensitive to HDACis than their later-stage counterparts. The CCD-841Con normal colonic cell line is also of particular interest for this project; our collaborators have observed that while the CBP-Wnt inhibitor ICG-001 induced caspase activity, indicative of apoptosis, in SW480 and HCT-116 CRC cells, it did not do so in the CCD-841CoN line [3]. Therefore, there is a clearly demonstrated difference between the normal colonic line CCD-841CoN and CRC cell lines in the physiological response to ICG-001. Thus suggests differences between normal and neoplastic CRC cells in CBP-Wnt-mediated signaling and downstream phenotypic effects; differences in the association between CBP/p300-Wnt activity and cellular phenotype will be a fundamental focus of Aim 3 of this proposal. Therefore, we hypothesize that (1) the four cell lines to be tested in Aim 3 differ in their relative levels of CBP- versus p300-mediated Wnt activity, and (2) these differences in CBP/p300-Wnt activity influence the phenotypic characteristics of these cell lines, characteristics associated with each cell line's position along the pathway of neoplastic progression.

The first part of Aim 3 is to delineate the phenotypic characteristics of the four cell lines. SW480, SW620 cells and LT97 cells will be cultured as previously described [1,2,7]. CCD-841CoN cells will be cultured as described in the relevant information sheet available from the American Type Culture Collection. Cell growth/proliferation, differentiation, and apoptosis will be measured as described above; the effects of the HDACis butyrate and vorinostat on these processes will also be measured as described above. Growth in soft agar will be measured as previously described [7]. We will also confirm that culture of normal CCD-841CoN cells and LT97 microadenoma cells in the culture medium typically used for CRC cell lines (ie, αMEM plus 10% fetal bovine serum) will result in significantly reduced cell proliferation and viability, demonstrating a dependence of these less tumorigenic cells on additional growth factors. Wnt activity, in the presence and absence of HDACis, will be measured through the TOP Flash/FOPFlash reporter assay as well as the accumulation of active, dephosphorylated beta-catenin [1,2]. These measurements will form the core set of evaluations with respect to phenotypic differences in cell physiology and Wnt activity between the four cell lines studied in Aim 3.

Coimmunoprecipitation will be used to determine the levels of CBP- and p300-beta-catenin complexes in these four cell lines in the presence and absence of the HDACis, treated as described above. The association of CBP and p300 with Tcf1 and Tcf4, as well as the formation of BCT complexes will also be measured by coimmunoprecipitation assays. Cells will be cotreated with HDACis (butyrate or vorinostat, as described above) and with ICG-001, ICG-427, and/or IQ-1 (eg, ICG-001 and IQ-1 together), or with each of the small molecule agents alone, and the levels of Wnt activity, apoptosis, proliferation, differentiation, CBP- or p300-beta-catenin binding, and expression of survivin, c-myc, cyclin D1, EphB2, and EphB4 will be measured as described above. The same coimmunoprecipitation experiments will be performed to ascertain if the formation of complexes between CBP and p300 and Tcf proteins are altered in these cell lines. The levels of Wnt signaling present in each cell line will be measured using the luciferase reporter system. Repression of Wnt activity by one of the small molecule inhibitors would provide information as to whether the Wnt activity present in the cells is predominantly CBP- or p300-mediated, as explained previously. For example, repression by ICG-001 would specifically repress CBP-mediated Wnt activity; ICG-427 would specifically repress p300-mediated Wnt activity. In addition, determination of growth in soft agar will be performed as described [7], to determine whether tumorigenicity can be altered through modulation of CBP- and p300-specific Wnt transcriptional programs. Therefore, we will be correlating the phenotypic measurements of progression and tumorigenicity with (1) complex formation between CBP or p300 and beta-catenin and Tcfs, (2) Wnt activity as evaluated by reporter assays, and (3) expression of survivin, c-myc, cyclin D1, EphB2, and EphB4.

Consistent with our underlying hypothesis for Aim 3, we expect to observe differences between the four cell lines in the relative levels of CBP- versus p300-mediated Wnt activity, both in the presence and absence of HDACis. Thus, the relative levels of CBP–beta-catenin complexes versus p300–beta-catenin complexes will differ between the four cell lines, as will effects of the small molecule inhibitors on both endogenous- and HDACi-stimulated Wnt activity. For example, one of the cell lines may exhibit relatively higher levels of CBP–beta-catenin complexes compared with the other lines; it would be expected that the Wnt activity present in this cell line would be sensitive to, and repressed by, ICG-001, because most of the Wnt signaling in this cell line would be CBP mediated. In contrast, another cell line showing relatively higher levels of p300–beta-catenin complexes would exhibit greater sensitivity to the Wnt activity-repressing effects of ICG-427, which targets p300-mediated signaling. Differential sensitivity of the cell lines to HDACis, with respect to CBP/p300-Wnt activity, would also

be revealed by treatment with the small molecule inhibitors. For example, if ICG-001, but not ICG-427, represses induction of Wnt activity usually observed by treatment of a cell line with HDACis, that finding would support the hypothesis that HDACis predominantly influence CBP-mediated, but not p300-mediated, Wnt activity in those colonic cells.

Therefore, one possibility is that as cells progress along the neoplastic continuum, CBP-mediated Wnt activity will predominate over p300-mediated activity, which is consistent with the finding that the CBP-Wnt inhibitor ICG-001 specifically inhibits the growth of neoplastic as opposed to normal colonic cells [3]. This is also consistent with increased expression of the CBP-Wnt target EphB4, which is associated with more advanced tumorigenic phenotypes [67]. Thus, it is reasonable to assume both enhanced CBP-Wnt activity and EphB4 expression (and, possibly, decreased EphB2 levels) comparing cells with increasing neoplastic phenotypes (eg, CCD-841Con to LT97 to SW480 to SW620).

However, the greater sensitivity of LT97 adenoma cells to butyrate compared with carcinoma cell lines [8], suggests the possibility that changes in the relative levels of CBP- and p300-mediated Wnt activity may favor CBP-Wnt activity in the earlier stages of colonic carcinogenesis. Thus, phenotypic differences between cell types representative of phases in colonic neoplastic progression may be altered by CBP/p300-mediated Wnt activity. If so, we will attempt to use modulation of the levels of CBP- and p300-mediated Wnt activity as a tool to alter the phenotype of LT97 cells in the direction of the less tumorigenic normal cell line CCD-841CoN or the more tumorigenic CRC cell line SW480. Both CCD-841CoN normal colonic cells and SW480 CRC cells have been shown by our collaborators to significantly differ in their phenotypic response to ICG-001, with SW480, but not CCD-841CoN, cells showing enhanced apoptosis when treated with this agent. This approach will determine whether modulation of CBP- and p300-mediated Wnt activity can transition an early colonic neoplasm (represented by LT97 cells) to phenotypes with greater or lesser tumorigenicity. The strategy will use molecular and pharmacological tools to shift the ratio of CBP- versus p300-mediated Wnt activity of LT97 cells toward that observed in CCD-112CoN or SW480 cells, as ascertained by the experiments described above. This will be achieved using the small molecule agents ICG-001, ICG-427, or IQ-1, as well as expression vectors for CBP, p300, and DN300, and, if required, siRNA for CBP and p300. While expression vectors and siRNA may be used as secondary modulators of CBP and p300 activity, in all cases at least one of the small molecule inhibitors will be used, so as to modify Wnt-specific CBP- and p300-mediated gene expression and consequent cellular phenotypes. For example, while DN300 is expected to inhibit the totality of p300 activity, IQ-427 will specifically disrupt Wnt-specific p300 activity.

Concentrations of agents and treatment length will be determined empirically, until a defined phenotypic change is observed. We will measure Wnt signaling, apoptosis and apoptotic response to HDACis, proliferation and the growth suppressing effects of HDACis, differentiation, as well as growth in soft agar, as described above. We will also determine whether LT97 cells altered in the direction of a SW480-like phenotype are able to efficiently proliferate in the same cell culture medium as CRC cells. An endpoint for the process of phenotypic transition will be established; that is, a time point will be determined at which point any observed phenotypic modification of LT97 cells will be considered as "complete." For example, acquisition of the ability to grow in soft agar or to proliferate independent of a specialized culture medium, would be suggestive of transition to a more tumorigenic, SW480 cell-like phenotype. Further, enhanced sensitivity to the growth suppressive and apoptosis-inducing effects of HDACis such as butyrate are also suggestive of a more advanced tumorigenic phenotype. Conversely, we will have established phenotypic differences distinguishing CCD-841Con cells from LT97 cells (see above), and evaluation of these metrics will be used to ascertain if CBP- or p300-signaling modifications transition LT97 cells toward a more normal, CCD-841CoN-like cellular phenotype. Our hypothesis, consistent to our expectations in the first part of Aim 3, is that each of the four cell lines is characterized by its own profile of CBP- versus p300-mediated Wnt activity, and that forcing LT97 cells to exhibit a CBP/p300 Wnt profile of CCD-841CoN or SW480 cells will promote LT97 cells to exhibit specific phenotypic characteristics of those cell lines, respectively.

Dependent upon the differences that are observed between the four cell types, we expect that modulation of CBP/p300-mediated Wnt activity of LT97 cells, toward either that characteristic of CCD-841CoN cells or SW480 cells, will shift the LT97 cellular phenotype in those two directions, respectively. Once we have established a CBP/p300-mediated treatment regimen that is able to transition LT97 cells to lesser or greater tumorigenicity, we will conduct microarray analyses to determine the global changes in gene expression responsible for these CBP- or p300-mediated changes. LT97 cells will be treated with the particular combination of agents found to alter cell phenotype in the required directions (toward the CCD-841Con and SW480 phenotypes), or left untreated. Wnt signaling, apoptosis, and apoptotic response to HDACis, proliferation, differentiation, as well as growth in soft agar will be measured as described above. Measurements of the expression of survivin, cyclinD1, c-myc, EphB4, and EphB2 will also be performed; we would expect that transition of LT97 cells to a more tumorigenic phenotype would be characterized by increased expression of the first four genes and decreased expression of EphB2; this pattern would be expected to be reversed with transition of LT97 cells to a more normal colonic phenotype. However, this expectation is dependent upon whether a more tumorigenic phenotype is associated with increased CBP-mediated Wnt activity (see above).

At the defined time point at which phenotypic transition is considered complete, mRNA will be isolated with Oligotex mRNA Direct Kit. Genus Biosystems will perform the microarray processing and data analyses for these experiments, using the Agilent human whole genome (41,000+ human genes) oligo microarray. Targeted genes will be validated by Northern blot analyses or quantitative reverse transcription polymerase chain reaction (RT-PCR). A small set of selected discovered genes that are reasonably seen as major candidates for mediating

the observed changes in cellular phenotype, particularly those genes that are known to be Wnt pathway targets, will be further analyzed. These three microarray measurements (original LT97, CCD-112CoN-like LT97 and SW480-like LT97) will be repeated eight times to yield statistically significant quantitative data on changes in gene expression underlying the observed changes in cellular phenotype.

We will determine, by Western blot analyses, whether expression of these genes are modulated by treatment of LT97 cells by the small molecule inhibitors; further, using DN-Tcf4 to block Wnt activity, we will determine whether expression of these selected genes are directly or indirectly dependent upon Wnt signaling. The expression of selected genes will then be directly up- or downregulated through overexpression (expression vectors) or knockdown (siRNA) in order to recapitulate the phenotype changes resulting from the treatments (small molecule inhibitors, expression vectors/siRNA for CBP or p300) above. If changes in the expression of specific CBP/p300 Wnt target genes can mimic phenotypic changes induced by modulation of CBP- or p300-mediated Wnt signaling, this will strongly suggest that the relevant genes are downstream effectors of CBP- or p300-mediated Wnt signaling, and are at least partially responsible for the changes in cellular phenotype induced by the CBP- or p300-targeted treatments.

Interpretation of Results

We expect that LT97 cells will exhibit Wnt activity and modulation of this activity by HDACis, consistent with the general literature; however, this would be inconsistent with the controversial possibility that the earliest stages of colonic initiation do not exhibit Wnt activity [69]. We also expect to identify a subset of CBP- or p300-target genes that differ in expression between the original LT97 cells and the LT97 cells with modified phenotypes, and that subsequent directed modulation of selected genes will at least partially recapitulate the changes in LT97 cell phenotype induced by the methods for up- or downregulating CBP/p300-mediated Wnt activity. Given that CCD-841Con cells were shown to be relatively insensitive to the apoptosis-inducing properties of the CBP-Wnt inhibitor ICG-001 [3], it is possible that those cells already have sharply downregulated CBP-Wnt signaling. For example, it has been shown that inhibiting CBP-Wnt activity by CBP siRNA represses the ability of ICG-001 to downregulate CBP-Wnt signaling. This repression is due to the fact that most of the downregulation of CBP-Wnt activity had already occurred due to the siRNA [3]. By analogy, if CBP-Wnt signaling is naturally low in normal colonic cells, it is reasonable to expect that an inhibitor of that signaling will have little or no effect [3]. Therefore, it is possible that inhibition of CBP-Wnt activity to very low levels is associated with the CCD-841CoN phenotype; if so, a combination of ICG-001 and CBP siRNA, perhaps coupled with overexpression of p300, would be the optimal treatment regimen for transitioning LT97 cells to a more CCD-841CoN phenotype. In this case, the ICG-001 and CBP siRNA would both repress CBP-Wnt signaling and promote p300-Wnt signaling; overexpression of p300 would perhaps synergize to facilitate the switch from CBP- to p300-mediated Wnt activity. On the other hand, the promotion of CBP-Wnt activity over p300-Wnt activity may be more effective in inducing a more tumorigenic phenotype in LT97 cells.

The initial evaluation of functional significance of identified genes will be performed as Aim 3 of the current proposal, and more in depth analyses of physiological relevance of these genes will be incorporated into future projects that will build upon the findings of the present study. Future studies will also determine whether observed differences in gene expression are observed in a broad spectrum of CRC cell lines, characterized by different Wnt pathway activating mutations. The development of treatment regimens that can either promote or inhibit tumorigenesis of early stage colonic neoplasms, and the determination of the patterns of gene expression that mediate these changes in tumorigenic potential, may lead to novel chemopreventive and therapeutic approaches against CRC. Thus, for example, a treatment regimen identified that induces LT97 cells to transition to a more CCD-841Con phenotype can serve as the basis for in vivo studies aimed at developing CBP/p300-targeted therapeutics effective at suppressing colonic tumorigenesis, reversing early stage tumorigenesis, or treating established CRC.

Research Design: Pitfalls and Alternative Approaches

We have extensive experience with the methodologies to be used in this proposal. The potential pitfalls for the specific aims, and alternative approaches that will be used, is outlined as follows. Aim 1: Some effects of HDACis on CRC cell physiology are independent of the modulation of Wnt activity. Wnt-mediated effects of HDACis, working through CBP/p300, may be obscured by opposing non-Wnt effects of HDACis. If necessary, CRC cells stably transfected with an inducible form of DN-Tcf4, which represses Wnt activity, can be used to separate Wnt-specific and non-Wnt-specific effects of HDACis on cell physiology [1,2]. The repression of Wnt activity in DN-Tcf4 transfected cells can be used to ascertain the proportion of HDAC-induced apoptosis mediated by Wnt activity [1,2], including CBP- and p300-specific effects. It is possible, although unlikely, that we will observe that neither blockade of CBP-Wnt activity (ICG-001] or of p300-Wnt activity (ICG-427] influences the upregulation of Wnt activity and of apoptosis by HDACis. If this occurs, the results of the ICG-001/IQ-1 and ICG-001/ICG-427 combinatorial cotreatments will be further analyzed. In the unlikely event that HWA HCT-116 and DLD-1 cells do not exhibit CBP and p300 HAT activity due to their MSI status, which would be inconsistent with previous reports [3,60-63 and refs therein], we will substitute these cells with the HWA Colo201 cell line, which does not exhibit the MSI phenotype [60-63 and refs therein]. However, if HCT-116 and DLD-1 cells do exhibit, as expected, CBP and p300 activity, they are preferable to Colo201 cells because (1) Colo201 cells are semiadherent and more difficult to culture and transfect, (2) our collaborators have already established that HCT-116 cells are sensitive to the proapoptotic action of ICG-001, and (3) it is useful to evaluate the role of CBP/p300-mediated Wnt signaling in the action of HDACis in MSI-positive cells, such as HCT-116 and DLD-1, compared with non-MSI cells such as SW480 and SW620. Aim 2: CRC cell lines transfected with inducible DN-Tcf4 will be used if the findings suggest that effects of HDACis on cellular physiology (eg, apoptosis) that

are independent of Wnt activity are masking the Wnt-dependent effects measured here. If so, the DN-Tcf4 cell lines can be used to determine the effects of non-Wnt-mediated events through effective suppression of endogenous and HDACi activated Wnt activity as described in Aim 1 [1]. In the unlikely event that the MSI status of HCT-116 cells makes them unsuitable for the experiments of Aim 2, they will be substituted with the SW480 cell line. Aim 3: It is possible that LT97 cells will not exhibit Wnt activity, consistent with a recent report suggesting a lack of nuclear beta-catenin in early stage APC mutant neoplasms, but inconsistent with the predominant view in the literature that activated Wnt signaling is the earliest initiating event in colonic tumorigenesis. If this unexpected finding is observed, we will change the focus of Aim 3 from modulating CBP/300-mediated Wnt activity in LT97 cells to altering that activity in SW480 cells in order to transition these cells to a more (SW620) tumorigenic or less (LT97) tumorigenic phenotype, respectively. Therefore, if LT97 cells do not exhibit the expected endogenous Wnt activity, we will use SW480 cells as the model system for CBP/p300-Wnt induced changes in cellular phenotype, instead of the LT97 cell line. All experiments will be as outlined above, with the exception of the change in cell type. We fully expect that the well characterized, Wnt-positive SW480 cell line to effectively represent a suitable model system for the experiments of Aim 3, because these cells lie in between LT97 and SW620 cells in the continuum of colonic neoplastic progression, and the Wnt signaling pathway in these cells has been studied in detail in our laboratory. However, we believe that LT97 cells, if they exhibit Wnt activity, would represent a more effective model given that they are more sensitive to HDACis and are derived from an earlier stage of tumorigenesis that may be more amenable to treatment. However, the SW480 cell line represents a reasonable and effective alternative for the successful completion of Aim 3, if the LT97 cells prove unsuitable for these experiments. Assuming that LT97 cells exhibit Wnt activity as we expect, is possible that we will be unable to transition LT97 cell phenotypes into those more similar to CCD-841CoN and SW480 cells or that we will be unable to identify the gene expression profiles associated with any observed phenotypic changes. If so, we will change the objectives of the second half of Aim 3 and instead examine the patterns of CBP/p300-Wnt-mediated gene expression altered by treatment of colonic cells with HDACis. Our collaborators have already demonstrated that SW480 CRC, but not normal colonic, cells exhibit Wnt-mediated changes in cell physiology upon treatment with ICG-001, an agent which specifically disrupts interactions between CBP and beta-catenin and inhibits Wnt transcriptional activity [3]. Thus, SW4840 CRC and CCD-841CoN normal colonic clearly exhibit differences in CBP/p300-mediated Wnt signaling. Further, it is likely that HDACis, which preferentially induce apoptosis in neoplastic cells and upregulate Wnt activity [1,2], will modulate CBP/p300 signaling differently in SW480 and CCD-841CoN cells. Thus, this approach represents a reasonable alterative for the second part of Aim 3. However, if we are successful in modifying LT97 cell phenotypes and in identifying the CBP/p300- mediated Wnt targeted gene expression profiles responsible for the altered phenotypes, then the experiments outlined in the preceding paragraph will be performed as part of future, more in depth studies designed to determine the patterns of gene expression modulated by CBP and p300 throughout the entire process of colonic neoplasia, with an emphasis on those phenotypically relevant genes whose expression is modulated by HDACis.

Statistics

Student's *t*-test will be used to determine statistical significance ($P<.05$). We have successfully used this biostatistical method to evaluate data from our previous studies on Wnt signaling that were generated by experimental methodologies identical to, or similar to, those proposed in for the current project [1,2]. When appropriate, normality of data will be ascertained using the Kolmogorov-Smirnov test (with Dallal-Wilkinson-Lilliefor *P* values), the D'Agostino and Pearson test, or the Shapiro-Wilk test. Choice of normality test will depend upon sample, size; in most cases, Kolmogorov-Smirnov will be used. In the event that the data do not follow a normal distribution, the nonparametric Mann-Whitney U test will be used.

Results

Research on this proposal is ongoing. To date, findings from this proposal, which cover all three specific aims, have been published in the Journal of Cancer [61,62,63]. Thus, we have shown that CBP and p300 activities influence butyrate-mediated Wnt hyperactivation, that CBP activity is absolutely required for efficient hyperactivation of Wnt activity by butyrate, that the maintenance of high-Wnt activity cell fractions requires CBP-mediated Wnt activity, and that there are significant cell-type differences among neoplastic colonic cell lines, including early stage LT97 microadenoma cells, in the manner in which CBP versus p300 activity influences Wnt signaling and colonic cell physiology. Experiments are ongoing.

Discussion

This manuscript describes a R15 AREA grant proposal funded by the National Institutes of Health (National Cancer Institute) upon initial submission. Our findings with respect to this research [61,62,63] clearly demonstrate that CBP- and p300-mediated Wnt activities affect Wnt signaling hyperactivation, and influence apoptosis and proliferation of neoplastic colonic cells; further, CBP and p300 differ in how they affect these processes, and these differences likely influence colonic neoplastic initiation and progression.

The ultimate objective of this line of research, and its clinical relevancy, is to determine whether modulators of CBP/p300-mediated Wnt signaling, in combination with HDACis such as butyrate and the FDA, vorinostat, exert more efficacious antineoplastic effects against CRC than the small molecules or HDACis alone. We therefore envision the possible use of combinatorial treatment with HDACis and small molecule inhibitors of CBP/p300-mediated Wnt signaling in the role of chemoprevention (eg, dietary fiber/butyrate) of therapy to suppress tumor progression and/or as novel chemotherapeutic agents against advanced disease. This possibility would be advanced by in vivo studies demonstrating that specific combinations of HDACis and modulators of CBP/p300-Wnt activity result in marked suppression of intestinal tumorigenesis

in mouse models of human CRC. Future in vitro experiments will be aimed at dissecting the molecular mechanisms by which CBP and p300 modulate Wnt activity, and promote cell differentiation and apoptosis, in a large range of CRC cell lines. Further, we will also dissect the mechanisms, whereby HDACis influence CBP/p300-mediated Wnt activity. More in depth microarray analyses will be used to determine the full genetic programs up- or downregulated by HDACis through the CBP- or p300-mediated Wnt signaling, and identify downstream targets of CBP-Wnt versus p300-Wnt signaling. Further, we propose that mouse models of CRC initiation and progression, such as the Cre-Lox model of APC inactivation [74] be used to ascertain the in vivo chemopreventive efficacy of cotreatment with HDACis and ICG-001, ICG-427, and/or IQ-1, compared with these agents used in isolation. Because this mouse model can progress to carcinoma, it can be used to determine the role of CBP versus p300 Wnt signaling in the in vivo progression from normal cell to adenoma to carcinoma. Analyses of primary cells derived from human patients will be used to determine the relationship between relative levels of CBP- or p300-beta-catenin complexes and the expression of genes that are targets of CBP- versus p300-mediated Wnt activity. These studies will strengthen the clinical relevancy of our initial findings, to determine whether combinatorial use of HDACis with modulators of CBP/p300-mediated Wnt signaling represents an effective chemopreventive and therapeutic strategy against CRC. Therefore, the findings of the proposed study have the potential to lead to novel pharmacological agents that can enhance the antineoplastic action of HDACis for CRC chemoprevention and/or therapy.

Acknowledgments

This proposal was funded by the National Cancer Institute of the National Institutes of Health (1R15CA149589-01).

Conflicts of Interest

None declared.

Multimedia Appendix 1

This is the funded grant review.

[PDF File (Adobe PDF File), 102KB - resprot_v5i2e66_app1.pdf]

Multimedia Appendix 2

This is the funded grant award letter.

[PDF File (Adobe PDF File), 118KB - resprot_v5i2e66_app2.pdf]

References

1. Lazarova DL, Bordonaro M, Carbone R, Sartorelli AC. Linear relationship between Wnt activity levels and apoptosis in colorectal carcinoma cells exposed to butyrate. Int J Cancer 2004;110:523-531 [FREE Full text] [doi: 10.1002/ijc.20152] [Medline: 15122584]
2. Bordonaro M, Lazarova DL, Sartorelli AC. The activation of beta-catenin by Wnt signaling mediates the effects of histone deacetylase inhibitors. Exp Cell Res 2007;313:1652-1666 [FREE Full text] [doi: 10.1016/j.yexcr.2007.02.008] [Medline: 17359971]
3. Emami KH, Nguyen C, Ma H, Kim DH, Jeong KW, Eguchi M, et al. A small molecule inhibitor of beta-catenin/CREB-binding protein transcription [corrected]. Proc Natl Acad Sci U S A 2004;101:12682-12687 [FREE Full text] [doi: 10.1073/pnas.0404875101] [Medline: 15314234]
4. McMillan M, Kahn M. Investigating Wnt signaling: a chemogenomic safari. Drug Discov Today 2005;10:1467-1474. [doi: 10.1016/S1359-6446(05)03613-5] [Medline: 16243267]
5. Teo J, Ma H, Nguyen C, Lam C, Kahn M. Specific inhibition of CBP/beta-catenin interaction rescues defects in neuronal differentiation caused by a presenilin-1 mutation. Proc Natl Acad Sci U S A 2005;102:12171-12176 [FREE Full text] [doi: 10.1073/pnas.0504600102] [Medline: 16093313]
6. Miyabayashi T, Teo J, Yamamoto M, McMillan M, Nguyen C, Kahn M. Wnt/beta-catenin/CBP signaling maintains long-term murine embryonic stem cell pluripotency. Proc Natl Acad Sci U S A 2007;104:5668-5673 [FREE Full text] [doi: 10.1073/pnas.0701331104] [Medline: 17372190]
7. Richter M, Jurek D, Wrba F, Kaserer K, Wurzer G, Karner-Hanusch J, et al. Cells obtained from colorectal microadenomas mirror early premalignant growth patterns in vitro. Eur J Cancer 2002;38:1937-1945. [Medline: 12204677]
8. Kautenburger T, Beyer-Sehlmeyer G, Festag G, Haag N, Kühler S, Küchler A, Peters Wilbert H M, et al. The gut fermentation product butyrate, a chemopreventive agent, suppresses glutathione S-transferase theta (hGSTT1) and cell growth more in human colon adenoma (LT97) than tumor (HT29) cells. J Cancer Res Clin Oncol 2005;131:692-700. [doi: 10.1007/s00432-005-0013-4] [Medline: 16133571]

9. Brabletz T, Jung A, Spaderna S, Hlubek F, Kirchner T. Opinion: migrating cancer stem cells - an integrated concept of malignant tumour progression. Nat Rev Cancer 2005;5:744-749. [doi: 10.1038/nrc1694] [Medline: 16148886]
10. Bingham SA, Day NE, Luben R, Ferrari P, Slimani N, Norat T, Peeters Petra H M, European Prospective Investigation into CancerNutrition. Dietary fibre in food and protection against colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC): an observational study. Lancet 2003;361:1496-1501. [Medline: 12737858]
11. Peters U, Sinha R, Chatterjee N, Subar AF, Ziegler RG, Kulldorff M, Prostate, Lung, Colorectal,Ovarian Cancer Screening Trial Project Team. Dietary fibre and colorectal adenoma in a colorectal cancer early detection programme. Lancet 2003;361:1491-1495. [doi: 10.1016/S0140-6736(03)13173-X] [Medline: 12737857]
12. Bingham SA, Norat T, Moskal A, Ferrari P, Slimani N, Clavel-Chapelon F, Peeters Petra H M, et al. Is the association with fiber from foods in colorectal cancer confounded by folate intake? Cancer Epidemiol Biomarkers Prev 2005;14:1552-1556 [FREE Full text] [doi: 10.1158/1055-9965.EPI-04-0891] [Medline: 15941971]
13. Bingham SA. Mechanisms and experimental and epidemiological evidence relating dietary fibre (non-starch polysaccharides) and starch to protection against large bowel cancer. Proc Nutr Soc 1990;49:153-171. [Medline: 2172992]
14. Cummings JH, Pomare EW, Branch WJ, Naylor CP, Macfarlane GT. Short chain fatty acids in human large intestine, portal, hepatic and venous blood. Gut 1987;28:1221-1227 [FREE Full text] [Medline: 3678950]
15. Boffa LC, Lupton JR, Mariani MR, Ceppi M, Newmark HL, Scalmati A, et al. Modulation of colonic epithelial cell proliferation, histone acetylation, and luminal short chain fatty acids by variation of dietary fiber (wheat bran) in rats. Cancer Res 1992;52:5906-5912 [FREE Full text] [Medline: 1327519]
16. Heerdt BG, Houston MA, Augenlicht LH. Potentiation by specific short-chain fatty acids of differentiation and apoptosis in human colonic carcinoma cell lines. Cancer Res 1994;54:3288-3293 [FREE Full text] [Medline: 8205551]
17. Hague A, Elder DJ, Hicks DJ, Paraskeva C. Apoptosis in colorectal tumour cells: induction by the short chain fatty acids butyrate, propionate and acetate and by the bile salt deoxycholate. Int J Cancer 1995;60:400-406. [Medline: 7829251]
18. Medina V, Edmonds B, Young GP, James R, Appleton S, Zalewski PD. Induction of caspase-3 protease activity and apoptosis by butyrate and trichostatin A (inhibitors of histone deacetylase): dependence on protein synthesis and synergy with a mitochondrial/cytochrome c-dependent pathway. Cancer Res 1997;57:3697-3707 [FREE Full text] [Medline: 9288776]
19. Marks PA, Dokmanovic M. Histone deacetylase inhibitors: discovery and development as anticancer agents. Expert Opin Investig Drugs 2005;14:1497-1511. [doi: 10.1517/13543784.14.12.1497] [Medline: 16307490]
20. Lin H, Chen C, Lin S, Weng J, Chen C. Targeting histone deacetylase in cancer therapy. Med Res Rev 2006;26:397-413. [doi: 10.1002/med.20056] [Medline: 16450343]
21. Bordonaro M, Mariadason JM, Aslam F, Heerdt BG, Augenlicht LH. Butyrate-induced apoptotic cascade in colonic carcinoma cells: modulation of the beta-catenin-Tcf pathway and concordance with effects of sulindac and trichostatin A but not curcumin. Cell Growth Differ 1999;10:713-720 [FREE Full text] [Medline: 10547075]
22. Woodgett JR. Regulation and functions of the glycogen synthase kinase-3 subfamily. Semin Cancer Biol 1994;5:269-275. [Medline: 7803763]
23. Cook D, Fry MJ, Hughes K, Sumathipala R, Woodgett JR, Dale TC. Wingless inactivates glycogen synthase kinase-3 via an intracellular signalling pathway which involves a protein kinase C. EMBO J 1996;15:4526-4536 [FREE Full text] [Medline: 8887544]
24. Rubinfeld B, Souza B, Albert I, Müller O, Chamberlain SH, Masiarz FR, et al. Association of the APC gene product with beta-catenin. Science 1993;262:1731-1734. [Medline: 8259518]
25. Su LK, Vogelstein B, Kinzler KW. Association of the APC tumor suppressor protein with catenins. Science 1993;262:1734-1737. [Medline: 8259519]
26. Munemitsu S, Albert I, Souza B, Rubinfeld B, Polakis P. Regulation of intracellular beta-catenin levels by the adenomatous polyposis coli (APC) tumor-suppressor protein. Proc Natl Acad Sci U S A 1995;92:3046-3050 [FREE Full text] [Medline: 7708772]
27. Behrens J, von Kries J P, Kühl M, Bruhn L, Wedlich D, Grosschedl R, et al. Functional interaction of beta-catenin with the transcription factor LEF-1. Nature 1996;382:638-642. [doi: 10.1038/382638a0] [Medline: 8757136]
28. Molenaar M, van de Wetering M, Oosterwegel M, Peterson-Maduro J, Godsave S, Korinek V, et al. XTcf-3 transcription factor mediates beta-catenin-induced axis formation in Xenopus embryos. Cell 1996;86:391-399 [FREE Full text] [Medline: 8756721]
29. Korinek V, Barker N, Morin PJ, van WD, de WR, Kinzler KW, et al. Constitutive transcriptional activation by a beta-catenin-Tcf complex in APC-/- colon carcinoma. Science 1997;275:1784-1787 [FREE Full text] [Medline: 9065401]
30. Morin PJ, Sparks AB, Korinek V, Barker N, Clevers H, Vogelstein B, et al. Activation of beta-catenin-Tcf signaling in colon cancer by mutations in beta-catenin or APC. Science 1997;275:1787-1790 [FREE Full text] [Medline: 9065402]
31. Bienz M, Clevers H. Linking colorectal cancer to Wnt signaling. Cell 2000;103:311-320 [FREE Full text] [Medline: 11057903]
32. Roose J, Clevers H. TCF transcription factors: molecular switches in carcinogenesis. Biochim Biophys Acta 1999;1424:M23-M37. [Medline: 10528152]

33. Ahmed Y, Hayashi S, Levine A, Wieschaus E. Regulation of armadillo by a Drosophila APC inhibits neuronal apoptosis during retinal development. Cell 1998;93:1171-1182 [FREE Full text] [Medline: 9657150]
34. Romagnolo B, Berrebi D, Saadi-Keddoucci S, Porteu A, Pichard AL, Peuchmaur M, et al. Intestinal dysplasia and adenoma in transgenic mice after overexpression of an activated beta-catenin. Cancer Res 1999;59:3875-3879 [FREE Full text] [Medline: 10463573]
35. Hasegawa S, Sato T, Akazawa H, Okada H, Maeno A, Ito M, et al. Apoptosis in neural crest cells by functional loss of APC tumor suppressor gene. Proc Natl Acad Sci U S A 2002;99:297-302 [FREE Full text] [doi: 10.1073/pnas.012264999] [Medline: 11756652]
36. Wong MH, Huelsken J, Birchmeier W, Gordon JI. Selection of multipotent stem cells during morphogenesis of small intestinal crypts of Lieberkuhn is perturbed by stimulation of Lef-1/beta-catenin signaling. J Biol Chem 2002;277:15843-15850 [FREE Full text] [doi: 10.1074/jbc.M200184200] [Medline: 11854293]
37. Groden J, Joslyn G, Samowitz W, Jones D, Bhattacharyya N, Spirio L, et al. Response of colon cancer cell lines to the introduction of APC, a colon-specific tumor suppressor gene. Cancer Res 1995;55:1531-1539 [FREE Full text] [Medline: 7882361]
38. Morin PJ, Vogelstein B, Kinzler KW. Apoptosis and APC in colorectal tumorigenesis. Proc Natl Acad Sci U S A 1996;93:7950-7954 [FREE Full text] [Medline: 8755583]
39. Zhang T, Otevrel T, Gao Z, Gao Z, Ehrlich SM, Fields JZ, et al. Evidence that APC regulates survivin expression: a possible mechanism contributing to the stem cell origin of colon cancer. Cancer Res 2001;61:8664-8667 [FREE Full text] [Medline: 11751382]
40. Orford K, Orford CC, Byers SW. Exogenous expression of beta-catenin regulates contact inhibition, anchorage-independent growth, anoikis, and radiation-induced cell cycle arrest. J Cell Biol 1999;146:855-868 [FREE Full text] [Medline: 10459019]
41. Albuquerque C, Breukel C, van der Luijt Rob, Fidalgo P, Lage P, Slors Frederik J M, et al. The 'just-right' signaling model: APC somatic mutations are selected based on a specific level of activation of the beta-catenin signaling cascade. Hum Mol Genet 2002;11:1549-1560 [FREE Full text] [Medline: 12045208]
42. Bordonaro M, Lazarova DL, Sartorelli AC. Hyperinduction of Wnt activity: a new paradigm for the treatment of colorectal cancer? Oncol Res 2008;17:1-9. [Medline: 18488710]
43. Staal Frank J T, van NM, Strous GJ, Clevers HC. Wnt signals are transmitted through N-terminally dephosphorylated beta-catenin. EMBO Rep 2002;3:63-68 [FREE Full text] [doi: 10.1093/embo-reports/kvf002] [Medline: 11751573]
44. van NM, Meeldijk J, van der Zee Ruurd, Destree O, Clevers H. Wnt signaling controls the phosphorylation status of beta-catenin. J Biol Chem 2002;277:17901-17905 [FREE Full text] [doi: 10.1074/jbc.M111635200] [Medline: 11834740]
45. Bafico A, Liu G, Yaniv A, Gazit A, Aaronson SA. Novel mechanism of Wnt signalling inhibition mediated by Dickkopf-1 interaction with LRP6/Arrow. Nat Cell Biol 2001;3:683-686. [doi: 10.1038/35083081] [Medline: 11433302]
46. Mao B, Wu W, Li Y, Hoppe D, Stannek P, Glinka A, et al. LDL-receptor-related protein 6 is a receptor for Dickkopf proteins. Nature 2001;411:321-325. [doi: 10.1038/35077108] [Medline: 11357136]
47. Semënov MV, Tamai K, Brott BK, Kühl M, Sokol S, He X. Head inducer Dickkopf-1 is a ligand for Wnt coreceptor LRP6. Curr Biol 2001;11:951-961 [FREE Full text] [Medline: 11448771]
48. Holcombe RF, Marsh JL, Waterman ML, Lin F, Milovanovic T, Truong T. Expression of Wnt ligands and Frizzled receptors in colonic mucosa and in colon carcinoma. Mol Pathol 2002;55:220-226 [FREE Full text] [Medline: 12147710]
49. Jones SE, Jomary C. Secreted Frizzled-related proteins: searching for relationships and patterns. Bioessays 2002;24:811-820. [doi: 10.1002/bies.10136] [Medline: 12210517]
50. Kawano Y, Kypta R. Secreted antagonists of the Wnt signalling pathway. J Cell Sci 2003;116(Pt 13):2627-2634 [FREE Full text] [doi: 10.1242/jcs.00623] [Medline: 12775774]
51. Blitzer JT, Nusse R. A critical role for endocytosis in Wnt signaling. BMC Cell Biol 2006;7:28 [FREE Full text] [doi: 10.1186/1471-2121-7-28] [Medline: 16824228]
52. Bafico A, Liu G, Goldin L, Harris V, Aaronson SA. An autocrine mechanism for constitutive Wnt pathway activation in human cancer cells. Cancer Cell 2004;6:497-506 [FREE Full text] [doi: 10.1016/j.ccr.2004.09.032] [Medline: 15542433]
53. Suzuki H, Watkins DN, Jair K, Schuebel KE, Markowitz SD, Chen WD, et al. Epigenetic inactivation of SFRP genes allows constitutive WNT signaling in colorectal cancer. Nat Genet 2004;36:417-422. [doi: 10.1038/ng1330] [Medline: 15034581]
54. Janssen K, Alberici P, Fsihi H, Gaspar C, Breukel C, Franken P, et al. APC and oncogenic KRAS are synergistic in enhancing Wnt signaling in intestinal tumor formation and progression. Gastroenterology 2006;131:1096-1109. [doi: 10.1053/j.gastro.2006.08.011] [Medline: 17030180]
55. Huang D, Du X. Crosstalk between tumor cells and microenvironment via Wnt pathway in colorectal cancer dissemination. World J Gastroenterol 2008;14:1823-1827 [FREE Full text] [Medline: 18350618]
56. Waltzer L, Bienz M. Drosophila CBP represses the transcription factor TCF to antagonize Wingless signalling. Nature 1998;395:521-525. [doi: 10.1038/26785] [Medline: 9774110]
57. Hecht A, Vleminckx K, Stemmler MP, van RF, Kemler R. The p300/CBP acetyltransferases function as transcriptional coactivators of beta-catenin in vertebrates. EMBO J 2000;19:1839-1850 [FREE Full text] [doi: 10.1093/emboj/19.8.1839] [Medline: 10775268]

58. Li J, Sutter C, Parker DS, Blauwkamp T, Fang M, Cadigan KM. CBP/p300 are bimodal regulators of Wnt signaling. EMBO J 2007;26:2284-2294 [FREE Full text] [doi: 10.1038/sj.emboj.7601667] [Medline: 17410209]
59. Lévy L, Wei Y, Labalette C, Wu Y, Renard C, Buendia MA, et al. Acetylation of beta-catenin by p300 regulates beta-catenin-Tcf4 interaction. Mol Cell Biol 2004;24:3404-3414 [FREE Full text] [Medline: 15060161]
60. Ionov Y, Matsui S, Cowell JK. A role for p300/CREB binding protein genes in promoting cancer progression in colon cancer cell lines with microsatellite instability. Proc Natl Acad Sci U S A 2004;101:1273-1278 [FREE Full text] [doi: 10.1073/pnas.0307276101] [Medline: 14732695]
61. Lazarova DL, Wong T, Chiaro C, Drago E, Bordonaro M. p300 influences butyrate-mediated WNT hyperactivation in colorectal cancer cells. J Cancer 2013;4:491-501 [FREE Full text] [doi: 10.7150/jca.6582] [Medline: 23901349]
62. Lazarova DL, Chiaro C, Wong T, Drago E, Rainey A, O'Malley S, et al. CBP activity mediates effects of the histone deacetylase inhibitor butyrate on WNT activity and apoptosis in colon cancer cells. J Cancer 2013;4:481-490 [FREE Full text] [doi: 10.7150/jca.6583] [Medline: 23901348]
63. Lazarova D, Lee A, Wong T, Marian B, Chiaro C, Rainey C, et al. Modulation of Wnt activity and cell physiology by butyrate in LT97 microadenoma cells. J Cancer 2014;5:203-213 [FREE Full text] [doi: 10.7150/jca.8569] [Medline: 24563675]
64. Souleimani A, Asselin C. Regulation of c-myc expression by sodium butyrate in the colon carcinoma cell line Caco-2. FEBS Lett 1993;326:45-50 [FREE Full text] [Medline: 8325387]
65. Lallemand F, Courilleau D, Sabbah M, Redeuilh G, Mester J. Direct inhibition of the expression of cyclin D1 gene by sodium butyrate. Biochem Biophys Res Commun 1996;229:163-169. [doi: 10.1006/bbrc.1996.1774] [Medline: 8954100]
66. Kim EH, Kim HS, Kim SU, Noh EJ, Lee J, Choi KS. Sodium butyrate sensitizes human glioma cells to TRAIL-mediated apoptosis through inhibition of Cdc2 and the subsequent downregulation of survivin and XIAP. Oncogene 2005;24:6877-6889. [doi: 10.1038/sj.onc.1208851] [Medline: 16007142]
67. Kumar SR, Scehnet JS, Ley EJ, Singh J, Krasnoperov V, Liu R, et al. Preferential induction of EphB4 over EphB2 and its implication in colorectal cancer progression. Cancer Res 2009;69:3736-3745 [FREE Full text] [doi: 10.1158/0008-5472.CAN-08-3232] [Medline: 19366806]
68. Wolter F, Stein J. Resveratrol enhances the differentiation induced by butyrate in caco-2 colon cancer cells. J Nutr 2002;132:2082-2086 [FREE Full text] [Medline: 12097697]
69. Li Q, Su A, Chen J, Lefebvre YA, Haché Robert J G. Attenuation of glucocorticoid signaling through targeted degradation of p300 via the 26S proteasome pathway. Mol Endocrinol 2002;16:2819-2827. [doi: 10.1210/me.2002-0154] [Medline: 12456802]
70. Liu Y, Denlinger CE, Rundall BK, Smith PW, Jones DR. Suberoylanilide hydroxamic acid induces Akt-mediated phosphorylation of p300, which promotes acetylation and transcriptional activation of RelA/p65. J Biol Chem 2006;281:31359-31368 [FREE Full text] [doi: 10.1074/jbc.M604478200] [Medline: 16926151]
71. White NR, Mulligan P, King PJ, Sanderson IR. Sodium butyrate-mediated Sp3 acetylation represses human insulin-like growth factor binding protein-3 expression in intestinal epithelial cells. J Pediatr Gastroenterol Nutr 2006;42:134-141. [doi: 10.1097/01.mpg.0000189345.31010.89] [Medline: 16456404]
72. Stiehl DP, Fath DM, Liang D, Jiang Y, Sang N. Histone deacetylase inhibitors synergize p300 autoacetylation that regulates its transactivation activity and complex formation. Cancer Res 2007;67:2256-2264 [FREE Full text] [doi: 10.1158/0008-5472.CAN-06-3985] [Medline: 17332356]
73. Duranton B, Holl V, Schneider Y, Carnesecchi S, Gossé F, Raul F, et al. Polyamine metabolism in primary human colon adenocarcinoma cells (SW480) and their lymph node metastatic derivatives (SW620). Amino Acids 2003;24:63-72. [doi: 10.1007/s00726-002-0333-5] [Medline: 12624736]
74. Hinoi T, Akyol A, Theisen BK, Ferguson DO, Greenson JK, Williams BO, et al. Mouse model of colonic adenoma-carcinoma progression based on somatic Apc inactivation. Cancer Res 2007;67:9721-9730 [FREE Full text] [doi: 10.1158/0008-5472.CAN-07-2735] [Medline: 17942902]

Abbreviations

αMEM: alpha-minimal essential medium
APC: adenomatous polyposis coli
BCT: Beta-catenin-Tcf
CBP: CREB binding protein
CRC: colorectal cancer
CREB: cAMP response element binding
DN-Tcf4: dominant negative Tcf4
ESCs: embryonic stem cells
FAP: familial adenomatous polyposis
FDA: US Food and Drug Administration
GSK-3beta: glycogen synthase kinase-3 beta

HAT: histone acetyl transferase
HDACis: histone deacetylase inhibitors
HWA: high-fold induction of Wnt activity and apoptosis
LWA: low-fold induction of Wnt activity and apoptosis
MSI: microsatellite instability
MSS: microsatellite stable
NaB: sodium butyrate
PCAF: p300/CBP-associated factor
RT-PCR: reverse transcription polymerase chain reaction
SAHA: suberoylanilide hydroxamic acid
siRNA: small-interfering RNA
Tcf/Lef: transcription factor/lymphoid enhancer-binding factor
TSA: trichostatin A

Edited by G Eysenbach; submitted 01.01.16; peer-reviewed by G Piazza, V Ogryzko; comments to author 20.01.16; accepted 21.01.16; published 13.05.16.

Please cite as:
Bordonaro M, Lazarova DL
Determination of the Role of CBP- and p300-Mediated Wnt Signaling on Colonic Cells
JMIR Res Protoc 2016;5(2):e66
URL: http://www.researchprotocols.org/2016/2/e66/
doi:10.2196/resprot.5495
PMID:27177606

Protocol

Prediction of Preadolescent Overweight and Poor Cardiometabolic Outcome in Children up to 6 Years of Age: Research Protocol

Marlou LA de Kroon[1], MD PhD; Alet Wijga[2], PhD; Yvonne Vergouwe[1], PhD; Martijn W Heijmans[3], PhD; Vincent WV Jaddoe[4], MD PhD; Jos WR Twisk[3], PhD; Hein Raat[1], PhD

[1]Erasmus University Medical Center, Department of Public Health, Rotterdam, Netherlands

[2]National Institute of Public Health and the Environment, Prevention and Health Services, Bilthoven, Netherlands

[3]The EMGO Institute for Health and Care Research, VU University Medical Center, Amsterdam, Netherlands

[4]Erasmus University Medical Center, The Generation R Study Group, Rotterdam, Netherlands

Corresponding Author:
Marlou LA de Kroon, MD PhD
Erasmus University Medical Center
Department of Public Health
Wytemaweg 80
Rotterdam, 3015 CN
Netherlands
Phone: 31 107030163
Fax: 31 107030047
Email: m.dekroon@erasmusmc.nl

Abstract

Background: Dynamic risk estimations may enable targeting primary prevention of overweight and overweight-related adverse cardiometabolic outcome in later life, potentially serving as a valuable addition to universal primary prevention. This approach seems particularly promising in young children, as body mass index (BMI) changes at a young age are highly predictive of these outcomes, and parental lifestyle interventions at a young age are associated with improved long-term outcome.

Objective: This paper describes the design of our study, which aims to develop digitized tools that can be implemented in the Dutch Child Health Care (CHC) system or by pediatricians for children up to 6 years of age. These tools will enable (1) dynamically predicting the development of overweight, hypertension or prehypertension, low high-density lipoprotein cholesterol (HDL-C) values, and high total cholesterol to HDL-C ratio by early adolescence and (2) identifying children who are likely to have poor cardiometabolic outcome by the age of 5-6 years and by the age of 10 years.

Methods: Data will be obtained from the Generation R (n=7893) and Prevention and Incidence of Asthma and Mite Allergy (PIAMA; n=3963) cohorts, two Dutch prenatally recruited cohorts. We will select candidate predictors that can be assessed during the first visit and/or during subsequent visits to the CHC center or pediatrician, including sex; parental age, education level, and BMI; smoking exposure; ethnicity; birth weight; gestational age; breastfeeding versus formula feeding; and growth data through the age of 6 years. We will design dynamic prediction models that can be updated with new information obtained during subsequent CHC visits, allowing each measurement to be added to the model. Performance of the model will be assessed in terms of discrimination and calibration. Finally, the model will be validated both internally and externally using the combined cohort data and then converted into a computer-assisted tool called *Pro*COR (Prediction Of Child CardiOmetabolic Risk).

Results: This is an ongoing research project financed by the Dutch government. The first results are expected in 2016.

Conclusions: This study may contribute to the national implementation of digitized tools for assessing the risk of overweight and related cardiometabolic outcome in young children, enabling targeted primary prevention, ultimately yielding relevant health gains and improved resource allocation.

(JMIR Res Protoc 2016;5(2):e85) doi:10.2196/resprot.5158

KEYWORDS

overweight; (pre-)hypertension, High-Density Lipoproteins, forecasting, dynamic risk estimation; Child Health Services; pediatrics, prevention

Introduction

The prevalence of childhood overweight and obesity is increasing worldwide, including the Netherlands [1,2]. Hypertension or prehypertension and low high-density lipoprotein cholesterol (HDL-C) values are related adverse cardiometabolic risk factors that are also highly prevalent in children. The prevalence of hypertension is approximately 3.5%, 9%, and 19% among normal weight, overweight, and obese children, respectively [3-5]. Moreover, 6.2% of normal weight children have low HDL-C levels [6]. Overweight, hypertension, and low HDL-C level in childhood generally persist into adulthood, but are usually asymptomatic. Importantly, the presence of these risk factors in childhood can be detrimental, increasing the lifetime risk of developing severe health complications such as coronary heart disease and type 2 diabetes [7-14].

Once an individual becomes overweight, this condition is usually difficult to reverse, even among children, as changing one's lifestyle is difficult, and people often revert to their old habits resulting in even poorer health due to weight fluctuations [15]. Therefore, the European Society of Cardiology states that *primary* lifelong prevention of overweight and related poor cardiometabolic outcome deserves high priority beginning at birth [16]. Primary preventive interventions are particularly important in children aged less than 6 years, as changes in body mass index (BMI) below this age are more predictive of later overweight and poor cardiometabolic outcome than BMI changes after this age [17,18]. Moreover, parental lifestyle interventions when the child is young are associated with improved long-term outcome [19]. In addition, the American Academy of Pediatrics found that early intervention can yield better success in children with high cardiometabolic risk [20,21].

The EPODE (Ensemble Prévenons l'Obésité Des Enfants) program in northern France is a universal primary approach designed to prevent overweight in children by involving the family unit and society as a whole, for example, by changing the environment and influencing social norms. The merits of this approach have clearly been demonstrated [22]. Therefore, the program was successfully adopted, converted, and implemented in the Netherlands as the Youth on Healthy Weight (in Dutch: *Jongeren op Gezond Gewicht*, or JOGG) program [23]. Despite the introduction of this program, however, the prevalence of overweight remains relatively high, particularly among children from a low socioeconomic background [24]. Therefore, in addition to this universal approach, there is increasing interest in targeting primary prevention to children with the highest risk of becoming overweight and developing related poor cardiometabolic outcome. These risks may be estimated using prediction models or so-called "clinical prediction rules," which use the best possible combination of risk factors to calculate the likelihood of a specific outcome.

Prototypes of such prediction models have been developed in the Netherlands within two Dutch cohort studies - the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study and the Terneuzen cohort study - and in other countries, including India [25]. The two aforementioned Dutch prototypes are based on the presence of several predictors at birth, including paternal and maternal BMI [26], and on the trajectory of BMI standard deviation scores (BMI SDS) from 2 to 6 years of age [27]. Both Dutch prediction models have fair performance, indicating that targeted primary prevention of overweight and related poor cardiometabolic outcome is feasible with the help of evidence-based prediction models [26,27].

Here, we present the design of our study, which aims to develop dynamic prediction models to estimate the risk of young children (up to 6 years of age) developing overweight, hypertension or prehypertension, low HDL-C levels, and/or a high total cholesterol to HDL-C ratio by early adolescence. The resulting prediction models will be converted into easy-to-use tools called *Pro***C**OR (PRediction Of Child CardiOmetabolic Risk), which can be applied both in the Dutch preventive Child Health Care (CHC) system and by pediatricians.

Because the Dutch CHC reaches more than 95% of all children of all ethnicities through 16 regular visits from birth until the age of 6 years, this approach will enable targeted primary prevention for children in this age group. The *Pro***C**OR tools will provide risk estimations by taking into account the accumulation and changes in exposure to multiple risk factors throughout life, including familial risk factors [28], smoking exposure, physical inactivity, and changes in BMI [29].

Because we cannot exclude the possibility that children may already have an adverse cardiometabolic profile at this young age, thereby indicating the need for treatment, our secondary aim is to develop risk estimation models to assess the need for further diagnostics of poor cardiometabolic outcome at age 5-6 years and at age 10 years, two ages at which regular visits are made to the Dutch CHC centers.

The study design includes (1) data collection; (2) the development, external validation, and, if required, updating of dynamic prediction rules within two large Dutch cohort studies; and (3) an assessment of whether the resulting tools can be implemented in practice. Therefore, the study will also focus on risk communication, as this is an important aspect that can affect the likelihood of successful implementation.

The outcomes of the prediction rules will be assessed in early adolescence, because BMI SDS values measured between 10 and 18 years of age are highly correlated with adult BMI SDS values and body fat mass [17]. Moreover, as discussed above, hypertension/prehypertension, low HDL-C levels, and high total cholesterol levels often persist from childhood into adulthood, particularly from adolescence [10-12]. Our study proposal has been awarded a TOP Prevention Grant from ZonMw (title: "Targeted primary prevention of overweight and cardiometabolic risk using dynamic risk assessments from infancy onward in Child Health Care"; 200500006) , offering the opportunity to innovate in terms of both content and collaboration. See Multimedia Appendices 1, 2 and 3 for the reviewers' comments on the original version of the research proposal.

Methods

Stakeholder Group

For the study results to be useful, the developed tools must ultimately be implemented in practice. Therefore, a group of stakeholders has been established and comprises CHC physicians and nurses, pediatricians, general practitioners, dieticians, epidemiologists, programmers, scientists, and policy makers. In several phases of the study, parents will also be involved to ensure maximum communication regarding risk assessments with parents and maximum implementation of the *Pro*COR tools in the CHC.

Design and Setting

This study is embedded in the Generation R (n=7893) and PIAMA (n=3963) cohorts. These large, longitudinal Dutch cohorts provide independent datasets with many uniform variables regarding fetal life, pregnancy, birth, and early growth.

The Generation R study is a population-based, multiethnic cohort study composed of children born to 9778 mothers living from 2002 through 2006 in Rotterdam, the Netherlands [30]. Of all children who were eligible at the time of birth (n=7893), 61% participated in the follow-up study. In this cohort, children of diverse ethnic origins are well represented, including Caucasian (56%), Surinamese (9%), Turkish (7%), and Moroccan (6%) children. Three questionnaires were sent to the participating mothers during their pregnancy. Questionnaires were also sent when the child was 2, 6, 12, and 18 months of age and 2, 3, 4, 5, and 7 years of age. During pregnancy, the participants visited the research center in early, mid, and late pregnancy. From birth through 5 years of age, data regarding growth, development, and medical conditions among the Generation R participants were collected during their routine visits to the CHC centers. At the age of 5-6 years, all participating children and their parents were invited to visit the research center for a medical examination. The data collection of children 9-10 years of age was recently completed.

The PIAMA birth cohort is a population-based prospective cohort comprising 4146 women who were pregnant at baseline [31]. Because 183 women were lost to follow-up before any data regarding the child were collected, the study began with 3963 newborn children who were born in 1996-1997 in various regions of the Netherlands. Questionnaires were sent to the participants during pregnancy, when the child was 3 months of age, annually thereafter from 1 through 8 years of age, and at 11, 14, and 17 years of age. At 8, 12, and 16 years of age, subgroups of participating children were invited for a medical examination. The cohort consists primarily of Caucasians and includes children from both urban and rural areas [31].

Both the Generation R study and the PIAMA study were conducted in accordance with the guidelines established by the Declaration of Helsinki and were approved by the respective medical ethics committees (MECs). Written informed consent was obtained from all participating parents. The MEC for the Generation R study was the MEC of Erasmus Medical Center (MEC 217.595/2002/202). The MECs of the participating institutes for the PIAMA cohort were MEC Rotterdam (132.636/1994/39, 137.326/1994/130 and P04.0071C/MEC 2004-152), MEC Groningen (94/08/92, P04.0071C/ M 4.019912, June 28, 2004, and 12-019/K), and MEC-TNO Utrecht (95/50, February 28, 1996, CCMO Utrecht P000777C, 2000, P04.0071C, 2004, 07-337/K, May 20, 2008, and 12-019/K, May 25, 2012).

Overweight and Poor Cardiometabolic Outcome

The outcomes of the dynamic prediction models measured at age 10-15 years are as follows:

- overweight, defined using the International Obesity TaskForce (IOTF) cutoff values [32];
- abdominal overweight, defined based on the findings of the Fifth National Growth Study in the Netherlands, which will be available in the near future [2];
- hypertension or prehypertension, based on systolic and diastolic blood pressure and defined by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents [33]; and
- low HDL-C level or high total cholesterol to HDL-C ratio, in which low HDL-C is defined as <0.9 mmol/L and high total cholesterol is defined as >6.3 mmol/L. Because total cholesterol to HDL-C ratio in childhood quite accurately predicts subclinical adult atherosclerosis, including coronary heart disease, it will be useful to obtain both total cholesterol and HDL-C values [13,14].

The outcomes of the risk estimation models at ages 5-6 years and 10 years are hypertension or prehypertension and a low HDL-C level and high total cholesterol to HDL-C ratio, according to the aforementioned definitions.

Candidate Predictors

The candidate predictors that were used to develop the two Dutch prototypes [26,27] will also be used to develop the new prediction models. In addition, other candidate predictors will be selected from the literature, including relatively novel risk factors such as child's height and gross motor skills [34,35]. The stakeholder group will also provide advice—via discussion rounds—regarding the final selection of clinically relevant candidate predictors. The candidate predictors can be divided into the following two categories: (1) predictors that are currently routinely collected by the CHC and (2) predictors that may be routinely collected by the CHC in the near future.

The candidate predictors for the dynamic prediction models are as follows:

- Demographics and general characteristics

Sex and ethnicity of the child, urbanization grade, parity of the mother, and the education level and age of both parents.

- Prenatal/perinatal factors
- Child characteristics: birth weight, gestational age, head circumference, Apgar scores (at 1 and 5 minutes), meconium in the amniotic fluid, formula feeding immediately after birth.
- Parent characteristics: cesarean or vaginal delivery, use of vitamins and/or minerals by the mother, smoking (including second-hand smoke exposure), BMI of the mother before

and after pregnancy, BMI of the father, and blood pressure of both parents.

- At the age of 3 months

Body weight and body length, smoking exposure, and breast milk and/or formula.

- At the age of 1 year

Body weight and height, smoking exposure, breast milk and/or formula, data from the food frequency questionnaire (FFQ), dietary salt, and BMI of the mother.

- At the age of 5-6 years

Body height and weight, smoking exposure, FFQ, dietary salt, and physical activity.

- Between birth and the age of 6 years
- Periodic measurements of height and weight, collected by the CHC.
- Periodic measurements of gross motor skills, collected by the CHC.

For the prediction models to estimate the risk of poor cardiometabolic outcome, with the aim to assess the need for further diagnostics (blood pressure measurements and blood tests), the aforementioned candidate predictors will be used at the age of 5-6 years. At 10 years of age, the growth measurements and any other variables that can vary over time such as passive smoking between 6 and 10 years of age will be included as well.

Development of the Prediction Models

Dynamic risk prediction models will be developed in both cohorts. Missing values will be taken into account using advanced imputation techniques [36].

To design the dynamic risk prediction models, we will choose a statistical technique that can account for clustering of the data due to the collection of repeated measurements over time within children. This approach makes it possible to introduce repeatedly assessed risk factor information for children between birth and the age of 6 years into the model. For comparison purposes, the initial model (created at birth) will be updated with new information obtained at each visit, including the age of the child [37].

The statistical technique used in this study will be determined based on a comparison between existing simple and advanced statistical methods in order to handle repeatedly measured independent variables and a non-time-varying outcome variable in a prediction model, as described by Chen et al [38] and Tu et al [39]. We will compare the applicability of these methods for the development of prediction models for use by epidemiologists and clinical practitioners, and we will test the predictive quality of these models.

Backward selection will determine the final risk prediction models. The initial regression model, including all potential predictors, will be fitted in the dataset. To ensure sufficient power during the modeling process, we will optimize the balance between the number of variables and outcome “events” in the models [40].

Next, variables that have weak associations will be omitted from the model. We will use the Akaike information criterion (AIC) as a stopping rule to determine which variables should be removed from the model. For a single predictor, AIC equates to selection at P=.157 [40]. This relatively high P value results in the inclusion of weaker predictors in the model at the cost of potentially selecting a nuisance variable. Such a model usually performs well in new subjects [40].

Performance of the Prediction Models

The performance of the prediction models will be studied in terms of both discrimination and calibration. Discriminative ability expresses how well the model can distinguish between preadolescent children with the outcome and preadolescent children without the outcome. Discriminative ability will be assessed with the area under the receiver operating characteristic curve [41]. To reflect how well the predicted and observed values agree, the calibration slope will be estimated in a regression model using the linear predictor as the sole variable. The linear predictor is calculated by multiplying the model’s regression coefficients with the predictor values for each child and then summing these values (including the intercept). Under ideal conditions, this slope is 1, which means that the predicted and observed probabilities agree over the entire range of predictions [42]. Furthermore, the explained variability will be assessed, providing an overall measure of performance [43]. We will also decide on the cutoff values to be used in practice, taking into account sensitivity, specificity, and positive and negative predictive values for different categories of predicted probabilities.

Validation and Updating

We will use bootstrapping techniques to internally explore the need to correct for optimism in regression coefficients and performance measures of the dynamic risk prediction models. The dynamic risk prediction models, which will be developed in the oldest cohort (PIAMA), will be externally validated in the youngest cohort (Generation R). Validation is essential in order to determine the ability of a model to reliably predict the outcome in other populations and settings. If necessary, the models will be updated based on the validation results in both cohorts. Thus, we will study whether the models either remain stable or improve by removing or adding predictors that are available in the validation data. Finally, the model will be fit to the combined PIAMA and Generation R data, with the goal of achieving optimal precision of the estimated coefficients.

Development and Pilot Testing of the Prediction Tools

After the models have been developed, they will be converted into computer-assisted tools (the *Pro*COR tools). These tools will be easily applicable in CHC, providing for repeated risk assessments, thereby aiding CHC professionals in their decision to give advice, offer extra follow-up consults, and/or refer children and their parents for preventive intervention or further diagnostics. By consulting with experts in a Delphi study, we will determine which cutoff values will be used for these actions, with the aim of achieving the optimal balance between

sensitivity, specificity, positive and negative predictive values, and the perceived diagnostic and therapeutic burden for the parents and their children. Finally, the feasibility of the implementation will be assessed in a pilot study to be conducted in three CHC centers within the Netherlands. In this pilot, we will study the reach, frequency, and percentage of children with a predicted high risk of overweight and/or poor cardiometabolic outcome, acceptability of risk communication and risk assessments, satisfaction, the potential for stigmatization, protocol compliance, advice and referrals, maintenance, and time spent. For this purpose, questionnaires will be developed both for parents and for CHC professionals. Approval will be requested from the MEC before the start of the pilot study.

Results

This is an ongoing research project, and the first results are expected in 2016. The study began in December 2013 and is funded by the Health Research and Development Council of the Netherlands (ZonMw Grant no. 200500006).

Discussion

Our study will provide an individualized approach for primary prevention of overweight and poor cardiometabolic outcome by combining risk estimates with the existing general approach. This individualized, targeted approach will bridge an existing gap in the primary prevention of overweight and related adverse cardiometabolic outcomes. This is likely both important and relevant, given that the effects of secondary prevention of overweight and obesity have been disappointing—even among younger children—particularly over the long run [44]. Moreover, the success of universal primary prevention has been less pronounced in groups from lower socioeconomic backgrounds [22,24]. Importantly, the *Pro***C**OR tools will also enable the identification of children who already have high blood pressure and an abnormal lipid profile, thereby offering these children additional diagnostics and treatment options by their pediatrician; this is particularly relevant, as these adverse cardiometabolic outcomes tend to persist into adolescence and even adulthood, and are usually asymptomatic [10-12].

The success of the *Pro***C**OR tools when applied in early childhood will be reflected in the possibility to refer children with increased risk to a primary preventive program. Although such primary preventive interventions are relatively scarce, and although the majority of efforts have focused on developing secondary preventive interventions, several studies have demonstrated the potential benefit of applying primary preventive interventions in this extremely young age group [45-47]. In addition, primary preventive interventions aimed at the most susceptible individuals are often more effective than interventions that target the entire population [48]. Therefore, participating JOGG cities in the Netherlands have opted to implement interventions that are similar to Mini-MEND, a program aimed at children and families with increased risk at the age of 2-4 (or 5) years; this program is currently being evaluated in Australia and the United States [49-51]. Mini-MEND is the younger-age equivalent of MEND (Mind, Exercise, Nutrition, Do It!), a family-based intervention that was designed for older children and was found to be cost-effective in a randomized controlled trial [52].

The *Pro***C**OR tools can also be linked to Web-based content, including educational materials, advice, and/or referrals to evidence-based intervention programs, thus stimulating a healthy lifestyle and/or health care–seeking behavior. Finally, the risk estimates generated by the *Pro***C**OR tools can also be used to study the effectiveness of interventions, as a risk assessment of future overweight and related cardiometabolic outcomes is likely to be more predictive than the currently used definition of overweight using the cutoffs established by the IOTF [53].

Other methods have been developed to identify children who are at high risk for becoming overweight and/or developing adverse cardiometabolic outcome; such methods include the use of a single risk factor, combining risk factors, and developing risk models, risk algorithms, and risk charts. For example, in both Sweden and the United States, risk charts have been developed to predict adult overweight based on a single BMI measurement during childhood [54,55]. Another study performed in the United States reported crude risk estimates of being overweight by the age of 12 years based on one, two, or three BMI values measured between 2 and 4½ years of age [56]. In the United Kingdom, an overweight risk algorithm was developed to identify at-risk children at age 3 years based on predictors that were assessed in the first year of life [57]. To date, however, most risk models have not been dynamic and barely took into account individual BMI development. Moreover, extremely high-performance prediction models are required before acceptable large-scale implementation is possible in practice.

A strength of our study is that we will include additional candidate predictors, thereby helping optimize the performance—and hence the cost-effectiveness—of these models. Moreover, performing repeat risk assessments enables clinicians to both adapt to and individualize the strategies for each child based on new findings. This approach may contribute to the realization of more tailor-made primary prevention programs, with the aim of reversing the high risk of overweight and adverse cardiometabolic outcome in preadolescence.

One potential limitation of our study is that the outcomes of the prediction models were examined in early adolescence; moreover, the cohort data do not currently offer the opportunity to study these outcomes at adulthood. However, the timing of puberty is associated with adult obesity and poor cardiometabolic outcome [58]. On the other hand, the correlation between BMI SDS at age 10 years and BMI SDS at young adulthood is high (>0.7), suggesting that preventing high BMI SDS by the age of 10 years is relevant in terms of health outcome at adulthood [17]. In future studies, we will expand the prediction models with health outcomes at later ages.

By providing longitudinal guidance to children, the Dutch CHC is highly specialized with respect to the growth and development of children, suggesting that performing dynamic risk assessments is a very feasible approach in this setting. Therefore, the Dutch CHC is ideally positioned to help improve resource allocation by identifying high-risk children and excluding children with relatively low risk.

Finally, the tools that emerge from this study will be made available via the Internet, provided that stakeholders—including parents and/or their representatives—voice the need for Web-based access to the tools.

A potential disadvantage associated with applying the *Pro*COR tools is that it may cause harm due to stigmatization and parental and/or individual concerns. Therefore, we will investigate the effects of risk communication on possible unwanted side effects in the pilot study. At the same time, we must bear in mind that any potential harm due to the application of current cutoff points for overweight and/or obesity are currently unknown; moreover, the effectiveness of interventions that are based on risk assessments can only be studied after the prediction tools have been developed. Therefore, assuming that prediction tools with high sensitivity, specificity, and negative and positive predictive values can be developed, the next logical step would be to perform a randomized controlled trial designed to evaluate the effects of the prediction tools in combination with primary preventive intervention programs.

Acknowledgments

This study is funded by the Health Research and Development Council of the Netherlands (ZonMw Grant no. 200500006). The researchers are not dependent upon this funding source.

Authors' Contributions

MLAdK is the principal investigator (PI) and designed the study, contributed to all aspects of its development, and is the primary author of this manuscript. AW is a co-PI and contributed to the development of all aspects of the study; in addition AW is the PI of the PIAMA cohort study; YV is a co-PI at Erasmus Medical Center, and MWH is a co-PI at VU University Medical Center (both contributed to the development of the methodological section of the study); VJ helped write the manuscript and is the PI of the Generation R cohort study. JWRT and HR supervised the development of the study protocol. All authors have read, contributed to, and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Review 1.

[PDF File (Adobe PDF File), 89KB - resprot_v5i2e85_app1.pdf]

Multimedia Appendix 2

Review 2.

[PDF File (Adobe PDF File), 82KB - resprot_v5i2e85_app2.pdf]

Multimedia Appendix 3

Review 3.

[PDF File (Adobe PDF File), 83KB - resprot_v5i2e85_app3.pdf]

References

1. Wang Y, Lobstein T. Worldwide trends in childhood overweight and obesity. Int J Pediatr Obes 2006;1(1):11-25. [Medline: 17902211]
2. Schönbeck Y, Talma H, van DP, Bakker B, Buitendijk SE, Hirasing RA, et al. Increase in prevalence of overweight in Dutch children and adolescents: a comparison of nationwide growth studies in 1980, 1997 and 2009. PLoS One 2011;6(11):e27608 [FREE Full text] [doi: 10.1371/journal.pone.0027608] [Medline: 22110687]
3. Sorof JM, Lai D, Turner J, Poffenbarger T, Portman RJ. Overweight, ethnicity, and the prevalence of hypertension in school-aged children. Pediatrics 2004 Mar;113(3 Pt 1):475-482. [Medline: 14993537]
4. Salvadori M, Sontrop JM, Garg AX, Truong J, Suri RS, Mahmud FH, et al. Elevated blood pressure in relation to overweight and obesity among children in a rural Canadian community. Pediatrics 2008 Oct;122(4):e821-e827. [doi: 10.1542/peds.2008-0951] [Medline: 18829779]
5. Maldonado J, Pereira T, Fernandes R, Carvalho M. Blood pressure distribution of a sample of healthy Portuguese children and adolescents: the AVELEIRA registry. Rev Port Cardiol 2009 Nov;28(11):1233-1244 [FREE Full text] [Medline: 20222347]

6. Guerrero-Romero F, Rodríguez-Morán M. Prevalence of dyslipidemia in non-obese prepubertal children and its association with family history of diabetes, high blood pressure, and obesity. Arch Med Res 2006 Nov;37(8):1015-1021. [doi: 10.1016/j.arcmed.2006.06.003] [Medline: 17045120]
7. Smith SC. Multiple risk factors for cardiovascular disease and diabetes mellitus. Am J Med 2007 Mar;120(3 Suppl 1):S3-S11. [doi: 10.1016/j.amjmed.2007.01.002] [Medline: 17320520]
8. Expert Panel on Integrated Guidelines for Cardiovascular HealthRisk Reduction in ChildrenAdolescents, National Heart, Lung,Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics 2011 Dec;128 Suppl 5:S213-S256 [FREE Full text] [doi: 10.1542/peds.2009-2107C] [Medline: 22084329]
9. Singh AS, Mulder C, Twisk J W R, Mechelen van W, Chinapaw M J M. Tracking of childhood overweight into adulthood: a systematic review of the literature. Obes Rev 2008 Sep;9(5):474-488. [doi: 10.1111/j.1467-789X.2008.00475.x] [Medline: 18331423]
10. Porkka KV, Viikari JS, Akerblom HK. Tracking of serum HDL-cholesterol and other lipids in children and adolescents: the Cardiovascular Risk in Young Finns Study. Prev Med 1991 Nov;20(6):713-724. [Medline: 1766943]
11. Franks PW, Hanson RL, Knowler WC, Moffett C, Enos G, Infante AM, et al. Childhood predictors of young-onset type 2 diabetes. Diabetes 2007 Dec;56(12):2964-2972 [FREE Full text] [doi: 10.2337/db06-1639] [Medline: 17720898]
12. Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. Circulation 2008 Jun 24;117(25):3171-3180 [FREE Full text] [doi: 10.1161/CIRCULATIONAHA.107.730366] [Medline: 18559702]
13. Frontini MG, Srinivasan SR, Xu J, Tang R, Bond MG, Berenson GS. Usefulness of childhood non-high density lipoprotein cholesterol levels versus other lipoprotein measures in predicting adult subclinical atherosclerosis: the Bogalusa Heart Study. Pediatrics 2008 May;121(5):924-929. [doi: 10.1542/peds.2007-1472] [Medline: 18450895]
14. Schmidt MD, Dwyer T, Magnussen CG, Venn AJ. Predictive associations between alternative measures of childhood adiposity and adult cardio-metabolic health. Int J Obes (Lond) 2011 Jan;35(1):38-45. [doi: 10.1038/ijo.2010.205] [Medline: 20877285]
15. Montani J, Viecelli AK, Prévot A, Dulloo AG. Weight cycling during growth and beyond as a risk factor for later cardiovascular diseases: the 'repeated overshoot' theory. Int J Obes (Lond) 2006 Dec;30 Suppl 4:S58-S66. [doi: 10.1038/sj.ijo.0803520] [Medline: 17133237]
16. Perk J, De BG, Gohlke H, Graham I, Reiner Z, Verschuren M, Scholte op Reimer Wilma J M, European Association for Cardiovascular Prevention & Rehabilitation (EACPR), ESC Committee for Practice Guidelines (CPG). European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J 2012 Jul;33(13):1635-1701 [FREE Full text] [doi: 10.1093/eurheartj/ehs092] [Medline: 22555213]
17. de Kroon Marlou L A, Renders CM, van Wouwe Jacobus P, van Buuren S, Hirasing RA. The Terneuzen Birth Cohort: BMI change between 2 and 6 years is most predictive of adult cardiometabolic risk. PLoS One 2010;5(11):e13966 [FREE Full text] [doi: 10.1371/journal.pone.0013966] [Medline: 21103047]
18. Stocks T, Renders CM, Bulk-Bunschoten A M W, Hirasing RA, van Buuren S, Seidell JC. Body size and growth in 0- to 4-year-old children and the relation to body size in primary school age. Obes Rev 2011 Aug;12(8):637-652. [doi: 10.1111/j.1467-789X.2011.00869.x] [Medline: 21426479]
19. Reinehr T, Kleber M, Lass N, Toschke AM. Body mass index patterns over 5 y in obese children motivated to participate in a 1-y lifestyle intervention: age as a predictor of long-term success. Am J Clin Nutr 2010 May;91(5):1165-1171 [FREE Full text] [doi: 10.3945/ajcn.2009.28705] [Medline: 20219965]
20. Haemer M, Cluett S, Hassink SG, Liu L, Mangarelli C, Peterson T, et al. Building capacity for childhood obesity prevention and treatment in the medical community: call to action. Pediatrics 2011 Sep;128 Suppl 2:S71-S77 [FREE Full text] [doi: 10.1542/peds.2011-0480G] [Medline: 21885648]
21. Brunzell JD, Davidson M, Furberg CD, Goldberg RB, Howard BV, Stein JH, et al. Lipoprotein management in patients with cardiometabolic risk: consensus conference report from the American Diabetes Association and the American College of Cardiology Foundation. J Am Coll Cardiol 2008 Apr 15;51(15):1512-1524 [FREE Full text] [doi: 10.1016/j.jacc.2008.02.034] [Medline: 18402913]
22. Borys J, Le Bodo Y, Jebb SA, Seidell JC, Summerbell C, Richard D, Visscher T L S, et al. EPODE approach for childhood obesity prevention: methods, progress and international development. Obes Rev 2012 Apr;13(4):299-315 [FREE Full text] [doi: 10.1111/j.1467-789X.2011.00950.x] [Medline: 22106871]
23. Preventing Childhood Obesity. URL: http://www.epode-european-network.com/en/een-news/227.html [accessed 2016-04-17] [WebCite Cache ID 6gpmzG5S3]
24. Romon M, Lommez A, Tafflet M, Basdevant A, Oppert JM, Bresson JL, et al. Downward trends in the prevalence of childhood overweight in the setting of 12-year school- and community-based programmes. Public Health Nutr 2009 Oct;12(10):1735-1742. [doi: 10.1017/S1368980008004278] [Medline: 19102807]

25. Sachdev H P S, Osmond C, Fall C H D, Lakshmy R, Ramji S, Dey Biswas S K, Barker D J P, et al. Predicting adult metabolic syndrome from childhood body mass index: follow-up of the New Delhi birth cohort. Arch Dis Child 2009 Oct;94(10):768-774 [FREE Full text] [doi: 10.1136/adc.2008.140905] [Medline: 19015213]
26. Steur M, Smit HA, Schipper C Maarten A, Scholtens S, Kerkhof M, de Jongste Johan C, et al. Predicting the risk of newborn children to become overweight later in childhood: the PIAMA birth cohort study. Int J Pediatr Obes 2011 Jun;6(2-2):e170-e178. [doi: 10.3109/17477166.2010.519389] [Medline: 20883125]
27. de Kroon Marlou L A, Renders CM, van Wouwe Jacobus P, Hirasing RA, van Buuren S. Identifying young children without overweight at high risk for adult overweight: the Terneuzen Birth Cohort. Int J Pediatr Obes 2011 Jun;6(2-2):e187-e195. [doi: 10.3109/17477166.2010.526220] [Medline: 21091137]
28. McMillen IC, Rattanatray L, Duffield JA, Morrison JL, MacLaughlin SM, Gentili S, et al. The early origins of later obesity: pathways and mechanisms. Adv Exp Med Biol 2009;646:71-81. [doi: 10.1007/978-1-4020-9173-5_8] [Medline: 19536665]
29. Mahoney LT, Burns TL, Stanford W, Thompson BH, Witt JD, Rost CA, et al. Coronary risk factors measured in childhood and young adult life are associated with coronary artery calcification in young adults: the Muscatine Study. J Am Coll Cardiol 1996 Feb;27(2):277-284 [FREE Full text] [Medline: 8557894]
30. Jaddoe Vincent W V, van Duijn Cornelia M, van der Heijden Albert J, Mackenbach JP, Moll HA, Steegers Eric A P, et al. The Generation R Study: design and cohort update until the age of 4 years. Eur J Epidemiol 2008;23(12):801-811. [doi: 10.1007/s10654-008-9309-4] [Medline: 19101808]
31. Brunekreef B, Smit J, de Jongste J, Neijens H, Gerritsen J, Postma D, et al. The prevention and incidence of asthma and mite allergy (PIAMA) birth cohort study: design and first results. Pediatr Allergy Immunol 2002;13 Suppl 15:55-60. [Medline: 12688626]
32. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 2000 May 6;320(7244):1240-1243 [FREE Full text] [Medline: 10797032]
33. National High Blood Pressure Education Program Working Group on High Blood Pressure in ChildrenAdolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 2004 Aug;114(2 Suppl 4th Report):555-576. [Medline: 15286277]
34. van Dommelen P, de Kroon MLA, Cameron N, Schönbeck Y, van Buuren S. The impact of height during childhood on the national prevalence rates of overweight. PLoS One 2014;9(1):e85769 [FREE Full text] [doi: 10.1371/journal.pone.0085769] [Medline: 24465694]
35. D'Hondt E, Deforche B, Gentier I, De Bourdeaudhuij I, Vaeyens R, Philippaerts R, et al. A longitudinal analysis of gross motor coordination in overweight and obese children versus normal-weight peers. Int J Obes (Lond) 2013 Jan;37(1):61-67. [doi: 10.1038/ijo.2012.55] [Medline: 22508339]
36. van Buuren S. Broken stick model. In: Keiding N, Morgan BTJ, Wikle CK, van der Heijden P , editor. Flexible Imputation of Missing Data (Chapman & Hall/CRC Interdisciplinary Statistics). Boca Raton: Taylor & Francis Group; 2012.
37. Hansen BE, Buster Erik H C J, Steyerberg EW, Lesaffre E, Janssen Harry L A. Prediction of the response to peg-interferon-alfa in patients with HBeAg positive chronic hepatitis B using decline of HBV DNA during treatment. J Med Virol 2010 Jul;82(7):1135-1142. [doi: 10.1002/jmv.21778] [Medline: 20513075]
38. Chen Y, Ferguson KK, Meeker JD, McElrath TF, Mukherjee B. Statistical methods for modeling repeated measures of maternal environmental exposure biomarkers during pregnancy in association with preterm birth. Environ Health 2015;14:9 [FREE Full text] [doi: 10.1186/1476-069X-14-9] [Medline: 25619201]
39. Tu Y, Tilling K, Sterne Jonathan A C, Gilthorpe MS. A critical evaluation of statistical approaches to examining the role of growth trajectories in the developmental origins of health and disease. Int J Epidemiol 2013 Oct;42(5):1327-1339 [FREE Full text] [doi: 10.1093/ije/dyt157] [Medline: 24038715]
40. Steyerberg EW: Selection of main effects. Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating. New York: Springer; 2009:978-990.
41. Harrell FE, Califf RM, Pryor DB, Lee KL, Rosati RA. Evaluating the yield of medical tests. JAMA 1982 May 14;247(18):2543-2546. [Medline: 7069920]
42. Cox DR. Two Further Applications of a Model for Binary Regression. Biometrika 1958 Dec;45(3/4):562 [FREE Full text] [doi: 10.2307/2333203]
43. Nagelkerke NJD. A note on the general definition of the coefficient of determination. Biometrika 1991;78:691-692.
44. Bocca G, Corpeleijn E, van den Heuvel ER, Stolk RP, Sauer PJ. Three-year follow-up of 3-year-old to 5-year-old children after participation in a multidisciplinary or a usual-care obesity treatment program. Clin Nutr 2014;33(6):1095-1100. [Medline: 24377431]
45. Barlow J, Whitlock S, Hanson S, Davis H, Hunt C, Kirkpatrick S, et al. Preventing obesity at weaning: parental views about the EMPOWER programme. Child Care Health Dev 2010 Nov;36(6):843-849. [doi: 10.1111/j.1365-2214.2010.01107.x] [Medline: 20645998]
46. Polacsek M, Orr J, Letourneau L, Rogers V, Holmberg R, O'Rourke K, et al. Impact of a primary care intervention on physician practice and patient and family behavior: keep ME Healthy---the Maine Youth Overweight Collaborative. Pediatrics 2009 Jun;123 Suppl 5:S258-S266. [doi: 10.1542/peds.2008-2780C] [Medline: 19470601]

47. Wen LM, Baur LA, Simpson JM, Rissel C, Wardle K, Flood VM. Effectiveness of home based early intervention on children's BMI at age 2: randomised controlled trial. BMJ 2012;344:e3732 [FREE Full text] [Medline: 22735103]
48. Olsen NJ, Mortensen EL, Heitmann BL. Predisposition to Obesity: Should We Target Those Most Susceptible? Curr Obes Rep 2012 Mar;1(1):35-41 [FREE Full text] [doi: 10.1007/s13679-011-0004-5] [Medline: 22448345]
49. Sacher P, Wolman J, Chadwick P, Swain C. Mini-MEND: MEND's early years healthy lifestyle programme for 2–4 year olds and their families. Nutrition Bulletin 2008 Nov;33(4):364-367. [Medline: 18297835]
50. Hardy S, Lowe A, Unadkat A, Thurtle V. Mini-MEND: an obesity prevention initiative in a children's centre. Community Pract 2010 Jun;83(6):26-29. [Medline: 20586375]
51. Wolman J, Skelly E, Kolotourou M, Lawson M. Sacher P: Tackling toddler obesity through a pilot community-based family intervention. Community Pract 2008 2008;81(1):28. [Medline: 20586375]
52. Sacher PM, Kolotourou M, Chadwick PM, Cole TJ, Lawson MS, Lucas A, et al. Randomized controlled trial of the MEND program: a family-based community intervention for childhood obesity. Obesity (Silver Spring) 2010 Feb;18 Suppl 1:S62-S68 [FREE Full text] [doi: 10.1038/oby.2009.433] [Medline: 20107463]
53. Cole TJ, Lobstein T. Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. Pediatr Obes 2012 Aug;7(4):284-294. [doi: 10.1111/j.2047-6310.2012.00064.x] [Medline: 22715120]
54. He Q, Karlberg J. Prediction of adult overweight during the pediatric years. Pediatr Res 1999 Dec;46(6):697-703. [Medline: 10590026]
55. Guo SS, Wu W, Chumlea WC, Roche AF. Predicting overweight and obesity in adulthood from body mass index values in childhood and adolescence. Am J Clin Nutr 2002 Sep;76(3):653-658 [FREE Full text] [Medline: 12198014]
56. Nader PR, O'Brien M, Houts R, Bradley R, Belsky J, Crosnoe R, National Institute of Child HealthHuman Development Early Child Care Research Network. Identifying risk for obesity in early childhood. Pediatrics 2006 Sep;118(3):e594-e601. [doi: 10.1542/peds.2005-2801] [Medline: 16950951]
57. Weng SF, Redsell SA, Nathan D, Swift JA, Yang M, Glazebrook C. Estimating overweight risk in childhood from predictors during infancy. Pediatrics 2013 Aug;132(2):e414-e421 [FREE Full text] [doi: 10.1542/peds.2012-3858] [Medline: 23858427]
58. Sandhu J, Ben-Shlomo Y, Cole TJ, Holly J, Davey Smith G. The impact of childhood body mass index on timing of puberty, adult stature and obesity: a follow-up study based on adolescent anthropometry recorded at Christ's Hospital (1936-1964). Int J Obes (Lond) 2006 Jan;30(1):14-22. [doi: 10.1038/sj.ijo.0803156] [Medline: 16344844]

Abbreviations

AIC: Akaike information criterion
BMI: body mass index
BMI SDS: BMI standard deviation scores
CHC: Child Health Care
FFQ: food frequency questionnaire
HDL-C: high-density lipoprotein cholesterol
IOTF: International Obesity TaskForce
JOGG: Jongeren op Gezond Gewicht (in English: Youth on Healthy Weight)
MEC: medical ethics committee
MEND: Mind, Exercise, Nutrition, Do It!
PIAMA: Prevention and Incidence of Asthma and Mite Allergy
ProCOR: PRediction Of Child CardiOmetabolic Risk

Edited by G Eysenbach; submitted 05.10.15; peer-reviewed by C Hawke; comments to author 19.12.15; revised version received 22.01.16; accepted 22.01.16; published 23.06.16.

Please cite as:
de Kroon MLA, Wijga A, Vergouwe Y, Heijmans MW, Jaddoe VWV, Twisk JWR, Raat H
Prediction of Preadolescent Overweight and Poor Cardiometabolic Outcome in Children up to 6 Years of Age: Research Protocol
JMIR Res Protoc 2016;5(2):e85
URL: http://www.researchprotocols.org/2016/2/e85/
doi:10.2196/resprot.5158
PMID:27339755

Proposal

Supporting Goal-Oriented Primary Health Care for Seniors with Complex Care Needs Using Mobile Technology: Evaluation and Implementation of the Health System Performance Research Network, Bridgepoint Electronic Patient Reported Outcome Tool

Carolyn Steele Gray[1,2], MA, PhD; Walter P Wodchis[2,3,4], MAE, MA, PhD; Ross Upshur[1,5], MA, MSc, MD, CCFP, FRCPC; Cheryl Cott[6], DipPT, BPT, MSc, PhD; Brian McKinstry[7], MD, FRCPE, FRCGP; Stewart Mercer[8], MBChB, BSc, MSc, PhD, MRCGP, FRCGP; Ted E Palen[9], PhD, MD; Tim Ramsay[10,11], PhD; Kednapa Thavorn[4,10,11], PhD; Project Collaborators And Technology Partner, QoC Health Inc[1]

[1]Bridgepoint Collaboratory, Lunenfeld-Tanenbaum Research Institute, Sinai Health System, Toronto, ON, Canada

[2]Institute of Health Policy, Management and Evaluation,, Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada

[3]Toronto Rehabilitation Institute, Toronto, ON, Canada

[4]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada

[5]Department of Family and Community Medicine, Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada

[6]Department of Physical Therapy, University of Toronto, Toronto, ON, Canada

[7]The Usher Institute of Population Health Sciences and Informatics, Centre for Population Health Sciences, University of Edinburgh, Edinburgh, United Kingdom

[8]School of Medicine, University of Glasgow, Glasgow, United Kingdom

[9]Institute for Health Research, Colorado Permanente Medical Group and Kaiser Permanente Institute for Health, Denver, CO, United States

[10]Ottawa Methods Centre, Ottawa Hospital Research Institute, The Ottawa Hospital, Ottawa, ON, Canada

[11]School of Epidemiology, Public Health and Preventative Medicine, University of Ottawa, Ottawa, ON, Canada

Corresponding Author:
Carolyn Steele Gray, MA, PhD
Bridgepoint Collaboratory
Lunenfeld-Tanenbaum Research Institute
Sinai Health System
1 Bridgepoint Drive
AM.37
Toronto, ON M4M 2B5
Canada
Phone: 1 416 461 8252 ext 2908
Fax: 1 416 461 0656
Email: carolyn.steelegray@sinaihealthsystem.ca

Related Article:

This is a corrected version. See correction statement: http://www.researchprotocols.org/2016/4/e194/

Abstract

Background: Older adults experiencing multiple chronic illnesses are at high risk of hospitalization and health decline if they are unable to manage the significant challenges posed by their health conditions. Goal-oriented care approaches can provide better care for these complex patients, but clinicians find the process of ascertaining goals “too complex and too-time consuming,” and goals are often not agreed upon between complex patients and their providers. The electronic patient reported outcomes (ePRO) mobile app and portal offers an innovative approach to creating and monitoring goal-oriented patient-care plans to improve patient self-management and shared decision-making between patients and health care providers. The ePRO tool also supports proactive patient monitoring by the patient, caregiver(s), and health care provider. It was developed with and for older adults with complex care needs as a means to improve their quality of life.

Objective: Our proposed project will evaluate the use, effectiveness, and value for money of the ePRO tool in a 12-month multicenter, randomized controlled trial in Ontario; targeting individuals 65 or over with two or more chronic conditions that require frequent health care visits to manage their health conditions.

Methods: Intervention groups using the ePRO tool will be compared with control groups on measures of quality of life, patient experience, and cost-effectiveness. We will also evaluate the implementation of the tool.

Results: The proposed project presented in this paper will be funded through the Canadian Institute for Health Research (CIHR) eHealth Innovation Partnerships Program (eHIPP) program (CIHR–143559). The expected completion date of the study is November, 2019.

Conclusions: We anticipate our program of work will support improved quality of life and patient self-management, improved patient-centered primary care delivery, and will encourage the adoption of goal-oriented care approaches across primary health care systems. We have partnered with family health teams and quality improvement organizations in Ontario to ensure that our research is practical and that findings are shared widely. We will work with our established international network to develop an implementation framework to support continued adaptation and adoption across Canada and internationally.

(JMIR Res Protoc 2016;5(2):e126) doi:10.2196/resprot.5756

KEYWORDS

eHealth/mHealth solutions; complex care needs; seniors; patient-centered care; goal-oriented care; primary health care; implementation; pragmatic trial; health outcomes; cost-effectiveness analysis

Introduction

Background: Understanding Seniors With Complex Care Needs and Their Challenges

Canadian and international health care systems require solutions on how to address the needs of a relatively small population that take up a large portion of health care resources. In Ontario, 10% of the population accounts for 79% of total system costs [1], with similar trends found in other parts of Canada [2] and internationally [3-5]. Most high-cost users are seniors, older adults, with multiple chronic conditions and complex care needs who are living in the community [6]. Beyond the cost issues, older adults experiencing multimorbidity are at higher risk of poor health outcomes and experience lower quality of life as compared with individuals experiencing a single illness only [7,8].

Understanding complex older adults, however, goes beyond how much they cost the health system or the number of chronic conditions they experience. It is important to understand the challenges faced by older adults from a bio-psycho-social perspective, which acknowledges broader social, environmental, and contextual issues that impact on the health care needs of these patients as well as their ability to manage [9]. A systematic review of the literature revealed that over half of the elderly population experiences multimorbidity, with a higher prevalence among those in the lower socioeconomic strata [7]. These social and contextual factors increase older adults' vulnerability, which has been found to be associated with low quality of care delivery [10].

It is difficult for providers to support older adults with complex care needs because they have few (if any) tools, like clinical practice guidelines, to guide decision making [11]. This is problematic because providers are trying to help patients manage multiple conditions, many with discordant, competing symptoms and treatments that potentially run counter to each other [12]. It has been argued that these patients greatly benefit from patient-centered care approaches, which allow for individualized and holistic methods to address their highly variable needs [13,14]. At the provider level, patient-centered care approaches require a strong patient-provider relationship built on communication, respect, shared responsibility, and support for the patient as a whole person [13,15-17]. At the system level, patient-centered care can address poor care coordination issues experienced by complex patients [18].

Patient-centered care approaches are viewed as crucial to address the needs of this patient population [19,20], and can be supported by adopting goal-oriented care approaches [21]. Goal setting is also a key feature of coordinated care plans intended to support coordination and continuity of care for older adults, and others, with complex needs [22]. Goal-oriented approaches can help patients to prioritize their competing issues to help improve quality of life, while supporting primary health care providers and clinicians who have little evidence to draw on to support their older adult patients with complex care needs. However, clinicians find the process of ascertaining goals "too complex and too-time consuming" [23]. Additionally, goals are often not agreed upon between complex patients and their providers [24]. It is not surprising then that complex patients report not feeling engaged with their primary care provider in the management of their health conditions [25].

Primary health care providers require tools to overcome barriers to adopting goal-oriented care approaches to address the needs of a growing population of older adults with complex needs. Since April 2013, we have undergone a multiphased, user-centered design evaluation approach to develop the electronic patient reported outcomes (ePRO) mobile app and portal; a tool designed to meet the needs of older adults with complex care needs and their primary care providers. This study will evaluate the use, effectiveness, and monetary value of the ePRO tool through a cluster randomized controlled trial with an embedded case study of implementation and will answer the following primary research questions: (1) Does ePRO improve quality of life, care experience, and self-management in older adults with complex needs? (2) Is ePRO cost-effective for older

adults with complex needs from the perspective of the health care system? (3) What are the most important implementation factors to effectively scale and spread ePRO in primary health care settings?

The ePRO tool's focus on improving goal-oriented care for seniors experiencing complex chronic disease and disability living in the community marks a new contribution to the mHealth space. The proposed project will additionally provide instructive advances in rigorous evidence from a trial.

The Electronic Patient Reported Outcomes Tool: An eHealth Solution for Community-Dwelling Complex Seniors

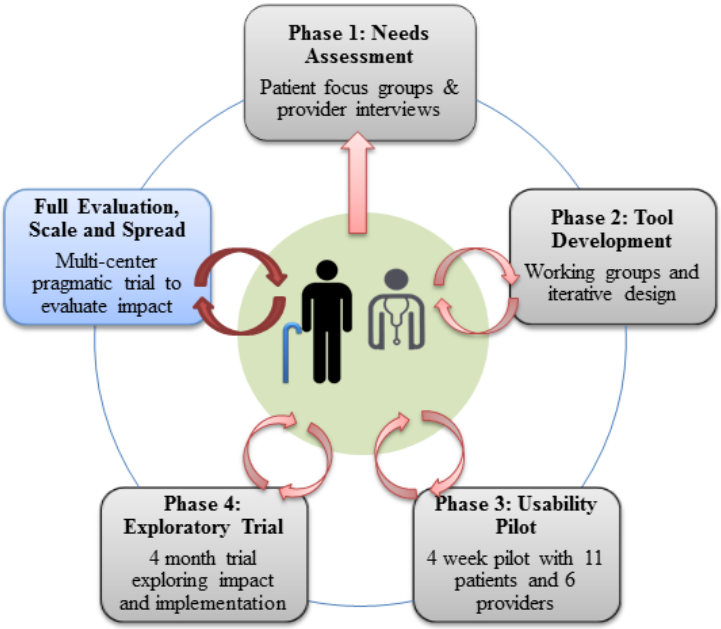
Electronic Patient Reported Outcomes Tool Development

To develop and test the ePRO tool, we have drawn on the principles of design research, which suggest that the development and adoption of technologies into real world environments requires an iterative approach where designs are progressively adjusted and refined based on emerging design principles, evolving needs, and end-user feedback [26,27]. User-centered technology development emphasizes the need to incorporate user feedback as part of the design, testing, and implementation process [28], while design research highlights the need to use rigorous research methods and evaluations in order to support capturing and incorporating user feedback [29]. We then iteratively engaged in end-user codevelopment of the tool through a mutliphased approach.

At the outset of the development process we broadly intended to develop a solution to support community-dwelling patients, including older adults, with complex needs and their providers in primary health care settings. Figure 1 provides a visual depiction of our iterative design and development method, which included patient, caregiver, and primary health care provider input at each phase. The proposed eHealth Innovation Partnerships Program (eHIPP) grant will support the final phase of this work, the full evaluation, scale, and spread phase depicted in Figure 1 (Adapted from [30]).

In Phase 1, we conducted a user-needs assessment using qualitative interpretive descriptive data collection and analysis methods. Focus groups were conducted with patients and caregivers with findings being published last year [31]. In Phase 2, we conducted a tool development phase in which we used findings from Phase 1 to develop a prototype, which was tested with three working groups: (1) patient and caregiver working group, (2) primary health care provider working group, and (3) expert and research team working group. The working groups assessed the feasibility and usability of the first prototype, and another round of redesign was conducted based on user and expert feedback [30]. We next conducted a usability pilot in Phase 3, with 11 patients and six primary health care providers from one Family Health Team in Toronto, Canada. The aim of the usability pilot was to determine the utility, functionality, and usability of the ePRO tool. Findings from this study informed further modification to the tool to improve usability [32]. The exploratory trial, Phase 4, began September 2015 and will be completed by August 2016.

Figure 1. Development approach.



The Electronic Patient Reported Outcomes Tool

The ePRO tool includes two features: My Goals and Outcome Measures. See Multimedia Appendix 1 for wire frames of the portal and mobile system.

Feature #1: My Goals

The My Goals feature allows patients and providers to collaboratively create goal-oriented patient care plans, and helps patients to track outcomes related to their goals using a mobile device. To set up goals patients (and caregivers if the patient chooses) sit down with their primary care providers during a

visit in the physician's office or in the patient's home in the case of home visiting patients, and use a portal to create goals. Once a goal is added to the patients' care plan, their mobile app will prompt them to report on outcomes related to that goal using the mobile device. Caregivers can enter data into the mobile device or on the portal on behalf of the patient if the patient requires assistance. Patients would either share their login information or caregivers can be given their own login to provide them with access. Specified-measureable-attainable-realistic-time specific (SMART) goal principles are used to guide goal set-up as this is an approach often used by primary care providers. We additionally incorporate goal-attainment scaling to create consistent goal attainment measures [33], which can then be used as a standardized patient outcome measure for patients with complex needs [21].

To create a SMART goal, the patient (with or without a caregiver) and primary care provider collaboratively specify the goal itself (eg, walk 20 minutes each day), the importance of that goal to the patient, perceived achievability of the goal, the timing of the goal (eg, achieved in 2 weeks), and any supports and resources available and/or required (eg, referrals needed or community services available like walking programs). Once the properties of the SMART goal are established, the patient and provider set up the monitoring protocol to allow the patient to report on their progress. Monitoring questions can be written by the patient and provider using question templates (ie, Likert scales, 10-point scales, visual analogue scales, open comment boxes, photos), or can be selected from the question bank created by the provider or any other provider in a single practice using the system.

In addition to the customizable monitoring questions, there are two established monitoring questions asked of each goal. The first asks patients to comment on how they are doing generally in relation to the goal to provide contextual information on their progress (patients or caregivers type into an open text box). The second is a modified standard goal attainment scale [33] to assess goal progress depicted in Table 1.

Table 1. Goal attainment scale monitoring.

Score	Goal achievement
+2	Much better than expected
+1	Better than expected
0	Goal (expected goal specified by patient and provider)
−1	Less than expected
−2	Much less than expected

Goal set-up can be completed in a 30-minute care planning appointment, which includes the time required to engage in a collaborative discussion between the provider and the patient to identify appropriate goals. Typically providers and patients will only focus on one or two goals at a time, which is more manageable for the patient.

Feature #2: Outcome Measures

The Outcome Measures feature is intended to help patients, their caregivers, and primary care providers to monitor patients' symptoms and outcomes that were identified as important by patients with complex care needs in the first phase of our tool development [31]. Similar to the My Goals feature, once symptom monitoring is added to the patient's Outcome Measures their mobile app will prompt them to report on symptoms on the mobile device.

The health status scales included were chosen in earlier stages of development of the tool based on: (1) patient, caregiver, and provider identification of the symptoms and outcomes most important for patients with complex needs to measure, (2) psychometric properties of the tools, and (3) relevance and demonstrated use of the tools in primary health care delivery. We included the patient reported outcome measurement information system (PROMIS) global health scale (GHS), pain interference, and health assessment questionnaires (HAQ) all of which are valid and reliable for patients with chronic illness [34-36]. The PROMIS and HAQ instruments have undergone rigorous validity and reliability testing, which include psychometric assessments as well as qualitative, quantitative, and mixed-methods research [36]. A systematic review of patient-reported outcome measurement tools funded by the Canadian Institutes of Health Research identified the PROMIS tools, in particular the GHS, to be among the more effective tools used to measure patient health outcomes [37]. The patient health questionnaire (PHQ9) and the generalized anxiety disorder (GAD7) tool were included as these are often used in primary health care practice, with demonstrated reliability and validity [38,39]. We also included monitoring protocols identified as important to these patients including: weight, blood pressure, heart rate, blood glucose, mood and emotion, sleep patterns, diet, and physical activity and walking logs. These protocols had been previously developed and tested with seniors by our technology partner.

Patients, their caregivers, and providers can track patient progress on goals and view their symptoms, vitals, and outcome data on the portal. Monitoring frequency is up to the patient and provider and can occur daily, weekly, or monthly depending on the goal or symptom being monitored. Patients are also able to track their progress on their mobile device and can then make adjustments to their routines if declines or low health status are indicated. Patients also have the option to monitor and track progress using the portal only rather than mobile device if they prefer to work on the computer. Providers can use monitoring data at the point-of-care to focus discussion on key patient concerns/issues, which can help to prioritize patient needs and support improved decision-making. As a clinician stated after

participating in our usability pilot "you get that snapshot just before [the patient] comes in. You have a whole lot of data that is very efficient."

Electronic Patient Reported Outcomes Tool Technology Readiness Level

The ePRO tool is at a Technology Readiness Level 7 as it has already undergone early implementation and acceptability testing through the usability pilot. By August 2016, we will have moved to a Level 8 after the completion of our exploratory trial in which we began integration of the system into family health teams (FHTs) with early testing of outcomes. The Could Connect platform used to deliver the ePRO solution is at a Technology Readiness Level 9, actual technology proven through operations. The Cloud Connect platform is fully built and has been validated in several studies with different patient populations. This readiness level has been validated through a vendor preapproval process through the Canadian Federal Government.

Electronic Patient Reported Outcomes Electronic Patient Reported Outcomes Data Security

All data captured within the ePRO tool and by extension on the QoC Health, Inc. platform, where the ePRO tool is housed, is secured through industry standard encryption mechanisms, which are compliant with Canadian and American data security standards as legislated under the Personal Information Protection and Electronic Documents Act, 2015 (in Canada) [40] and Health Insurance Portability and Accountability Act, 1996 (in the United States) [41].

Change Management and Implementation Plan

We will adopt Canada Health Infoway's Change Management Framework [42] to support adoption of the ePRO tool for this study. This framework was designed to support the implementation of eHealth technologies, and identifies six core elements that should be addressed when implementing new eHealth solutions in health care settings including: governance and leadership, stakeholder engagement, communications, workflow analysis and integration, training and education, and monitoring and evaluation. These elements have guided our development to date as implementation considerations should be an ongoing process aligned with the development of eHealth solutions [43]. Table 2 provides an overview of the framework and how we have and will address each element as part of our development and implementation of the ePRO tool for this project. Our focus is on change management at the intervention sites with emphasis on organizational leaders and providers. In developing the ePRO tool, we have found that health care provider buy-in is among our greatest challenges and as such this will be a large focus of our change management strategy.

Table 2. ePRO tool change management strategy.

Change management element	Activities/strategies for adopting ePRO tool
Governance and leadership: mechanisms used to guide, steer or regulate the project. Also includes leadership activities in relation to change management.	With support from the decision-making partners and academic leads, site leads will be identified who will support the implementation process at the two intervention sites. These individuals will be engaged early in the process and will be informed about the value and need for the solution, including identifying the potential for the technology to improve outcomes, and reduce resource use. Decision-making partners and site leads will ensure that this message is shared with providers and other key stakeholders, will meet with the research team regularly, and will provide guidance on the change management activities outlined below.
Stakeholder engagement: activities that will support involvement by stakeholders expected to change. Behaviors must be defined, understood, and considered.	Stakeholder engagement with providers and patients has been integral to the design and development of the ePRO tool. We have learned that ongoing and continuous engagement with providers is particularly important to support uptake. As such we will: 1. Schedule several early meetings with providers at each site to introduce technology and field questions. 2. Leverage our civic partnerships as well as existing relationships with intervention sites to improve provider and patient engagement throughout the project.
Communications: how stakeholders will be informed of the change to initiate appropriate actions/behaviors.	We will use regular meetings, as well as our online messaging portal to track system errors, concerns, and suggestions for improvement from the research team to the technology partner (called the issue tracker), and short report/communications to update provider stakeholders on the progress of the project as needed. Providers, and patients, who are enrolled will have been provided with contact information for the team so they can easily share concerns, thoughts, and ideas on the tool at any time.
Workflow analysis and integration: understanding the current work process so that new tools can be sustainably embedded.	We will conduct a workflow analysis as part of this study to assess feasibility and usability of the ePRO tool into Ontario primary care practices. We will draw on methods and analysis from the workflow analysis, which was conducted as part of the usability pilot. Workflow analysis will be taken into consideration when interpreting our findings, and inform iterative changes to the tool to improve usability and uptake.
Training and education: activities needed to build capacity and skills among stakeholders expected to change.	Training and education are built into the research design. We plan on running at least one training session for providers and patients who are enrolled in the study and more as needed. Findings from the usability pilot indicated the need for ongoing information and potential training opportunities. As such we have developed user manuals for providers and patients. Refresher training sessions will be offered at 3, 6, and 9 months to all participants.
Monitoring and evaluation: reviewing and evaluating the change management process.	As part of our broader implementation plan we will include an evaluation of the change management process as part of our study. We will conduct readiness assessments prior to piloting, and will include questions regarding the change management approach in our follow-up interviews with organizational leaders and providers at intervention sites.

Capacity for Integration of Electronic Patient Reported Outcomes Into Existing Models of Care

The ePRO tool is designed to work within existing models of primary health care in Ontario such as FHTs, which are made up of an interprofessional team of physicians, nurse practitioners, and other health care providers delivering primary health care services to patients [44]. The ePRO tool can further be adopted by any integrated primary health care teams and/or primary health care models adopting care coordination plans as part of usual care. The decision-making partners for this project, Health Quality Ontario (HQO) and the Association of Family Health Teams of Ontario (AFHTO), will support integrating ePRO into existing models of primary health care. HQO is mandated, in part, to support quality improvement of the primary care sector through supporting the adoption of a standardized care coordination plan among other change ideas. AFHTO is similarly dedicated to supporting the sharing and implementation of best practices to FHTs across Ontario as a means to deliver better health and value to patients.

Methods

Developmental Evaluation of the Electronic Patient Reported Outcomes Tool

To address our three research questions, we will conduct a pragmatic cluster randomized controlled trial with an embedded case study of implementation at four sites. We will adopt a developmental evaluation approach in which evaluation questions are used to support decision-making and modifications to improve interventions and programs [45]. As is consistent with developmental evaluations, we seek to capture outcome, process, and context measures to identify how the ePRO tool impacts on patient, provider, and system outcomes, identify processes and contexts that may be influencing outcomes, and implementation of the tool to support scale and spread. The literature on telemedicine assessment suggests the need to capture both the impact of interventions but also the contextual factors that influence outcomes [46]. Additionally, eHealth and mobile technology adoption can be understood as a complex health intervention [47], which are highly influenced by contextual factors [48]. Developmental evaluations such as ours

proposed here are particularly important in assessment of complex systems [49].

Setting and Site Recruitment

We will use FHTs in Ontario, Canada as cluster sites to test the ePRO tool. Working with AFHTO we will identify 22 FHTs that vary in terms of geographic location and then randomly assign sites as either intervention or control. Using our change management framework as a guide, we will seek ongoing engagement through weekly or biweekly communication with executive directors and lead physicians at each intervention and control site. Posters and pamphlets describing the technology and trial will be delivered to providers and patients at the intervention sites. Communication both written and electronic, including a question and answer portal system, will be used at both intervention and control sites to ensure ongoing engagement as a means to minimize loss to follow-up for comparative measurement.

Sample Size Calculation

We will recruit 30 patients from each site, resulting in a total of 660 patients enrolled in the study. This sample size will provide 80% power derived from a power calculation based on a minimal clinically important difference of our core measure of quality of life (the assessment of quality of life, AQoL-4D) of 0.06 [50], an expected standard deviation in AQoL of 0.22 [51], an expected intraclass correlation coefficient of 0.01 (calculated based on total primary care use over a 1-year period among a 10% sample of the Ontario population, which served here as a proxy measure for patient outcomes), and an expected attrition rate of 10%. The expected attrition rate is derived from the recent study of the Change Foundation Partnership Advancing Transitions in Healthcare, which employed a very similar technology platform through a collaboration between QoC Health and the Health System Performance Research Network.

Population and Patient Recruitment

Eligible patients will need to be rostered at FHTs recruited to participate, over age 65, have two or more chronic conditions, and have had 10 or more visits to their primary health care provider within the last 12 months. These variables have been associated with a high complexity score [52] and can be pulled from most primary practice electronic medical record (EMR) systems without the need for a full chart review. Given that the smallest FHTs have three or four physicians with a roster of at least 6000 patients, we anticipate more than 300 eligible patients in each practice from which to recruit patients, as has been found in the FHT practice where the ePRO tool was developed, therefore requiring no more than a 10% participation rate. Patients deemed eligible based on EMR records will be randomly selected and placed on an ordered list of eligible patients for recruitment into the study that will be used to recruit patients until our required complement of patients is enrolled at each team.

Patient recruitment will occur either during a scheduled visit or by phone within 1 month of the study start date. Administrators at the FHTs will seek permission from eligible patients to be contacted by a member of the research team. Contact information for patients who agree will be provided to the research team to obtain consent and enrolment. To enroll in the study, patients must: (1) be able to provide informed consent, (2) be willing to complete surveys at baseline, 3-, 6-, 9-, and 12-month intervals, (3) allow the researchers to extract health information from the EMR, (4) allow use of their health card number to link their study data to health administrative data, and (5) for patients at intervention sites, be willing to keep track of their health on an ongoing basis for a period of 12 months with an electronic device or via a Web-based portal if they are selected to be a part of the intervention group. Patients at intervention sites will also need to have the physical capability to use a tablet or smartphone or have a caregiver who is willing to use the device with them. At this time our tool is only English enabled so either the patient or caregiver will also need to speak and read English.

Controlling for Bias and Contamination to Optimize Internal Validity

The clustered trial will control for contamination by clinical teams who are engaging with patients in setting goals with the ePRO in the intervention arm. We will ensure that providers who engage in this study do not provide care in multiple practices that are included in intervention and control arms of the study. Patient contamination should be prevented by selecting patients who are enrolled to the FHTs and have received most care within the team. Our random assignment of FHTs to intervention and control arms will occur after teams have consented to participate in the study; however, there may be a bias from teams who agree to participate from those who decline. We will compare participating from nonparticipating sites on practice geography, size (number of patients and number of physicians), and other characteristics based on membership information held by AFHTO. Patients who enroll in the study at intervention sites will likely be more technologically advanced than similar multimorbid patients who do not participate. We cannot measure technological literacy for nonparticipating patients at intervention sites but we will compare intervention and control patients to ensure comparability on study measures of technology use included in our baseline patient surveys. Patients in both intervention and control sites will also be asked to report on other disease management programs and activities that they are using. Similarly providers in both arms will be asked to report on other patient monitoring and goal-setting tools that they are using. We may expect that providers and patients already using such tools would have reasons to be both more but also less interested to participate in this study. The study design itself does not encourage bias in either direction.

Training

Providers and patients recruited at intervention sites will receive training on how to use the ePRO tool prior to the start of the trial. Intervention patients will receive one-on-one training with a research assistant; this typically takes 30 minutes (as was found in our usability pilot). Provider training will occur in a group setting. Training will be led by a member of the research team and will take between 30 and 60 minutes. In our usability pilot, we found that a single training session was not sufficient for either patients or providers to fully learn to use the tool. As

such, we will provide patients and providers with a manual and training video on how to use the tool and portal, and offer refresher training for patients at intervention sites at 3, 6, and 9 months.

Outcome, Process and Context Measures

Pragmatic Trial Measures

The pragmatic trial will address research questions 1 and 2: does ePRO improve patient quality of life, care experience, and self-management in older adults with complex needs? Is ePRO cost-effective for older adults with complex needs from the perspective of the health care system? It should be noted that evaluation of the current tool will focus on whether the goal setting and patient use of the tool results in changes in health outcomes. We will not be able to assess whether changes in specific activity was associated with changes in health outcomes.

Patient quality of life, experience, and self-management will be captured using validated scales. Our primary measure of patient-oriented outcome is health-related quality of life measured by the AQoL-4D. The AQoL-4D takes only minutes to complete, has been validated in a community-dwelling older adult population, and has demonstrated responsiveness and predictive validity with regard to entrance to long-term care [51]. The AQoL-4D captures four core dimensions of health-related quality of life (independent living, relationships, mental health, and senses) that map closely onto factors that are identified in the ePRO tool [30]. Patient experience will be captured using measures from the patient-experience survey deployed to all FHTs from AFHTO and our other collaborating partner HQO. Using these measures would allow us to compare our findings with patient experience scores from FHTs across Ontario.

We will measure patient self-management using the 13-item patient activation measure (PAM) [53]. PAM classifies self-management capability into one of four categories ranging from only belief that their role as a patient is important, to certainty that they can take action even when under stress [54]. The PAM has been associated with better primary care experience [55] and improved health outcomes among multimorbid patients [56]. Finally we will look at goal-attainment scaling as captured by the ePRO tool for intervention patients, comparing outcomes captured at the start of the intervention to the end. Goal-attainment has been argued to be one of the most important outcome measures for complex patients [21].

With regard to our second research question, efficiency will be assessed using a cost-effectiveness analysis from health care system and societal perspectives. For the health care system perspective, only costs that are borne to the government, such as costs of intervention and costs of health services incurred during the 1-year follow-up period, will be considered. Costs of the intervention will be estimated based on anticipated real-world licensing and ongoing access costs for software, hosting and data management costs, program support, managed device costs, application support, training, incremental data plan costs (depending on volume of use in the intervention group), and costs for the Cloud Connect platform. These estimates will include any costs provided as in-kind contributions to the present study that would be recovered in a real-world adoption.

We will collect health care numbers from all participants and link all study measures with health administrative data (HAD) housed at the Institute of Clinical Evaluative Sciences (ICES; a research institute that collects a wide array of linked health datasets in Ontario). We will use HAD to follow total 1-year use and measure total direct costs to government for all health care services in both the intervention and control groups. Over 85% of total direct costs can be measured using a cost methodology for HAD implemented at ICES by WW [57]. For costs for which there is a service- or product-specific claim and a charge (eg, for prescriptions, fee for service physician visits) we will use the payment charge that is provided on those claims. For acute care hospitalization and emergency department (ED) costs we will multiply visit records in the Discharge Abstract Database and National Ambulatory Care Reporting System with encounter-specific resource intensity weights (also known as ambulatory cost weights in ED) and a provincial cost per weighted case.

Ontario also has separate databases to track post-acute rehabilitation and complex continuing care as well as inpatient mental health. In each case, we will use the appropriate resource intensity weight for that particular care setting but multiply, where necessary, by Ontario-specific weighted costs where these are not calculated and available through the Canadian Institute for Health Information. These cost weightings have been employed by our team in prior and current studies, following our costing methodology and using administrative data [1]. Capitation payments for primary care physicians in Ontario will also be calculated based on the payment rate and the particular model of primary care for each patient's physician in each month of the study period. This method has been used in published studies of population-based health care costs [6,58].

From a societal perspective, administrative data will be combined with patient-reported health service use and costs (with patient-reported costs reported in the final 3-month period assumed to be representative for the last 6 months of the study) to provide an estimate of 1-year societal costs. Caregiver time costs will be estimated using the average industrial wage. We will also include patients' and their caregiver(s') time and expenditures related to health care for the past 3 months using measures that have been implemented as part of a standardized patient survey across 12 primary care research teams in the Canadian Institute for Health Research (CIHR) Community-Based Primary Health Care Team Grant competition (WW is a primary investigator for one team using this tool).

We will capture patient and provider demographic and characteristic information such as age, gender, ethnicity, chronic illness profile, socioeconomic status, and information technology (IT) skills to provide contextual information about our users to support our analysis. From the patient perspective, this will allow us to do case matching to control group. These contextual factors have also been found to impact the adoption and

implementation of eHealth tools [59] and as such should be included in our analysis of barriers and facilitators.

Case Study Measures

Our third research question (What are the most important implementation factors to effectively scale and spread ePRO in primary health care settings?) will be answered through our case study design. A subset of four intervention sites will be selected to capture process and additional context measures to develop an implementation framework to support scale and spread of the ePRO tool. Cases will be selected based on a most different design, ensuring that we capture practices that differ in terms of location (rural vs urban) and organizational design (ie, the number of diversity of providers at the practice). Implementation relates to the processes required to put an intervention or new model of care into use [60]. Implementation factors are important to assess to determine how best to scale and spread (ie, increasing coverage, range, and sustainability [61] of the ePRO tool). In terms of scale, we are interested in what additional features/capabilities could be added to the tool to meet patient and provider needs not yet addressed, and in terms of spread we seek to determine provider, organizational, and health system enablers and barriers to adopting the tool in primary care practices broadly across Canada and internationally.

Given the importance of patient-centered care delivery for seniors with complex care needs we will additionally capture provider level effectiveness through provider interviews guided in-part by the Assessment of Chronic Illness Care (ACIC) tool. The ACIC has been used to help health care teams improve care delivered to patients with chronic illness [62], and it can also be used to measure change in care delivery. We will draw on the self-management and clinical information systems scales of the ACIC to craft interview questions as these are most relevant to our intervention.

Process measures will be captured through the post-study system usability questionnaire (PSSUQ) to assess use and experience using the ePRO by patients and providers. The PSSUQ is a 19-item usability questionnaire comprised of three subscales (system usefulness, information quality, and interface quality) [63]. The PSSUQ has demonstrated reliability and validity [64], and has been used to assess satisfaction and experience with similar mHealth technologies [63], which are key aspects of innovation model testing [65]. Patient and provider experience with the ePRO will additionally be captured through patient focus groups and provider interviews.

We will capture organization and system level context measures related to implementing the ePRO through post-intervention interviews with providers and organizational leaders. Factors such as supportive resources (ie, IT support), logistical issues (ie, integration of the tool into provider workflows), appropriate training and time to learn new systems, and organizational level support have been found to be pivotal in adopting new eHealth systems [59,66,67]. These factors are reflected in the change management framework used to guide development and implementation of ePRO (outlined in Table 2). The framework will be used to help shape interview guides and inform analysis. System level factors found to impact eHealth adoption, such as noncentralized systems, lack of standardization of data systems, legal requirements, and financial incentives (or disincentives) [66], will also be captured.

Outcome, process, and context measures that will be captured as part of the pragmatic trial and case study are outlined in Table 3 below.

Table 3. Outcome, process, and context measures for the developmental evaluation of ePRO.

Concept	Measurement level	Variable	Tool/method	Data collection
Outcome: intervention and control sites				
	Patient	Quality of Life	AQoL-4D[a]	Baseline, 3, 6, 9, and 12 months
		Self-management	PAM[b]	Baseline, 3, 6, 9, and 12 months
		Patient experience	Patient experience survey (from AFHTO[c] and HQO[d])	Baseline, 3, 6, 9, and 12 months
		Goal-attainment captured by ePRO tool–intervention sites only	Goal attainment scaling. Completed as part of the intervention.	Over 12 months
	System	Efficiency	Cost-effectiveness analysis: data from AQoL-4D, ICES[e], patient self-report, and published literature	Pre and post-intervention
Process: intervention sites				
	Patient	Tool experience	PSSUQ[f] post-study system usability questionnaire	3, 6, 9, and 12 months
			Patient focus groups	6 months and post-intervention
	Provider	Tool experience	PSSUQ[f]	6 and 12 months
			Provider interviews	6 months and post-intervention
		Delivering patient-centered care	Provider interviews–drawing on Assessment of Chronic Illness Care tool	6 months and post-intervention
	Organization	Provider workflows	Provider interviews	Post-intervention
Context: intervention and control sites				
	Patient	Demographic characteristics	EMR[g] extraction; patient information sheet	Baseline
	Provider	Demographic characteristics	Provider information sheet	Baseline
	Organization	Size; description of the organization; resources; support; training	Document analysis; provider and leaders interviews	6 months and post-intervention
	System	Structure; standardization of data systems; legal requirements; funding	Document analysis; provider and leaders interviews	6 months and post-intervention

[a]Assessment of Quality of Life-4D

[b]patient activation measure

[c]Association of Family Health Teams of Ontario

[d]Health quality Ontario

[e]Institute of Clinical Evaluative Sciences

[f]Post-study system usability questionnaire

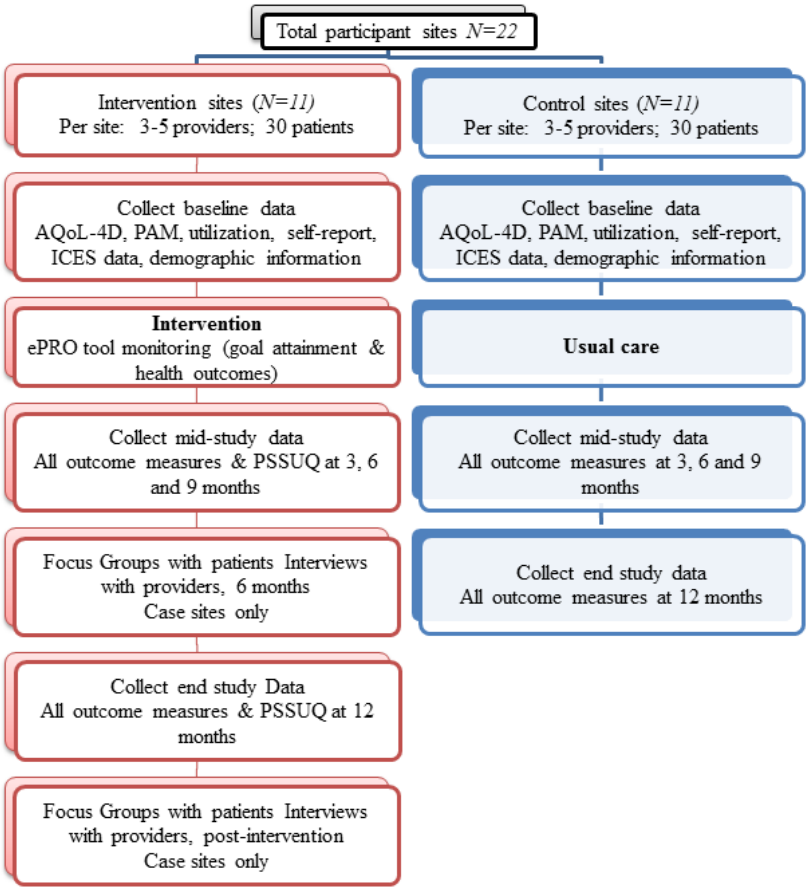
[g]electronic medical record

Data Collection

As can be noted from the Table 3 data collection will happen at baseline, 3-, 6-, 9 and 12-month time-points in the study, as well as post intervention (within 2 months of the end of the trial) at case study sites. Patients will not be asked to complete all surveys in a single sitting and will be given up to 2 weeks to complete surveys with the help of a research assistant at a location of the patients choosing (ie, in their home or at their FHT) at each data collection time point. Qualitative data collection will occur at 6 months and post intervention as four case study sites. Patient focus groups will have between three and four focus groups at each site with six to eight patients and caregivers participating in each. Keeping focus groups to a maximum of eight participants is a standard recommendation in focus group methodology [68] as it provides ample opportunity for each participant to voice their insights and perspectives. Focus groups will last between 60 and 90 minutes. Interviews will be conducting with the providers participating

at the four case study sites and will last up to 60 minutes. Figure 2 visually depicts the data collection method.

Figure 2. ePRO evaluation data capture diagram.



Data Analysis Strategy

Our data analysis strategy is broken up into our pragmatic trial analysis and case study analysis. The pragmatic trial analysis focuses on answering research questions 1 and 2 while our case study analysis will address question 3.

Pragmatic Trial Analysis

Comparisons between intervention sites and control sites across measures of location, practice size, academic affiliation, and other practice measures will be conducted. Similarly, we will compare patients on all baseline measures of age, sex, morbidity, socioeconomic circumstances, social roles (ie, caregiver availability and responsibility) and ethnicity, IT capability, and experience. Cohen's-D and statistical differences will be used to determine differences in practice and patient measures that may need to be controlled for in statistical regressions if there are any such differences.

Statistical analyses will be undertaken to address the research study question 1. ePRO tool effectiveness will be determined by analyzing patient outcome data. Overall domain scores for AQoL-4D, patient experience, and PAM, will be calculated, including changes in scores between baseline and follow-up periods within groups and between intervention and control groups. Statistical comparisons between the intervention and control groups will be made using mixed-effects regression models to account for the clustering effect of patients within FHTs.

To address research study question 2, total cost for each patient including costs of the intervention and costs of health services over the 1-year follow-up period after the start of the intervention will be compared between intervention and control groups. Additional analyses will use patient-reported costs to estimate costs from the societal perspective. Results of the cost-effectiveness analysis will be expressed as the incremental cost per quality-adjusted life years (QALYs) gained, calculated as the difference in costs divided by the difference in QALYs between intervention and control groups. QALYs will be calculated using the total area under the curve approach, with linear interpolation between assessment points and baseline adjustment for comparisons [69]. We will use mixed-effects regression analyses to separately estimate the difference in health care costs between the intervention and control groups, and include any covariates that are observed to be different between groups in baseline comparisons.

In addition, we will calculate an incremental net benefit (INB) by subtracting incremental costs from a product of willingness to pay and incremental health benefits. If the INB is greater than zero, ePRO is considered as a cost-effective option. The 95%

confidence interval will be calculated using a nonparametric bootstrapping method. Results from the simulations will also presented as cost effectiveness acceptability curves, which show the probabilities that ePRO being cost-effective over a range of potential willingness to pay [70]. We will conduct a scenario analysis, whereby the effect of a complete case only will be used to estimate the cost-effectiveness. Because of the 12-month follow-up during the study, costs and health outcomes will not be discounted. We will also conduct a budget impact analysis to estimate the financial consequences of implementing ePRO for a primary care provider and at the system level across a province depending on the number of primary providers.

Case Study Analysis

Single case and cross-case comparative analysis will be used to assess process and outcome measures captured at intervention sites in order to answer research question 3. Experience with the tool and feasibility of adopting the tool will be captured by analyzing data from the PSSUQ, patient focus groups, and provider interviews. Standard descriptive statistics will be used to analyze the PSSUQ across the three subdomains captured by the tool and comparisons between intervention sites will be made using *t* tests or Mann-Whitney tests as appropriate.

Focus group, interview, and field note data will be analyzed using qualitative descriptive methods [71]. Focus groups and interviews will be recorded and transcribed verbatim by an external source. Transcripts will be checked for accuracy against the audio record and analyzed through the assistance of NVivo 11 software. Two researchers trained in qualitative research will read the transcripts and record key themes, compare, and discuss findings.

Through comparing findings across the four FHTs and by engaging international research partners to discuss implementation factors of health care systems in Scotland and at Kaiser Permanente Colorado, we will aim to refine the change management and implementation frameworks used to guide the study to inform the development of an implementation strategy for the ePRO tool internationally.

Results

The proposed project presented in this paper will be funded through the CIHR eHIPP program (CIHR–143559). The expected completion date of the study is November, 2019.

Discussion

Impact

Anticipated Outcomes From Adopting the Electronic Patient Reported Outcomes Tool

Using innovative technology to support the adoption of goal-oriented care for older adults with complex needs in primary care settings can have a significant impact on patient, provider, and health system outcomes. Our primary outcome of interest at the patient level is quality of life. For older adults with complex needs and their caregivers, an easy to use tool that supports goal-oriented patient care can support individualized discussions between providers and patients, can simplify patient- and joint-decision making processes, particularly for individuals with multiple chronic conditions, and can help patients to understand and articulate their needs [21]. By supporting goal-oriented care, the ePRO tool can enhance the quality of primary health care delivery by improving patient-provider interactions at the point of care, which has been found to improve health-related quality of life, and support positive health behavior change in chronic disease patients [72].

For health care providers the tool can help to address the challenges associated with delivering goal-oriented care [23,24], while providing patient-centered data to help make decisions about their care. The system can help providers to improve chronic illness management for their older adult patients with complex care needs by giving them a tool to help support patient self-management, as well as offer a clinical information system that provides monitoring data to help manage these patients; two key aspects of chronic illness care management in Wagner's Chronic Care Model [73].

For the health system, our tool has the potential to increase access to primary health care services through mobile monitoring, and reduce unnecessary health care use. Our usability findings show early evidence of the tools ability to support patient self-management, which has been shown to help avoid declines and unnecessary health care use for patients with chronic disease [74,75]. With scale and spread of the tool it could further support system integration by allowing providers across the system to communicate about patient care plans, goals, and outcomes, which could lead to better management and slower decline over the longer term.

Anticipated Ethical, Social, and Legal Issues That May Arise

Given the multiphased nature of our design, we have received four separate ethics approvals from all appropriate Research Ethics Boards to develop and test our tool. Among concerns we have addressed are (1) data security, which is addressed by ensuring our tool is PHIPA compliant, (2) provider liability for monitoring, which is addressed by ensuring participants are aware that the tool is not an emergency device nor is it monitored on a regular basis by providers, and (3) ensuring providers do not deny needed care. This last issue is addressed as our studies do not require that control patients be denied engaging in goal setting or monitoring with their providers should it be done as part of their usual care. We can draw on our experience running the usability pilot and exploratory trial to ensure we address, monitor, and evaluate our performance in relation to these important issues.

National and International Scalability of the Electronic Patient Reported Outcomes Tool

We have developed and tested the ePRO tool in FHTs, an interprofessional primary care delivery model prominent in Ontario [44]. There are currently 184 FHTs across Ontario serving over 3 million Ontarians in over 200 communities [76]. The ePRO tool could be rolled out to any of these FHTs, and would be particularly useful to those serving older adults with complex care needs. Furthermore, as we designed the ePRO

tool to align with the goal-setting section embedded in the Coordinated Care Plan, the tool can be scaled further to any primary care team adopting Coordinated Care Plans as part of their management of chronically ill patients. Additionally, the Coordinated Care Plan being used in Ontario is derived from common elements found in care planning from other jurisdictions including: British Columbia, Nova Scotia, Ireland, Scotland, England, the Netherlands, Sweden Australia, and the United States [22], suggesting the potential for international applicability.

International scalability is further supported through our partnerships developed with support from a CIHR Planning and Dissemination Grant awarded in 2014. The grant supported the development of a partnership between the Health System Performance Research Network and the Bridgepoint Campus of the Lunenfeld-Tanenbaum Research Institute (formerly Bridgepoint Collaboratory for Research and Innovation) in Ontario, with Kaiser Permanente Colorado in the United States and the Universities of Glasgow and Edinburgh and the National Health Service in Scotland. The international partnership was founded on a shared interest in supporting older adults with complex care needs in primary care settings in all three countries. Through site visits, and knowledge sharing via team teleconferences and reporting we identified an interest and opportunity to adopt the ePRO tool in Scotland and Kaiser Colorado, and plan to run feasibility pilots in these two settings. Findings from the pilots will further support spread and scalability of the tool nationally and internationally.

Acknowledgments

We would like to acknowledge the contribution of our collaborators on this project: Dr. Renee Lyons (Founding Bridgepoint Research Chair in Complex Chronic Disease, Emeritus), Dr. Kerry Kuluski (Research Scientist at the Bridgepoint Campus of the Lunenfeld-Tanenbaum Research Institute in Sinai Health System and Assistant Professor (status only) at the Institute for Health Policy, Management and Evaluation at the University of Toronto), Ms. Lee Faiclough (Vice-President, Quality Improvement from Health Quality Ontario), Ms. Sandie Seaman (Health Quality Ontario) Ms. Angie Heydon (CEO, Association of Family Health Teams of Ontario), and our patient and caregiver collaborators Bob Alexander and Valerie Hepburn. We would also like to acknowledge our technology partner QoC Health, Inc. in particular Sarah Sharpe (Co-founder), Chancellor Crawford (Co-founder & CEO), Ray Shih (Co-founder & President) and Sue Bhella (Project Manager) for their ongoing partnership in developing this technology and for preparation of materials in support of our CIHR eHIPP grant. Funding support for development of the ePRO tool came from the Ontario Ministry of Health and Long-term Care's Health Research Fund (#06034) via the Health System Performance Research Network at the University of Toronto. International partnerships and work have been supported through a CIHR Planning and Dissemination Grant (CIHR-137200). The views reflected in this manuscript are those of the research team and not the funders.

Conflicts of Interest

None declared.

Multimedia Appendix 1

The ePRO tool.

[PPTX File, 1MB - resprot_v5i2e126_app1.pptx]

Multimedia Appendix 2

eHIPP reviewer comments.

[PDF File (Adobe PDF File), 108KB - resprot_v5i2e126_app2.pdf]

References

1. Drummond D. Public Services for Ontarians: A Path to Sustainability and Excellence. 2012. Commission on the Reform of Ontario's Public Services URL: http://www.fin.gov.on.ca/en/reformcommission/chapters/report.pdf [accessed 2016-05-31] [WebCite Cache ID 6bvmr6fL4]
2. Reid R, Evans R, Barer M, Sheps S, Kerluke K, McGrail K, et al. Conspicuous consumption: characterizing high users of physician services in one Canadian province. J Health Serv Res Policy 2003;8:215-224. [doi: 10.1258/135581903322403281] [Medline: 14596756]
3. Heslop L, Athan D, Gardner B, Diers D, Poh BC. An analysis of high-cost users at an Australian public health service organization. Health Serv Manage Res 2005;18:232-243. [doi: 10.1258/095148405774518633] [Medline: 16259671]
4. Department of Health. Department of Health. Long Term Health Conditions. United Kingdom: Department of Health; 2012. Third edition of Long Term Conditions Compendium URL: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/216528/dh_134486.pdf [accessed 2016-05-31] [WebCite Cache ID 6ggnOxWoe]

5. Emanuel EJ. Where are the health care cost savings? JAMA 2012;307:39-40. [doi: 10.1001/jama.2011.1927] [Medline: 22215161]
6. Rosella LC, Fitzpatrick T, Wodchis WP, Calzavara A, Manson H, Goel V. High-cost health care users in Ontario, Canada: demographic, socio-economic, and health status characteristics. BMC Health Serv Res 2014;14:532 [FREE Full text] [doi: 10.1186/s12913-014-0532-2] [Medline: 25359294]
7. Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A, et al. Aging with multimorbidity: a systematic review of the literature. Ageing Res Rev 2011;10:430-439. [doi: 10.1016/j.arr.2011.03.003] [Medline: 21402176]
8. Bayliss EA, Bosworth HB, Noel PH, Wolff JL, Damush TM, Mciver L. Supporting self-management for patients with complex medical needs: recommendations of a working group. Chronic Illn 2007;3:167-175. [doi: 10.1177/1742395307081501] [Medline: 18083671]
9. Schaink A, Kuluski K, Lyons R, Fortin M, Jadad A, Upshur R, et al. A scoping review and thematic classification of patient complexity: offering a unifying framework. JOC 2012;2:1-9. [doi: 10.15256/joc.2012.2.15]
10. Wenger NS, Solomon DH, Roth CP, MacLean CH, Saliba D, Kamberg CJ, et al. The quality of medical care provided to vulnerable community-dwelling older patients. Ann Intern Med 2003;139:740-747. [Medline: 14597458]
11. Upshur REG. Do clinical guidelines still make sense? No. Ann Fam Med 2014;12:202-203 [FREE Full text] [doi: 10.1370/afm.1654] [Medline: 24821890]
12. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. JAMA 2005;294:716-724. [doi: 10.1001/jama.294.6.716] [Medline: 16091574]
13. Institute of Medicine (US) Committee on Quality of Health Care in America. A new health system for the 21st century. In: Crossing the Quality Chasm: A New Health System for the 21st Century. Washington, DC: National Academies Press; 2001:1-8.
14. Boyd C, Fortin M. Future of multimorbidity research: how should understanding of multimorbidity inform health system design? Public Health Reviews 2010;32:451-474.
15. Lutz BJ, Bowers BJ. Patient-centered care: understanding its interpretation and implementation in health care. Sch Inq Nurs Pract 2000;14:165-183; discussion 183. [Medline: 10983489]
16. International Alliance of Patients Organizations. Patient Centred Healthcare Indicators Review. 2012. URL: http://www.patientsorganizations.org/attach.pl/1441/1484/IAPO%20Patient-Centred%20Healthcare%20Indicators%20Review.pdf [accessed 2016-05-31] [WebCite Cache ID 6hvcfE3MU]
17. Frampton S, Guastello S, Brady C, Hale M, Horowitz S, Bennet Smith S, et al. Patient-Centered Care Improvement Guide. 2008. URL: http://planetree.org/wp-content/uploads/2012/01/Patient-Centered-Care-Improvement-Guide-10-28-09-Final.pdf [accessed 2014-04-28] [WebCite Cache ID 6PBCL4U4q]
18. Burgers JS, Voerman GE, Grol R, Faber MJ, Schneider EC. Quality and coordination of care for patients with multiple conditions: results from an international survey of patient experience. Eval Health Prof 2010;33:343-364. [doi: 10.1177/0163278710375695] [Medline: 20801976]
19. Upshur C, Weinreb L. A survey of primary care provider attitudes and behaviors regarding treatment of adult depression: what changes after a collaborative care intervention? Prim Care Companion J Clin Psychiatry 2008;10:182-186 [FREE Full text] [Medline: 18615167]
20. Sinnott C, Mc HS, Browne J, Bradley C. GPs' perspectives on the management of patients with multimorbidity: systematic review and synthesis of qualitative research. BMJ Open 2013;3:e003610 [FREE Full text] [doi: 10.1136/bmjopen-2013-003610] [Medline: 24038011]
21. Reuben DB, Tinetti ME. Goal-oriented patient care--an alternative health outcomes paradigm. N Engl J Med 2012;366:777-779. [doi: 10.1056/NEJMp1113631] [Medline: 22375966]
22. Ontario Medical Association. Key Elements to Include in a Coordinated Care Plan. 2014. URL: https://www.oma.org/Resources/Documents/CoordinatedCarePlan_June2014.pdf [accessed 2016-03-12] [WebCite Cache ID 6fwUBwZGi]
23. Ekdahl AW, Hellström I, Andersson L, Friedrichsen M. Too complex and time-consuming to fit in! Physicians' experiences of elderly patients and their participation in medical decision making: a grounded theory study. BMJ Open 2012;2 [FREE Full text] [doi: 10.1136/bmjopen-2012-001063] [Medline: 22654092]
24. Kuluski K, Gill A, Naganathan G, Upshur R, Jaakkimainen RL, Wodchis WP. A qualitative descriptive study on the alignment of care goals between older persons with multi-morbidities, their family physicians and informal caregivers. BMC Fam Pract 2013;14:133 [FREE Full text] [doi: 10.1186/1471-2296-14-133] [Medline: 24010523]
25. Schoen C, Osborn R, Squires D, Doty M, Pierson R, Applebaum S. New 2011 survey of patients with complex care needs in eleven countries finds that care is often poorly coordinated. Health Aff (Millwood) 2011;30:2437-2448 [FREE Full text] [doi: 10.1377/hlthaff.2011.0923] [Medline: 22072063]
26. Brown AL. Design experiments: theoretical and methodological challenges in creating complex interventions in classroom settings. Journal of the Learning Sciences 1992;2:141-178. [doi: 10.1207/s15327809jls0202_2]
27. Collins A. Toward a design science of education. In: Scanlon E, O'Shea T, editors. New Directions in Educational Technology. Berlin, Germany: Springer Berlin Heidelberg; 1992:15-22.

28. Devi K, Sen A, Hemachandran K. A working framework for the user-centered design approach and a survey of the available methods. International Journal of Scientific and Research Publications 2012;2:1-8 [FREE Full text] [WebCite Cache ID http://www.ijsrp.org/research_paper_apr2012/ijsrp-apr-2012-05.pdf]
29. Collins A, Joseph D, Bielaczyc K. Design research: theoretical and methodological issues. Journal of the Learning Sciences 2004;13:15-42. [doi: 10.1207/s15327809jls1301_2]
30. Steele Gray C, Khan AI, Kuluski K, McKillop I, Sharpe S, Bierman AS, et al. Improving patient experience and primary care quality for patients with complex chronic disease using the electronic patient-reported outcomes tool: adopting qualitative methods into a user-centered design approach. JMIR Res Protoc 2016;5:e28 [FREE Full text] [doi: 10.2196/resprot.5204] [Medline: 26892952]
31. Steele Gray C, Miller D, Kuluski K, Cott C. Tying eHealth tools to patient needsxploring the use of eHealth for community-dwelling patients with complex chronic disease and disability. JMIR Res Protoc 2014;3:e67. [doi: 10.2196/resprot.3500]
32. Steele Gray C, Gill A, Khan AI, Hans P, Kuluski K, Cott C. The electronic patient reported outcome tool: testing usability and feasibility of a mobile app and portal to support care for patients with complex chronic disease and disability in primary care settings. JMIR mHealth uHealth 2016;4:e58 (forthcoming).
33. Bovend'Eerdt TJH, Botell RE, Wade DT. Writing SMART rehabilitation goals and achieving goal attainment scaling: a practical guide. Clin Rehabil 2009;23:352-361. [doi: 10.1177/0269215508101741] [Medline: 19237435]
34. Cella D, Riley W, Stone A, Rothrock N, Reeve B, Yount S, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. J Clin Epidemiol 2010;63:1179-1194 [FREE Full text] [doi: 10.1016/j.jclinepi.2010.04.011] [Medline: 20685078]
35. Broderick JE, Schneider S, Junghaenel DU, Schwartz JE, Stone AA. Validity and reliability of patient-reported outcomes measurement information system instruments in osteoarthritis. Arthritis Care Res (Hoboken) 2013;65:1625-1633 [FREE Full text] [doi: 10.1002/acr.22025] [Medline: 23592494]
36. Fries JF, Cella D, Rose M, Krishnan E, Bruce B. Progress in assessing physical function in arthritis: PROMIS short forms and computerized adaptive testing. J Rheumatol 2009;36:2061-2066. [doi: 10.3899/jrheum.090358] [Medline: 19738214]
37. Bryan S, Broesch J, Dalzell K, Davis J, Dawes M, Doyle-Waters M, et al. Centre for Clinical Epidemiology & Evaluation. Vancouver, BC: Centre for Clinical Epidemiology & Evaluation; 2013. What are the most effective ways to measure patient health outcomes of primary health care integration through PROM (Patient Reported Outcome Measurement) instruments? URL: http://www.c2e2.ca/sites/default/files/files/2013/04/PROMS-Report-Final-Apr-23-2013.pdf [accessed 2016-05-31] [WebCite Cache ID 6fwV6ediu]
38. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16:606-613 [FREE Full text] [Medline: 11556941]
39. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166:1092-1097. [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
40. Government of Canada Justice Laws. Personal Information Protection and Electronic Documents Act. 2000. URL: http://laws-lois.justice.gc.ca/eng/acts/p-8.6/ [accessed 2016-06-03] [WebCite Cache ID 6hzkMxLWS]
41. United States Congress. The Health Insurance Portability and Accountability Act of 1996 (HIPAA). 1996. URL: https://www.congress.gov/bill/104th-congress/house-bill/3103 [accessed 2016-06-03] [WebCite Cache ID 6hzkqK6xp]
42. Canada Health Infoway. 2013. A Framework and Toolkit for Managing eHealth Change: People and Processes URL: https://www.infoway-inforoute.ca/en/ [accessed 2016-03-12] [WebCite Cache ID 6fwVInaOv]
43. van Gemert-Pijnen JEWC, Nijland N, van LM, Ossebaard HC, Kelders SM, Eysenbach G, et al. A holistic framework to improve the uptake and impact of eHealth technologies. J Med Internet Res 2011;13:e111 [FREE Full text] [doi: 10.2196/jmir.1672] [Medline: 22155738]
44. Glazier R, Zagorski B, Rayner J. Comparison of Primary Care Models in Ontario: By Demographics, Case Mix and Emergency Department Use, 2008/09 to 2009/10.: Institute for Clinical Evaluative Sciences URL: http://www.ices.on.ca/Publications/Atlases-and-Reports/2012/Comparison-of-Primary-Care-Models [accessed 2015-11-06] [WebCite Cache ID 6cqYaUd0G]
45. Patton M. Utilization-Focused Evaluation, 4th edition. Saint Paul: SAGE Publications, Inc; 2008.
46. Ekeland AG, Bowes A, Flottorp S. Methodologies for assessing telemedicine: a systematic review of reviews. Int J Med Inform 2012;81:1-11. [doi: 10.1016/j.ijmedinf.2011.10.009] [Medline: 22104370]
47. Agboola S, Hale TM, Masters C, Kvedar J, Jethwani K. "Real-world" practical evaluation strategies: a review of telehealth evaluation. JMIR Res Protoc 2014;3:e75 [FREE Full text] [doi: 10.2196/resprot.3459] [Medline: 25524892]
48. Campbell NC, Murray E, Darbyshire J, Emery J, Farmer A, Griffiths F, et al. Designing and evaluating complex interventions to improve health care. BMJ 2007;334:455-459 [FREE Full text] [doi: 10.1136/bmj.39108.379965.BE] [Medline: 17332585]
49. Patton M. Developmental Evaluation: Applying Complexity Concepts to Enhance Innovation and Use. New York: The Guilford Press; 2011.
50. Hawthorne G, Osborne R. Population norms and meaningful differences for the Assessment of Quality of Life (AQoL) measure. Aust N Z J Public Health 2005;29:136-142. [Medline: 15915617]

51. Osborne RH, Hawthorne G, Lew EA, Gray LC. Quality of life assessment in the community-dwelling elderly: validation of the Assessment of Quality of Life (AQoL) Instrument and comparison with the SF-36. J Clin Epidemiol 2003;56:138-147. [Medline: 12654408]
52. Upshur R, Wang L, Moineddin R, Nie J, Tracy S. The complexity score: towards a clinically relevant, clinician-friendly measure of patient multi-morbidity. International Journal of Patient Centred Medicine 2012;2:799-804.
53. Hibbard JH, Mahoney ER, Stockard J, Tusler M. Development and testing of a short form of the patient activation measure. Health Serv Res 2005;40(Pt 1):1918-1930 [FREE Full text] [doi: 10.1111/j.1475-6773.2005.00438.x] [Medline: 16336556]
54. Hibbard JH, Stockard J, Mahoney ER, Tusler M. Development of the Patient Activation Measure (PAM): conceptualizing and measuring activation in patients and consumers. Health Serv Res 2004;39(Pt 1):1005-1026 [FREE Full text] [doi: 10.1111/j.1475-6773.2004.00269.x] [Medline: 15230939]
55. Greene J, Hibbard JH, Sacks R, Overton V. When seeing the same physician, highly activated patients have better care experiences than less activated patients. Health Aff (Millwood) 2013;32:1299-1305. [doi: 10.1377/hlthaff.2012.1409] [Medline: 23836747]
56. Skolasky RL, Green AF, Scharfstein D, Boult C, Reider L, Wegener ST. Psychometric properties of the patient activation measure among multimorbid older adults. Health Serv Res 2011;46:457-478 [FREE Full text] [doi: 10.1111/j.1475-6773.2010.01210.x] [Medline: 21091470]
57. Wodchis W, Bushmeneva K, Nikitovic M, McKillop I. Guidelines on Person-Level Costing Using Administrative Databases in Ontario. Working Paper Series Volume 1. Toronto, Ontario, Canada: University of Toronto; 2013. URL: http://www.hsprn.ca/uploads/files/Guidelines_on_PersonLevel_Costing_May_2013.pdf [accessed 2016-03-12] [WebCite Cache ID 6fwWeI3kc]
58. de Olivieria C, Vigod S, Cheng J, Rehm J, Kurdyak P. Costs of mental health care services among high cost users in Ontario. In Canadian Association for Health Services and Policy Research Conference. Montreal, Quebec 2015:88.
59. Hage E, Roo JP, van Offenbeek MAG, Boonstra A. Implementation factors and their effect on e-Health service adoption in rural communities: a systematic literature review. BMC Health Serv Res 2013;13:19 [FREE Full text] [doi: 10.1186/1472-6963-13-19] [Medline: 23311452]
60. Damschroder L, Aron D, Keith R, Kirsh S, Alexander J, Lowery J. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. Implement Sci 2009;4:50-65.
61. Ilott I, Gerrish K, Pownall S, Eltringham S, Booth A. Exploring scale-up, spread, and sustainability: an instrumental case study tracing an innovation to enhance dysphagia care. Implement Sci 2013;8:128 [FREE Full text] [doi: 10.1186/1748-5908-8-128] [Medline: 24168667]
62. Improving Chronic Illness Care. 2015. Clinical Practice Change: Using the ACIC in Your Work URL: http://www.improvingchroniccare.org/index.php?p=User_Info&s=298 [accessed 2015-01-15]
63. Sheehan B, Lee Y, Rodriguez M, Tiase V, Schnall R. A comparison of usability factors of four mobile devices for accessing healthcare information by adolescents. Appl Clin Inform 2012;3:356-366 [FREE Full text] [doi: 10.4338/ACI-2012-06-RA-0021] [Medline: 23227134]
64. Lewis J. Psychometric Evaluation of the Post-Study System Usability Questionnaire: The PSSUQ. 1992 Presented at: Proceedings of the Human Factors and Ergonomics Society Annual Meeting; October, 1992; Boca Raton, FL p. 1259-1260. [doi: 10.1177/154193129203601617]
65. Parry GJ, Carson-Stevens A, Luff DF, McPherson ME, Goldmann DA. Recommendations for evaluation of health care improvement initiatives. Acad Pediatr 2013;13(Suppl):S23-S30. [doi: 10.1016/j.acap.2013.04.007] [Medline: 24268081]
66. Anderson JG. Social, ethical and legal barriers to e-health. Int J Med Inform 2007;76:480-483. [doi: 10.1016/j.ijmedinf.2006.09.016] [Medline: 17064955]
67. Tsiknakis M, Kouroubali A. Organizational factors affecting successful adoption of innovative eHealth services: a case study employing the FITT framework. Int J Med Inform 2009;78:39-52. [doi: 10.1016/j.ijmedinf.2008.07.001] [Medline: 18723389]
68. Kitzinger J. Qualitative research. Introducing focus groups. BMJ 1995;311:299-302 [FREE Full text] [Medline: 7633241]
69. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. Health Econ 2005;14:487-496. [doi: 10.1002/hec.944] [Medline: 15497198]
70. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. Health Econ 2001;10:779-787. [Medline: 11747057]
71. Sandelowski M. Whatever happened to qualitative description? Res Nurs Health 2000;23:334-340. [Medline: 10940958]
72. Maddigan SL, Majumdar SR, Johnson JA. Understanding the complex associations between patient-provider relationships, self-care behaviours, and health-related quality of life in type 2 diabetes: a structural equation modeling approach. Qual Life Res 2005;14:1489-1500. [Medline: 16110929]
73. Wagner EH, Austin BT, Von KM. Organizing care for patients with chronic illness. Milbank Q 1996;74:511-544. [Medline: 8941260]
74. Lorig KR, Sobel DS, Ritter PL, Laurent D, Hobbs M. Effect of a self-management program on patients with chronic disease. Eff Clin Pract 2001;4:256-262 [FREE Full text] [Medline: 11769298]

75. Holman H, Lorig K. Patient self-management: a key to effectiveness and efficiency in care of chronic disease. Public Health Rep 2004;119:239-243 [FREE Full text] [doi: 10.1016/j.phr.2004.04.002] [Medline: 15158102]
76. Ontario Ministry of Health and Long-Term Care. 2015. Family Health Teams URL: http://www.health.gov.on.ca/en/pro/programs/fht/ [accessed 2015-04-12] [WebCite Cache ID 6fwXzH9Za]

Abbreviations

ACIC: assessment of chronic illness tool
AFHTO: Association of Family Health Teams of Ontario
AQoL-4D: assessment of quality of life measure
CIHR: Canadian Institute for Health Research
ED: emergency department
eHIPP: eHealth Innovation Partnerships Program
EMR: electronic medical record
ePRO: electronic patient reported outcomes
FHT: family health team
GAD7: generalized anxiety disorder
GHS: global health scale
HAD: health administrative data
HAQ: health assessment questionnaires
HQO: Health Quality Ontario
ICES: Institute of Clinical Evaluative Sciences
INB: incremental net benefit
IT: information technology
PAM: patient activation measure
PHQ9: patient health questionnaire
PROMIS: patient reported outcome measurement information system
PSSUQ: post-study system usability questionnaire
QALYs: quality-adjusted life years
SMART: specified-measureable-attainable-realistic-time specific

Edited by G Eysenbach; submitted 11.03.16; this is a non–peer-reviewed article;accepted 13.04.16; published 24.06.16.

Please cite as:
Steele Gray C, Wodchis WP, Upshur R, Cott C, McKinstry B, Mercer S, Palen TE, Ramsay T, Thavorn K, Project Collaborators And Technology Partner, QoC Health Inc
Supporting Goal-Oriented Primary Health Care for Seniors with Complex Care Needs Using Mobile Technology: Evaluation and Implementation of the Health System Performance Research Network, Bridgepoint Electronic Patient Reported Outcome Tool
JMIR Res Protoc 2016;5(2):e126
URL: http://www.researchprotocols.org/2016/2/e126/
doi:10.2196/resprot.5756
PMID:27341765

Protocol

A Research Protocol to Test the Effectiveness of Text Messaging and Reminder Calls to Increase Service Use Referrals in a Community Engagement Program

Deepthi Satheesa Varma[1*], MSW, MPhil, PHD; Mark Hart[1*], EdD, MALS; Denise Sonya McIntyre[1*], BS; Evan Kwiatkowski[1*], MS; Linda Bauer Cottler[1*], MPH, PHD, FACE

College of Public Health and Health Professions and College of Medicine, Department of Epidemiology, University of Florida, Gainesville, FL, United States

[*]all authors contributed equally

Corresponding Author:
Deepthi Satheesa Varma, MSW, MPhil, PHD
College of Public Health and Health Professions and College of Medicine
Department of Epidemiology
University of Florida
2004 Mowry Road
PO Box 100231
Gainesville, FL, 32610
United States
Phone: 1 352 294 5941
Fax: 1 352 273 5365
Email: dvarma@ufl.edu

Abstract

Background: Mobile phoned–based interventions have been increasingly used in clinical populations to improve health and health care delivery. The literature has shown that mobile phone–based text messages (short message service, SMS) are instantaneous, cost effective, and have less chance of being misplaced. Studies using mobile phone based–text messages have reported text messages as effective reminders that have resulted in increased appointment attendance, adherence to treatment, and better self-management. There have been no reports of adverse events when using text messaging in terms of misreading or misinterpreting data, transmitting inaccurate data, losing verbal or nonverbal communication cues, privacy issues, or failure or delay in message delivery. However, the literature has cited a need for personalized messages that are more responsive to individual needs. In addition, there has been a dearth of information on the use of reminders in nonclinical populations.

Objective: The goal of this study is to assess the effectiveness of adding reminders in the form of text messaging versus reminder calls versus text messages and reminder calls to increase use of service referrals provided through community outreach.

Methods: A total of 300 participants will be recruited for the study. Each participant will be randomized to one of three arms: a group that receives only reminder calls (CALLSONLY); a group that receives only text message reminders (TEXTONLY); and a group that receives both reminder calls and text messages (CALLS+TEXT). All groups will receive their reminder intervention on the 15th and 45th day after baseline when they receive medical and social service referrals from the community health workers (CHWs). A standard script will be used to administer the call and text reminders and a 15-item telephone-based satisfaction survey will be administered to assess the participant satisfaction with the process of receiving periodic reminders.

Results: The study is in the recruitment and follow-up phase. The authors anticipate completion of recruitment, interventions, and data entry by July 2016. Preliminary results are expected to be available by September 2016.

Conclusions: This study will provide an opportunity to test the effectiveness of mobile-based interventions on nonclinical, community-recruited populations. In particular, such a protocol would increase the effectiveness of a community-based engagement program by instating a formal reminder system for all program members who receive social and/or medical service referrals during outreach in the community. Findings from this study would guide the development and implementation of reminder protocols for community-based engagement programs nationwide.

(JMIR Res Protoc 2016;5(2):e133) doi:10.2196/resprot.5854

KEYWORDS

text messaging; reminder calls; community engagement; referral use; mHealth

Introduction

Background

There has been a significant increase in the literature on mobile phone–based interventions (mHealth) to improve health care among clinical populations. At the end of 2014, over 3.6 billion people had at least one mobile subscription. It is estimated that by 2020, 4.6 billion people will have a mobile subscription [1]. Recent studies have expressed the need for harnessing the increasing availability and acceptability of mobile phones in health care to enhance contact with health services, self-management, and broadening the scope of mHealth applications [2,3]. Mobile phone–based text messages (short message service, SMS) have been described as 'instantaneous', 'direct', 'mobile', and 'not invasive and ubiquitous'. They also have less chance of being misplaced [4,5]. Other benefits of text messages include the ability to deliver the message wherever the person is, reducing dependence on health care professionals [6,7]. The interventions are also reported to be cost effective and more economical than telephone or postal reminders [6-8]. Studies have shown text messages as effective health care appointment reminders that can result in increased attendance, adherence to treatment, self-management, and maintenance of chronic conditions such as cardiovascular health, asthma, diabetes, obesity, and hypertension [5,6,9-12]. Research on missed health care appointments with a clinical population has shown that mobile phone–based interventions such as periodic phone call reminders and text messages increase the rate of attendance [13].

A study on improvement in attendance in primary care found the text messaging reminder group attended the clinic at a higher rate compared with the control group (odds ratio (OR) 1.59, 95% confidence interval (CI) 1.17-2.17, *P*=.005) [8]. Another study among persons with chronic disease showed the nonattendance rates in the text messaging (OR=0.62, 95%CI 0.41-0.93, *P*=.020) and telephone reminder groups (OR=0.53, 95%CI 0.35-0.81, *P*=.003) were significantly lower than the control group [14]. Text messaging, in weekly intervals, was found to be an effective strategy to enhance adherence to antiretroviral therapy compared with standard care among human immunodeficiency virus (HIV) patients and in improving HIV viral load suppression [15]. Text messaging interventions for smoking cessation and for effective health care service delivery processes were also found to be effective [16,17]. A study on treatment compliance among obstructive sleep apnea patients showed that message reminders via a mHealth application not only resulted in significantly higher treatment compliance but also was satisfactory to patients [18]. A block-randomized control study using a website and SMS-based reminder system among adolescents with asthma has found improvements in self-reported medication adherence (*P*=.011), quality of life (*P*=.037), and self-efficacy (*P*=.016) [19].

There have been no reports of adverse events when using text messaging in terms of misreading or misinterpreting data, transmitting inaccurate data, losing verbal or nonverbal communication cues, privacy issues, or failure or delay in message delivery [6]. Qualitative studies on content and type of text messages highlight the need for tailored and personalized messages that are "responsive to individual needs" [10,20,21]. The literature has captured the use of mHealth applications and reminders systems among clinical populations; however, there has been a dearth of information on the use of reminders in nonclinical populations.

Based on the literature, we proposed and were funded by the University of Florida's Clinical and Translation Science Award Program to carry out a pilot study aimed to apply the qualities of mobile phone–based interventions to improve the utilization rate of medical and social service referrals provided to community members by the community health workers (CHWs) at HealthStreet–the community engagement initiative at the University of Florida. HealthStreet aims to bridge the gap between the community and research by providing medical and social service referrals based on their individual needs and concerns while providing opportunities for community members to become involved in research. CHWs from HealthStreet assess community members at laundromats, grocery stores, libraries, hair salons, bus stops, senior centers, community centers, health fairs, and other places. The assessment includes demographic characteristics, medical history, health and neighborhood concerns, access to care, attitudes toward research, history of research participation, drug and alcohol history, and current medication use. Community members are then followed-up with at 30 and 60 days to assess use of services. Approximately 63% of HealthStreet's participants are African American, 30% did not see a doctor in the last 6 months in spite of having at least one health concern, and approximately 41% of HealthStreet's participants report having no medical insurance. Therefore, the medical and social service referrals provided by the CHWs are especially important to this population. Prior data on use of service referrals at HealthStreet showed that 81% of participants who received at least one referral did not use any relevant referrals. Nearly 1/3 of participants indicated a barrier to service use that would be resolved with a simple reminder. Several of them mentioned that they would have used the services, if they had had the referral details available when needed.

Using Fogg's Behavior Model [22], based on the persuasive power of technology for behavior changes [23], we hypothesize that simple mobile phone–based reminders will act as a "motivator" and a "trigger," thereby encouraging the individual to use the provided referral service. Further, by sending the details of the referrals during the reminder text or the call will also solve the barrier of losing the referral slip and/or not having the referral details at hand when required.

HealthStreet data also showed 72% of HealthStreet participants regularly use text messaging, which made mobile phone–based interventions an ideal choice for a pilot study. With the decreasing cost of mobile phones and text messaging services

and increasing availability of different service providers, mobile phone–based interventions could be considered an economical and efficient way to communicate.

We proposed to develop and test the effectiveness of a mobile phone–based intervention–referral reminder calls (CALLSONLY) versus text message reminders (TEXTONLY) versus both text message and reminder calls (CALLS+TEXT)–to increase the rate of service referral usage among HealthStreet participants. Additionally, this pilot study provided an opportunity to assess the HealthStreet participant's satisfaction receiving reminder text messages.

Overall Aim

The aim of this study is to increase use of service referrals provided through community outreach using a mHealth intervention (adding reminders in the form of text messages or reminder calls or text messages and reminder calls).

Specific Objectives

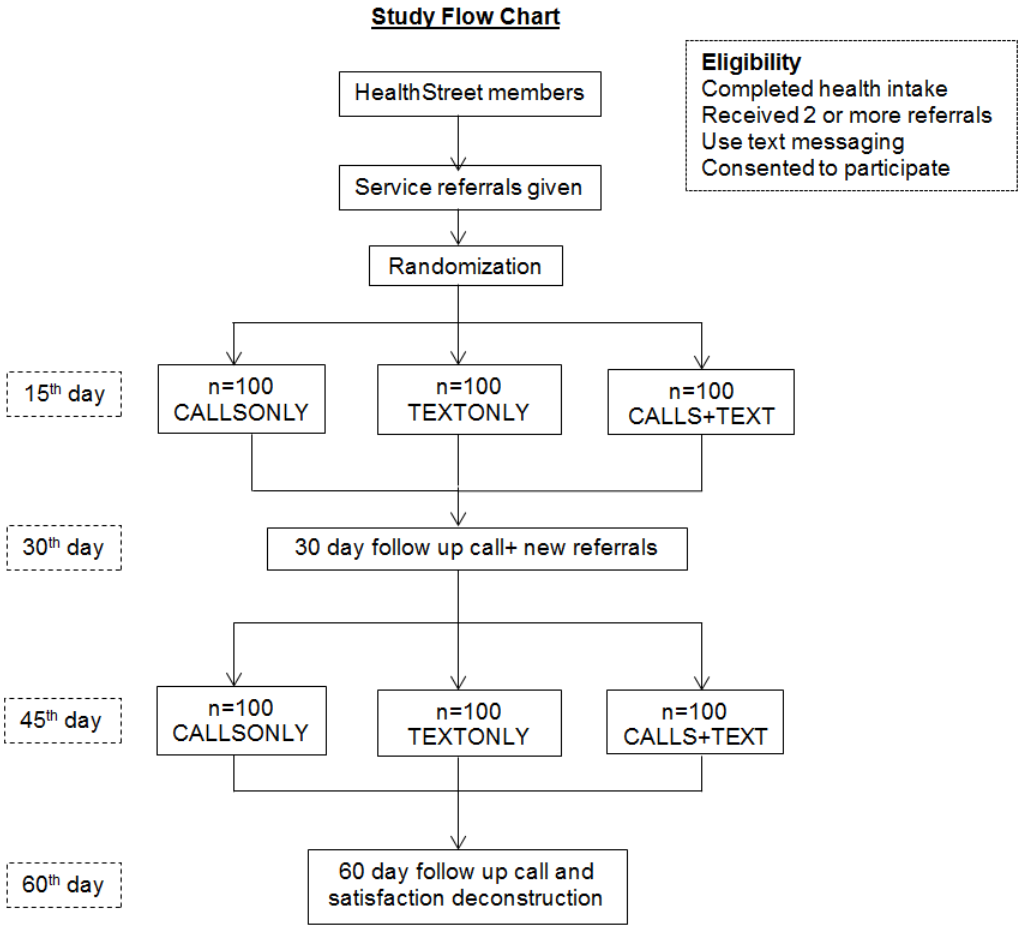
The specific objectives for this study are to: (1) develop an effective and personalized text messaging system to increase use of referrals given by HealthStreet CHWs, (2) compare the effectiveness of three new interventions on referral use (TEXTONLY vs CALLSONLY vs CALLS+TEXT) at 30 and 60 days post baseline, and (3) deconstruct the intervention through a satisfaction/feasibility survey to understand HealthStreet participants' satisfaction with these periodic reminders.

Methods

Study Design

A 12-month study is being conducted with 300 eligible community members from Alachua and Duval counties in North Central Florida. The study has three arms: a group that receives only reminder calls (CALLSONLY); a group that receives only text message reminders (TEXTONLY); and a group that receives both reminder calls and text messages (CALLS+TEXT) (Figure 1). All groups receive their reminder intervention on the 15thand 45th day after baseline when they receive referrals from the CHWs. All groups then receive HealthStreet's usual 30 and 60 day follow-up call that assesses use of the referrals provided at baseline. The 15thand 45thday, which falls in the middle of 0 to 30 days and 31 to 60 days, was decided for reminders because that will provide adequate number of days to use the referral from the baseline assessment date and/or the previous follow-up call date. All follow-up calls are made using the existing institutional review board–approved HealthStreet referral tracking protocol. Additionally, a satisfaction survey is also administered to all participants at 60 days to assess satisfaction with the different types of reminders and follow-up processes.

Figure 1. Study flow chart: recruitment and intervention groups.



Measures

To develop and implement a reminder call and text messaging protocol intervention to improve use of medical and social referrals provided to HealthStreet members by CHWs. The following measures are used:

Reminder calls: a standard script (Multimedia Appendix 1) is administered to remind the participant about the location, the date of contact with the HealthStreet CHWs as well as the service referrals provided to them at baseline. The call specifically reminds the person to use the referrals that were provided to them. Data on the use of referrals are collected only during the 30- and 60-day follow-up calls.

Text messaging: text messaging is conducted using the Qualtrics SMS (Figure 2) service, which is widely used in higher education research. The Qualtrics SMS service is compliant with the Health Insurance Portability and Accountability Act for data security and uses a secure local server for the data as it pushes out messages through an encrypted server. All data are stored in an internal secure server and only phone numbers and text messages are housed in the secure Qualtrics server. Once messages have been approved, and scheduled, they are sent out to their intended audience through an encrypted server that Qualtrics itself has the inability to track. Ultimately, this tool is a one-way directional message service, with only a confirmation text from the participants coming back to the researchers. This information, coupled with the backend analytic tools of Qualtrics, allows for data to be collected on who received the messages, which can then be compared with participant reported use of referrals.

This text messaging software is installed for this project on a computer at HealthStreet, Gainesville. An excel spread sheet with the participant's name, date of contact, and referral details generated by the REDCap database, is synchronized with a service that pushes out and tracks the messages. The secure encrypted database houses the participant's name, phone number, and service referral record, while separating it by various cohorts based on the date of referral and follow-up. On the designated day for text reminders, a predesigned template message (Figure 3) reminding them of their contact with the CHWs is used by the study coordinator to enter the participant's date, venue of contact with the CHW, and the list of referrals provided to him/her during the health intake. This message also prompts the participant to call HealthStreet in case they need more information regarding the referrals. This text messaging service is confidential and has the ability to also be embedded as a social media message, to use Quick Response codes if required, as well as track the delivery and receipt of messages through back-end analytic tools.

Satisfaction survey: a brief 15-item telephone-based survey is administered to assess the satisfaction with the process of receiving periodic reminders from HealthStreet. This survey assesses the participant's opinions regarding the content of the text message reminders received in this study, apart from the usual 60-day follow-up questions on use of the referrals received from HealthStreet. In particular, this survey aims to gather feedback about the participant's overall satisfaction with the reminder call and/or reminder text. The survey also assesses the participant's perception of the reminder length, frequency, and helpfulness. Finally, this survey evaluates if the participant used their referrals because of the reminders.

Figure 2. Qualtrics SMS surveys.

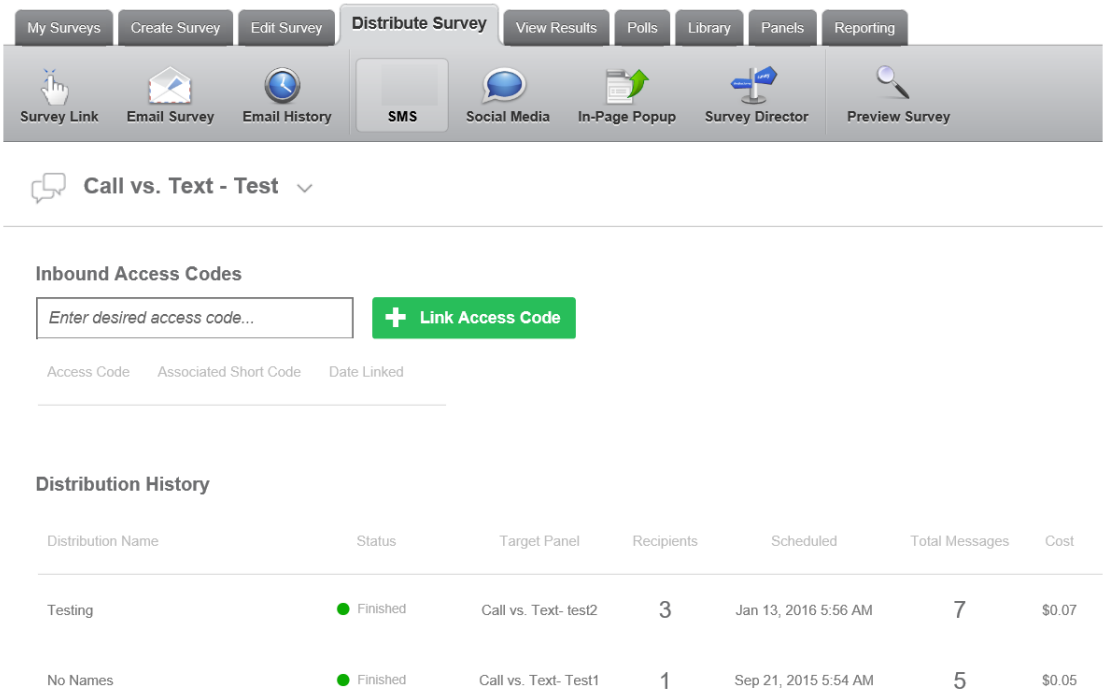
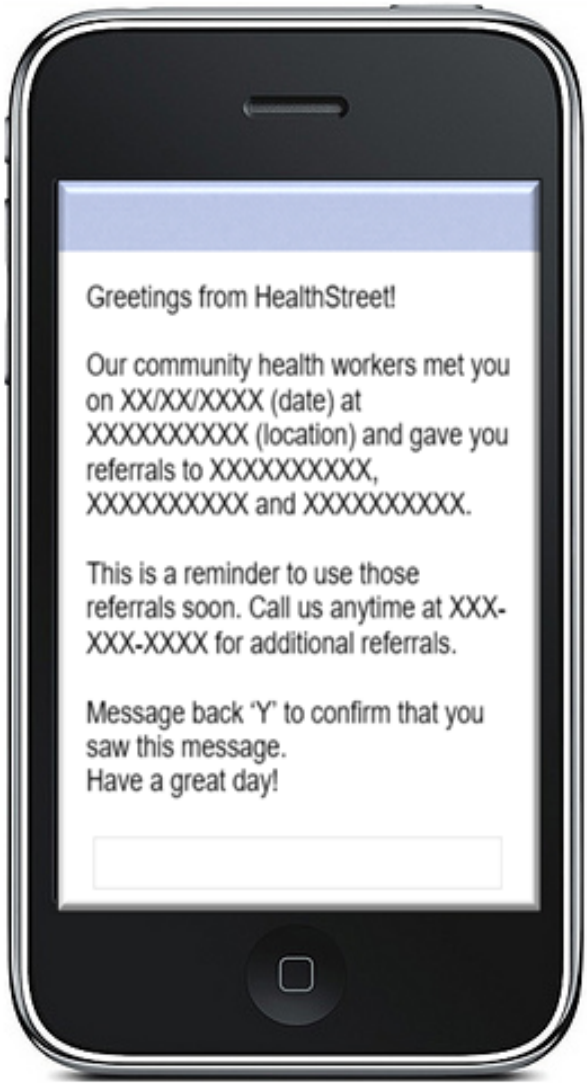


Figure 3. Script for text message reminder.



Staff Recruitment and Training

The study coordinator was trained on the scripts for reminder calls, administering the telephone-based satisfaction survey, randomization procedures, and study recruitment and intervention protocols. All CHWs and staff members were trained on administering the study informed consent and randomization letter distribution. The Qualtrics SMS software was also beta-tested using the proposed text reminder scripts.

Data Collection

There is no risk of this study interfering with HealthStreet data, because exporting this data does not affect the value of any data in HealthStreet's dataset. In addition to using data already collected by HealthStreet, this study collects data on the results of 15/45 day texts/calls reminders, and from the satisfaction survey. This data is kept separate from HealthStreet data, and is accessible to the Principal Investigator (PI), Co-PI, research statistician, and study coordinator.

Data Management

The data manager at HealthStreet along with the study coordinator assists the PI in all aspects of data management. All data are stored at HealthStreet, Gainesville and available only to the PI, Co-PI, research statistician, and the study coordinator. This study follows a data management process that is similar to what is being currently followed at HealthStreet using Microsoft Access on secured local servers. Data needed for the text messaging software are generated from a report run on HealthStreet data, without any risk of interfering with HealthStreet data quality. All data is stored in locked filing cabinets or on secure computer servers with security passwords.

Interventions

Every Monday, the research statistician generates a list of the names, participant's unique study identification (ID) number, contact numbers, and the list of referral services of participants who need to be contacted, either for a reminder call, text message, or for 30- or 60-day follow-up. The list is handed over to the study coordinator who takes the appropriate action for each participant, after verifying this list with the intervention tracking database to ensure that all participants on the list are indeed due for their assigned intervention. The same list and procedure is used for the program algorithm that sends text messages to the participants. All participants are assigned a HealthStreet personal identifier which is used to generate an excel sheet with the participant's date of contact, study ID,

randomization number, and 15th, 30th, 45th, and 60th day due dates for intervention.

Sample Size

The sample size for this study is 100 participants in each arm of the study. The planning compliance rate difference is 16% for a pair of treatments (22% vs 38%). The key nuisance parameter that affects planning is the probability of the second visit being compliant given the first visit is compliant. We shall presume a strong association for an individual, half way between independence and full dependence. Thus, for a treatment group with a compliance rate of 22%, the distribution would be 17% comply with one of two, and 13.5% comply with both. Under independence (complete dependence), 22% (5%) would comply to both, with the average 13.5%. For a treatment group with a compliance rate of 38%, the distribution would be 47.1% would comply with one of two, and 14.4% comply with both. With N=100 per group, and the above repeated measures structure, we have 80% power to detect a difference of 16% (22% vs 38%) (ie, personal means for two-trials of 0.44 vs. 0.76) at P=.017 (two-sided). Please note that we took a conservative approach using a strong within subject association. If it was weaker, power would be somewhat better.

Eligibility

Eligibility was determined by the following criteria: all community members between 18 and 80 years of age; all who complete a HealthStreet health intake with the CHWs in Alachua and Duval counties in North Central Florida; must use the text messaging feature on their mobile phone; and have received two or more medical or social service referrals.

Recruitment

Approximately 40 new community members are enlisted each week and 71% of them report using text messaging. We are recruiting 300 participants from Alachua and Duval counties and considered a 15% attrition rate at the 60-day follow-up. CHWs screen each participant for text capability during the health intake using the HealthStreet intake form. All eligible participants are informed about this study after the administration of the health intake. Those who express interest are given the study-specific informed consent that requests consent for receiving reminder phone calls and text messages by the CHW. All those who give consent are randomly assigned to one of three groups (n=100 each) to receive one of the interventions. The randomization letters, generated by a statistician blinded to the assignment, are sealed and all CHWs carry these letters and are trained on dispersing them. The CHW opens the letter in the presence of the participant and explains the assignment. Thereafter, the participant dates and initials the letter. The study coordinator and PI ensure appropriate implementation of the proposed recruitment and randomization procedures throughout the study period. A detailed tracking log is being maintained to track the date on which the text messages were sent and/or reminder calls were made and the participant's response to each of these interventions. This study has been reviewed and approved by the institutional review board at University of Florida.

Data Analysis

Data analysis will be performed using SAS 9.4. The primary outcome of this study is use of service referrals as reported at the 30- and 60-day follow-up calls. At each time point, participants will have either used no referrals, or used one or more referrals. The data will therefore be displayed in a 3 × 2 contingency table with treatments as columns and the use of referrals as rows. Chi-square tests will be used to analyze the use of referrals by treatment group.

Secondary analysis will include ordinal logistic regression with the use of referrals as the dependent variable and predictors including age, gender, race/ethnicity, access to health care, and others as dependent variables. This will be done separately within treatment categories. Logistic regression will also be used to analyze the number of referrals used at each time point. Additionally, the satisfaction survey data will be analyzed with respect to gender, age group, education, and type of reminders received to understand the acceptability of mobile phone–based interventions among community members.

Results

Current Status

Currently, the study is in the participant recruitment and follow-up phase. The authors anticipate completion of recruitment, interventions, and data entry by July 2016. The analysis of all data and the preliminary results should be available by September 2016.

Dissemination Policy

Study results will be published in high impact, peer-reviewed scientific journals.

Discussion

Trial Implications

This study aims to test the feasibility of using text messages and reminder calls to improve the use of social and medical service referrals provided to community members by CHWs. A second objective is to understand community member's satisfaction regarding receiving text messages and calls as reminders and obtain their suggestions for improving this channel of communication.

Previous data from HealthStreet has indicated "losing the referral slip" or "forgetfulness" as one of the important reasons for not using the medical and social service referrals provided by the CHWs to HealthStreet participants. These reminders will assist in removing the above mentioned barriers to utilization. Additionally, HealthStreet is currently planning to integrate reminder texts and calls to remind HealthStreet participants of their referrals, and various events organized at HealthStreet. Findings from this study will help to understand which type of reminders–TEXTONLY, CALLSONLY, or TEXT+CALLS–are most effective, useful and acceptable to the participants. The satisfaction survey administered in this study also gives us detailed information on participant's preferred frequency of reminders. Further, this pilot study will assist in calculating the

additional personnel and infrastructure including software related-cost involved in implementing a reminder protocol at HealthStreet. Most importantly, findings from this study could be applied to other community engagement initiatives around the country.

Conclusions

The aim of this pilot study is to assess the effectiveness of adding reminders in the form of text messaging versus standard reminder calls to increase use of service referrals provided through community outreach. This pilot project would provide an excellent opportunity to test the effectiveness of mobile-based interventions on a nonclinical, community-recruited population such as those served by HealthStreet. Currently, HealthStreet does not have a formal reminder system regarding the referrals provided during the initial contact by the CHWs. Based on the findings from this study HealthStreet would develop and implement a reminder protocol for all HealthStreet members who receive social and/or medical service referrals during community outreach, thereby increasing the effectiveness of HealthStreet in the community. Additionally, the findings from this study would be also beneficial to similar community-based engagement programs nationwide.

Acknowledgments

Research reported in this publication was supported by the University of Florida Clinical and Translational Science Institute, which is supported in part by the National Institutes of Health National Center for Advancing Translational Sciences under award number UL1TR001427. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Authors' Contributions

All authors drafted, read, and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Script for reminder calls.

[PDF File (Adobe PDF File), 24KB - resprot_v5i2e133_app1.pdf]

Multimedia Appendix 2

Protocol reviewer comments.

[PDF File (Adobe PDF File), 396KB - resprot_v5i2e133_app2.pdf]

References

1. GSMA Intelligence. The Mobile Economy 2015. 2015. URL: http://gsmamobileeconomy.com/global/GSMA_Global_Mobile_Economy_Report_2015.pdf [accessed 2016-06-06] [WebCite Cache ID 6i4Cw3fh8]
2. Kamis K, Janevic MR, Marinec N, Jantz R, Valverde H, Piette JD. A study of mobile phone use among patients with noncommunicable diseases in La Paz, Bolivia: implications for mHealth research and development. Global Health 2015;11:30 [FREE Full text] [doi: 10.1186/s12992-015-0115-y] [Medline: 26141528]
3. Källander K, Tibenderana J, Akpogheneta O, Strachan D, Hill Z, ten Asbroek AHA, et al. Mobile health (mHealth) approaches and lessons for increased performance and retention of community health workers in low- and middle-income countries: a review. J Med Internet Res 2013;15:e17 [FREE Full text] [doi: 10.2196/jmir.2130] [Medline: 23353680]
4. Kaplan WA. Can the ubiquitous power of mobile phones be used to improve health outcomes in developing countries? Global Health 2006:9 [FREE Full text] [doi: 10.1186/1744-8603-2-9] [Medline: 16719925]
5. Atun RA, Sittampalam SR. A review of the characteristics and benefits of SMS in delivering healthcare. In: Atun RA, editor. The Role of Mobile Phones in Increasing Accessibility and Efficiency in Healthcare. London, UK: Vodafone Group Plc; 2006:18-28.
6. Car J, Gurol-Urganci I, de Jongh T, Vodopivec-Jamsek V, Atun R. Mobile phone messaging reminders for attendance at healthcare appointments. Cochrane Database Syst Rev 2012;7:CD007458. [doi: 10.1002/14651858.CD007458.pub2] [Medline: 22786507]
7. Merchán-Baeza JA, Gonzalez-Sanchez M, Cuesta-Vargas A. Clinical effect size of an educational intervention in the home and compliance with mobile phone-based reminders for people who suffer from stroke: protocol of a randomized controlled trial. JMIR Res Protoc 2015;4:e33 [FREE Full text] [doi: 10.2196/resprot.4034] [Medline: 25757808]

8. Leong KC, Chen WS, Leong KW, Mastura I, Mimi O, Sheikh MA, et al. The use of text messaging to improve attendance in primary care: a randomized controlled trial. Fam Pract 2006;23:699-705 [FREE Full text] [doi: 10.1093/fampra/cml044] [Medline: 16916871]
9. Stephens J, Allen J. Mobile phone interventions to increase physical activity and reduce weight: a systematic review. J Cardiovasc Nurs 2013;28:320-329 [FREE Full text] [doi: 10.1097/JCN.0b013e318250a3e7] [Medline: 22635061]
10. Burner ER, Menchine MD, Kubicek K, Robles M, Arora S. Perceptions of successful cues to action and opportunities to augment behavioral triggers in diabetes self-management: qualitative analysis of a mobile intervention for low-income Latinos with diabetes. J Med Internet Res 2014;16:e25 [FREE Full text] [doi: 10.2196/jmir.2881] [Medline: 24476784]
11. Liu Z, Chen S, Zhang G, Lin A. Mobile phone-based lifestyle intervention for reducing overall cardiovascular disease risk in Guangzhou, China: a pilot study. Int J Environ Res Public Health 2015;12:15993-16004 [FREE Full text] [doi: 10.3390/ijerph121215037] [Medline: 26694436]
12. Militello L, Melnyk BM, Hekler EB, Small L, Jacobson D. Automated behavioral text messaging and face-to-face intervention for parents of overweight or obese preschool children: results from a pilot study. JMIR Mhealth Uhealth 2016;4:e21 [FREE Full text] [doi: 10.2196/mhealth.4398] [Medline: 26976387]
13. Gurol-Urganci I, de JT, Vodopivec-Jamsek V, Atun R, Car J. Mobile phone messaging reminders for attendance at healthcare appointments. Cochrane Database Syst Rev 2013;12:CD007458. [doi: 10.1002/14651858.CD007458.pub3] [Medline: 24310741]
14. Liew S, Tong SF, Lee VKM, Ng CJ, Leong KC, Teng CL. Text messaging reminders to reduce non-attendance in chronic disease follow-up: a clinical trial. Br J Gen Pract 2009;59:916-920 [FREE Full text] [doi: 10.3399/bjgp09X472250] [Medline: 19712544]
15. Horvath T, Azman H, Kennedy GE, Rutherford GW. Mobile phone text messaging for promoting adherence to antiretroviral therapy in patients with HIV infection. Cochrane Database Syst Rev 2012;3:CD009756. [doi: 10.1002/14651858.CD009756] [Medline: 22419345]
16. Vodopivec-Jamsek V, de Jongh T, Gurol-Urganci I, Atun R, Car J. Mobile phone messaging for preventive health care. Cochrane Database Syst Rev 2012;12:CD007457. [doi: 10.1002/14651858.CD007457.pub2] [Medline: 23235643]
17. Free C, Phillips G, Watson L, Galli L, Felix L, Edwards P, et al. The effectiveness of mobile-health technologies to improve health care service delivery processes: a systematic review and meta-analysis. PLoS Med 2013;10:e1001363 [FREE Full text] [doi: 10.1371/journal.pmed.1001363] [Medline: 23458994]
18. Isetta V, Torres M, González K, Ruiz C, Dalmases M, Embid C, et al. A New mHealth application to support treatment of sleep apnoea patients. J Telemed Telecare 2015. [doi: 10.1177/1357633X15621848] [Medline: 26672606]
19. Johnson K, Patterson BL, Ho YX, Chen Q, Nian H, Davison CL, et al. The feasibility of text reminders to improve medication adherence in adolescents with asthma. J Am Med Inform Assoc 2015. [doi: 10.1093/jamia/ocv158] [Medline: 26661717]
20. Ranney ML, Choo EK, Cunningham RM, Spirito A, Thorsen M, Mello MJ, et al. Acceptability, language, and structure of text message-based behavioral interventions for high-risk adolescent females: a qualitative study. J Adolesc Health 2014;55:33-40 [FREE Full text] [doi: 10.1016/j.jadohealth.2013.12.017] [Medline: 24559973]
21. Ahlers-Schmidt CR, Chesser AK, Nguyen T, Brannon J, Hart TA, Williams KS, et al. Feasibility of a randomized controlled trial to evaluate Text Reminders for Immunization Compliance in Kids (TRICKs). Vaccine 2012;30:5305-5309. [doi: 10.1016/j.vaccine.2012.06.058] [Medline: 22750044]
22. BJ Fogg's Behavior Model. Palo Alto, CA: BJ Fogg, Persuasive Technology Lab at Stanford University; 2007. What Causes Behavior Change? URL: http://www.behaviormodel.org/ [accessed 2016-02-16] [WebCite Cache ID 6i48xfzLf]
23. Fogg B. 4th International Conference on Persuasive Technology. Claremont, CA: ACM; 2009 Apr 26. A Behavior Model for Persuasive Design URL: http://bjfogg.com/fbm_files/page4_1.pdf [accessed 2016-02-16] [WebCite Cache ID 6i49yHWdI]

Abbreviations

CHWs: community health workers
CI: confidence interval
ID: identification
HIV: human immunodeficiency virus
OR: odds ratio
PI: principal investigator
SMS: short message service

Edited by G Eysenbach; submitted 08.04.16; peer-reviewed by S Liu, E Burner, W Lo; comments to author 06.05.16; accepted 19.05.16; published 28.06.16.

Please cite as:
Varma DS, Hart M, McIntyre DS, Kwiatkowski E, Cottler LB
A Research Protocol to Test the Effectiveness of Text Messaging and Reminder Calls to Increase Service Use Referrals in a Community Engagement Program
JMIR Res Protoc 2016;5(2):e133
URL: http://www.researchprotocols.org/2016/2/e133/
doi:10.2196/resprot.5854
PMID:27353040

Proposal

Risk Factors for Low Back Disorders in Saskatchewan Farmers: Field-based Exposure Assessment to Build a Foundation for Epidemiological Studies

Catherine Trask[1], PhD; Brenna Bath[1], PhD; Peter W Johnson[2], PhD; Kay Teschke[3], PhD

[1]University of Saskatchewan, Saskatoon, SK, Canada
[2]University of Washington, Seattle, WA, United States
[3]University of British Columbia, Vancouver, BC, Canada

Corresponding Author:
Catherine Trask, PhD
University of Saskatchewan
104 Clinic Place PO Box 23
Saskatoon, SK, S7N 5E5
Canada
Phone: 1 3069665544
Fax: 1 3069665544
Email: cmtrask@gmail.com

Abstract

Background: Studies of many geographical settings and agricultural commodities show that low back disorders are an important public health issue among farmers, who represent a special rural population. However, few studies have examined the impact of low back disorders on farmers' work or the strategies that they adopt to avoid associated pain and disability.

Objective: This study protocol will investigate 3 issues related to low back disorders in Saskatchewan farmers: (1) the vibration, heavy lifting, and awkward postures farmers encounter during their work that might contribute to low back disorders; (2) the impact low back disorders have on farmers in terms of their ability to work; and (3) the types of preventative measures and solutions that farmers implement to reduce the occurrence of low back pain.

Methods: To answer these questions, researchers will travel to 30 farms to make measurements of vibration, lifting, and posture during the farmers' regular work tasks. Farmers will be interviewed about any pain and/or disability using standardized interview questions. Farmers will also be asked about safety measures they have implemented at their farm, such as modified tools or equipment, to reduce the occurrence of low back disorders or pain.

Results: Data collection is currently underway for this study, with the intention to complete all data collection and analysis by the end of 2018.

Conclusions: Occupational determinants of health such as vibration, heavy lifting, and awkward postures are important in the development and progression of low back disorders, and the results of this study will allow for cost-effective epidemiological studies of these determinants in the future. In identifying prevention strategies, this study will also facilitate future research evaluating the effectiveness of safety measures.

(JMIR Res Protoc 2016;5(2):e111) doi:10.2196/resprot.5573

KEYWORDS

back pain; agriculture; occupational exposure; risk factors

Introduction

Low back disorders are a prevalent and expensive public health problem. Estimates of point prevalence of back pain in the US general population range from 12% to 33%, 1-year prevalence from 22% to 65%, and lifetime prevalence up to 84% [1-3]. In the Netherlands, the estimated total societal cost of back disorder is 1.7% of the country's gross national product [4]. There is an even greater impact in the agricultural industry; a recent systematic review found that the prevalence of musculoskeletal disorders was consistently higher in farmers than nonfarmer populations, with low back disorders being the most common regional musculoskeletal problem reported [5]. Most

surveillance studies have focused on low back disorders, which, as in other industries, represent the bulk of musculoskeletal disorders in farming [5-7]. Across studies of many types of farming, the average lifetime prevalence of low back pain was 75% (95% CI 67-82) and average 1-year prevalence was 48% (95% CI 42-55) [5]. Over the whole working population, low back injuries show particularly high disability, loss of work time, and economic burden [8]. Musculoskeletal disorders have been shown to decrease productivity in construction and industrial workers even when workers do not take time off [9], and farm income is lower when operators have musculoskeletal-related disability [10]. A survey of Iowa farmers showed that they had twice the risk of low back pain compared with the general working population and were 8 times more likely to make major changes in their work activities as a result of low back pain [11].

Reducing the occurrence of low back disorder requires high-resolution, cost-effective exposure assessment techniques to both study disorder mechanisms and identify any changes in exposure that may result from interventions. Epidemiological studies have identified some broad categories of working exposures that are probable risk factors for low back disorders in farmers. Manual material handling or "heavy lifting," has been shown to be a strong risk factor, with odds ratios ranging from 1.59 to 2.74 [6,12]. Driving tractors has been shown to increase the prevalence of sciatic pain (ie, leg pain associated with low back disorder), unspecified low back pain [13], and the prevalence of lower back and hip joint diseases [12]. This is suspected to be due to whole-body vibration (WBV) and twisted postures during farm vehicle operation, but previous studies have not assessed exposure adequately to determine potential mechanisms. Other categories of work exposure include awkward postures, independent of vehicle operation [6,12,14,15], high work pace and workload [16], and preexisting injury or working with an injury [6]. And, finally, agricultural work tasks have been identified as having high exposure to biomechanical risk factors, although this has yet to be confirmed epidemiologically [17].

However, multiple reviews have cited low-quality exposure assessments as a limiting factor in furthering the understanding of the relationship between farming and work-related musculoskeletal disorders [5,18-21]. Many epidemiological studies characterize exposure via job title or simple self-report, which lack the precision needed to characterize exposure-response relationships, and observation categories such as "low," "medium," and "high" are inadequate to detect changes in intervention studies. Some notable exceptions are studies using objective, directly measured exposure, identifying peak and cumulative muscle activity as independent contributors to injury [22], and inclinometer-assessed shoulder posture related to shoulder disorders [23]. Although these objective measures provide a lot of insight, such studies have been rare because of the cost and challenges associated with detailed exposure assessment. When multiple employers or worksites are involved, recruitment and travel can contribute substantially to the cost of on-site electronic data collection [24,25], rendering such measurements impractical for large-scale epidemiological research in the context of traveling to rural farms.

Where direct objective measurements are costly or not feasible, exposure modeling offers an alternative method to extend the utility of direct objective measurements and allow cost-efficient, quantitative exposure assessment for large numbers of workers. Exposure modeling involves concurrent direct objective measurement of exposure and collection of workplace, production, and other characteristics (via observation or surveys) that directly or indirectly increase or decrease physical exposures. The data are used in development of empirical statistical models where characteristics associated with exposure are used to predict exposures in situations where direct measurements cannot be made but where data on the other important work characteristics can be obtained instead. Because surveys are cheaper and allow for multiple measures, the models may provide better estimates of long-term average exposures than direct measurements, which are usually collected for a short time on a small number of individuals. This methodology has long been used in industrial hygiene to estimate a wide variety of airborne exposures [26] such as wood dust [27]. Exposure modeling has also been used successfully for physical exposures, including trunk posture [28], electromyography [29], and WBV [30,31]. An additional benefit of these models is that they identify important determinants of physical exposure and tasks or equipment associated with lower exposures, providing an insight into development of interventions and prevention strategies.

The need for injury prevention research in agriculture has been widely acknowledged [17,32]. Despite this, very few ergonomic interventions have been systematically evaluated in agricultural contexts. Most intervention studies examine exposures with and without modified tools or equipment during lab-based or simulated work [33-35], or in small, uncontrolled field studies [36,37]. Prerequisite for any systematic evaluation of an intervention is an intervention capable of having a substantial effect on adverse working exposures. Existing ergonomic interventions for agriculture (mostly unproven via scientific study) have been primarily targeted toward market fruit and vegetable, nursery, and dairy production [38] rather than large-scale crop farming operations. When identifying workplace controls and interventions, workers are an acknowledged source of information, through both the participatory ergonomics approach [39] and their independent work on equipment modifications and prototypes. It is anticipated that this will be particularly true among farmers given their self-direction and vested interest in productivity; many farmers also have fabrication capacity (ie, skills and equipment for carpentry, welding, and metal fabrication).

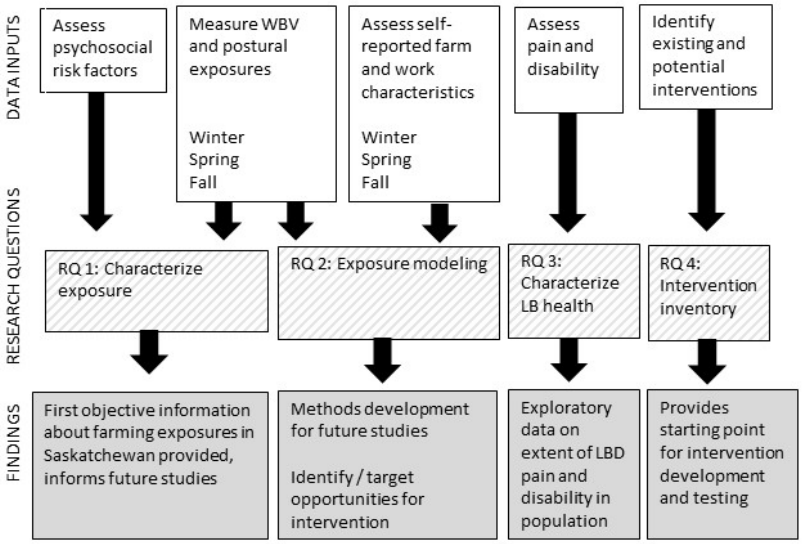
This paper describes the design and rationale of a field-based investigation of the risk factors for low back disorders in farmers. This study will quantify the level, duration, and frequency of whole-body (vehicle) vibration, awkward postures, manual material handling, and psychosocial risk factors encountered by farmers at work, then determine whether these exposures can be cost-effectively predicted, evaluated, and modeled using observed and self-reported farm and work task characteristics. Additionally, the study will explore the degree of severity of low back disorder–related pain and disability experienced by farmers, as well as farmer-initiated ergonomic

preventative measures, and opportunities for self-initiated prevention of low back disorders identified by farmers.

Methods

To meet its exposure assessment aims, researchers will travel to rural farms throughout the year to collect direct and self-reported exposure data, as well as low back health and information on farmer-initiated interventions. The relationship of collected data to research objectives is shown schematically in Figure 1.

Figure 1. Research design schematic showing the relationship between research questions the data collected in the study (white boxes), the research questions (striped boxes), and contributions to state of knowledge and future research (grey boxes).



Study Population, Recruitment, and Sampling Strategy

Farmers in the Canadian province of Saskatchewan are a unique rural population whose low back disorders are largely underserved by both research and occupational prevention efforts. There are 44,329 farms in Saskatchewan, producing commodities like grain, oil seeds, and pulses, as well as poultry, dairy, beef, and pork [40]. These farms require a variety of work tasks: operation of planting and harvesting machinery, equipment and building maintenance, and animal care. The physical demands of these tasks involve exposure to risk factors associated with low back disorders, and farmers have a large cumulative lifetime dose and one of the highest rates of point prevalence for low back pain. Farm work often starts at a very young age and continues beyond typical retirement age [5,41]; 52.7% of Canadian farm operators work more than 40 hours per week on their farm, and 48% also work off the farm [40].

The study will consist of a sample of 24 farms participating in the Saskatchewan Farm Injury Cohort Study. The first phase of this postal survey found that many Saskatchewan farms have mixed production; almost 89% produce grain, 52.7% produce beef, and 6.8% produce other animals [42]. For practical purposes, all eligible farms will reside within 400 km of Saskatoon. Adult principal farm operators will be invited to participate, first by post and then with a follow-up phone call. If farm operators decline to participate, the next randomly selected farm will be invited. In addition to principal farm operators, we will attempt to recruit an additional adult farm worker on each farm for measurement in order to expand the work roles and task types included in the study. Additional workers will be eligible if they perform farm tasks at least 12 weeks of the year. Given the occupational structure indicated by prior surveys of this group, we anticipate being able to assess 2 people on at least 50% of farms [42] for a total of 36 participants in the study. Each farm will be visited for on-site data collection 3 times during a calendar year for a total of 108 farm measurements. Measurements will be scheduled throughout a 1-year period to account for seasonal variability in work tasks and exposures: spring (planting, April-June), fall (harvest, August-September), winter (land and equipment maintenance, November-March).

Data Collection

Three types of data collection will be performed during measurement visits: direct measurement of exposure using direct objective measurements of physical exposures; a structured in-person interview on back health and occupational exposures; and a semistructured interview to identify any ergonomic or safety-related measures designed to reduce or mitigate exposure to low back risk factors. This data collection will be quite intensive. The recruitment, scheduling, and travel involved in on-farm data collection will be substantial but will provide an opportunity to collect information that will support hypothesis generation and evaluate measurement strategies for feasibility. Measurement protocols will be developed, pilot-tested, and refined with the collaboration of the Prairie Agricultural Machinery Institute (PAMI) and University of Saskatchewan research farms; this will ensure that the methods are feasible in farming contexts and minimize disruption of work activities.

Direct objective measurements of WBV, trunk posture, and manual material handling and a brief exposure self-report will be made on all 3 seasonal farm visits for the duration of farm work activities. Mounting, calibrating, and removing equipment will take approximately 20 minutes. Measurement visits will be scheduled by phone to determine a start time and the anticipated duration of measurements.

Direct Exposure Measurements

Whole-body vibration from vehicles will be measured according to the ISO 2631 guidelines [43] with triaxial accelerometer (Series 2A triaxial accelerometer, NexGen Ergonomics, Montreal, Canada) placed at the seat-operator interface. Vibration data will be recorded using a MWX8 DataLOG (Biometrics Ltd, Newport, UK) with a sampling rate of 1000 Hz, then analyzed using custom software to determine standard exposure metrics including time-weighted 8-hour root-mean-square (RMS) A(8); 8-hour vibration dose value, VDV(8); and 8-hour static compressive dose, Sed(8).

Trunk posture will be quantified using wearable, data-logging, battery-powered inertial sensors (I2M Inertial Measurement Unit, Human Motion Analysis), which allow for dynamic assessment and high-resolution data logging in 3 dimensions: flexion-extension, lateral flexion, and spinal rotation. These data will be analyzed using Human Motion Analysis software to develop common research exposure metrics: amplitude probability distribution function percentiles (10th, 50th, and 90th), rest periods, and percentage of time spent above key exposure levels: >15, >30, > 45, >60, and 90 degrees of trunk flexion [44].

Observation of Manual Handling

Manual material handling tasks, including vehicle and building maintenance, animal care, and seed preparation, will be video-recorded using a digital video camcorder (Sony Handycam HD). Exposure to manual handling will be summarized by reviewing the data with Observer XT event-logging software (Noldus Information Technology Inc, Leesburg, USA) into daily counts and durations, and then compared with risk assessment guidelines such as the National Institute for Occupational Safety and Health (NIOSH) lifting equation, American Conference of Industrial Hygienists (ACGIH) Lifting threshold limit value (TLV), University of Michigan's Three-Dimensional Static Strength Prediction Program (3DSSPP) and psychophysical acceptability tables [45,46].

In-Depth Interview on Exposure and Low Back Health

A structured, in-person, on-farm interview will be conducted once during the winter visit, at periods that will not be disruptive to workflow. The interview will include sections on working exposures to risk factors associated with low back disorders and adverse low back health. Farm, vehicle, and task characteristics potentially related to exposures (see Table 1) will be assessed using previously published questionnaire items, where available [28,30,47,48]. Exposure questions will assess "typical" exposures and the variability of exposures throughout the year.

Table 1. Directly measured exposure categories and potential determinants of exposure.

Exposure	Proposed measurement sample	Potential determinants of exposure
Whole-body vibration	21 farms × 6 vehicles each=126 vehicle measurements (anticipate 2 vehicles per visit)	Vehicle characteristics: type of vehicle or other vibrating equipment used, operating duration, vehicle weight, type of tire, type of transmission, seat type, seat and cab suspension. Driving surface characteristics. Driving tasks: duration of operation, typical speeds of operation.
Back posture	36 farmers × 3 days=108 posture measurements	Duration and frequency of farm tasks such as shoveling, vehicle maintenance, animal feeding and watering, birth and veterinary care, vehicle operation, and other tasks identified during the pilot phase. Horizontal reach distances, frequency and extent of bending or twisting and reaching overhead.
Manual handling	36 farmers × 3 days=108 hours of video (anticipate 1 hour of manual tasks per visit)	Duration and frequency of farm tasks such as shoveling, vehicle maintenance, animal feeding and watering, birth and veterinary care, vehicle operation, and other tasks identified during the pilot phase. Dimensions and estimated weights of materials handled, the heights over which they are transported, the use of lifting aids, horizontal distance of load from ankles, vertical distance of load from floor, movement distance, amount of twisting, lift frequency and duration, presence of handles.

Farmers will also be asked about psychosocial risk factors using Karasek's Job Content Questionnaire [49]. The low back health portion of the interview will use existing, validated instruments to collect in-depth information on the presence and extent of pain, and any interruption of work, family, leisure, and activities of daily living [50-53]. As part of inclinometer assessment of back posture, spine range of motion will be directly measured. These data will be used to characterize back structure and function. The in-depth, on-farm interview and assessment is anticipated to take 60-75 minutes. Items will use terms familiar to the workforce, refined during consultations with industry partners and during pilot testing. Images of key postures, tasks, and lifting activities will be offered to assist recall.

Developing an Intervention Inventory

An inventory of farmer-initiated interventions will be assembled using targeted questions during the in-depth, on-farm interview, anticipated to take 10-45 minutes depending on the number of safety measures in place. The focus will be on engineering interventions that involve physical changes to tools, equipment, machinery, or workstations, but administrative interventions such as work rest and micropause schedules will also be considered, as well as self-care strategies. Engineering interventions are preferred because they have been shown to have the greatest economic benefit [54] and, in contrast to administrative controls, are not as reliant on the farmer to remember to take action. Qualifying interventions may be

modifications currently or previously used by the farmer, repurposed or custom-built tools or equipment, interventions that are in the planning or fabrication stage, as well as interventions that have only been identified as a need but not yet implemented. When an intervention is identified, additional information will be collected to determine the nature and utility of the intervention; for example, what prompted implementation; how the device/practice was acquired or developed; strengths and limitations of the device/practice; satisfaction with the device/practice; and a "wish list" of any improvements to the device/practice. When possible, photographs of a device and video of its use will be collected and will be accessible on the project website. During pilot testing, a semistructured interview will be used to collect qualitative data on these topics. It is anticipated that this process will allow identification of critical intervention characteristics (low, medium, and high cost; short, medium, and long time frame for implementation/adoption) to provide more structure during study data collection.

Analysis

Direct Exposure Measurements

Analysis of these exposure data will include descriptive summaries for all measurement days combined as well as for each commodity, season, and other categories. Differences between categories will be assessed using mixed models with "farmer" and "farm" as random-effects terms. Repeated measures from all 3 visits will be used to estimate within-worker variability and compare it with between-worker variability, which can be used to develop cost-efficient sampling strategies as suggested by Burdorf and Van Riel [55]. Self-reported "typical" exposure and "annual variability" will be compared with direct measurements using linear regression modeling to determine the suitability of "overall" exposure estimates to represent daily exposures that are anticipated to be highly variable.

Exposure Prediction Modeling

All potential prediction variables will be summarized descriptively and tested for association with measured exposures using simple linear regression. Some example variables are listed in Table 1. As done in previous work, variables with a *P* value of less than .10 will be retained for further consideration [28-30]. Colinearity will be assessed before offering to the multiple regression model. Interactions will be considered where there is a theoretical basis or published evidence. Similar to prior work [28,56], hierarchical multiple linear regression models (ie, mixed-effects models) will be developed using "farmer" and "farm" as random-effects terms and potential predictor variables as fixed effects. Manual stepwise backward regression will be conducted and significant variables will be retained in the final model.

Intervention Inventory

Identified interventions will be cataloged into an inventory according to their application (ie, relevant commodities, tasks, and equipment). After a heuristic review by trained ergonomists (Drs PJ and CT), the cataloged interventions will be published on the project website. Interventions characteristics such as cost, time commitment, and associated barriers and facilitators will be summarized into frequencies. The NIOSH agricultural best practices guide [38] and International Labour Organization's Ergonomics Checkpoints guide [57] will provide a model for an intervention inventory, tailored to farming conditions encountered in Saskatchewan.

Sample Size

With regard to statistical power, Mathiassen et al [58] demonstrated that in relatively constrained industrial work, the number of subjects needed to detect significant differences depended on the sizes of the within- and between-subject variability components. In order to detect a 10% difference with 80% power, 15 subjects are required when measuring joint angle (using posture sensors as proposed in this study). Given that the work tasks involved in Saskatchewan farming are much less constrained than in most industrial settings, considerable heterogeneity in work exposures is expected, therefore 36 individuals with 3 repeated measurements are expected to provide an adequate sample size. The number of measurements (~36 subjects times 3 days=~108) is likely to limit the number of potential determinants in each empirical model of exposure. However, previous determinants of exposure studies required only 4 variables to predict posture [28] and 3 variables to predict vehicle vibration [30]. The proposed research anticipates including no more than 7 variables in the exposure prediction models, which should be well supported by the proposed sample size [59].

Because the primary research aims do not test typical exposure-response hypotheses, we cannot perform power calculations. We acknowledge that sample size will not make a representative sample of low back disorder prevalence or implementation of ergonomic interventions; however, these are preliminary explorations of this area intended to generate hypotheses and evaluate the feasibility of the methods for further study.

Ethics

The biggest potential burden for participants will be the amount of time required to set up and remove measurement equipment during busy workdays (approximately 15-25 minutes in total). Data collectors will thoroughly practice equipment preparation to mitigate this. The longer in-person interview (60-75 minutes in total) will be scheduled during the less busy winter season to minimize disruption of work activities. The study protocol and consent forms have been approved by the University of Saskatchewan Behavioural Research Ethics Board.

Results

Data collection is currently underway for this study, with the intention to complete all data collection and analysis by the end of 2018.

Discussion

Research Benefits: a Foundation for Future Studies

Outcomes of the proposed study will have value by providing methods for future research and immediate applicability to farmers and agricultural health and safety organizations. This

project will provide objective, high-quality, directly measured exposure information in the understudied population of rural famers. Providing high-quality data on the physical exposures in agriculture allows for comparison with exposures in other industries and occupations and, where available, exposure guidelines. Such comprehensive measurements of these determinants of health status are rare in agriculture and have not been conducted in Saskatchewan, where farm and agriculture revenue makes substantial contributions to the local economy. This study will also provide estimates of the extent and nature of low back disorder–related pain and disability in farmers; by better characterizing the scope of the problem of low back disorder it will provide rich information on low back disorders' effect on work and home life and back function.

The study will also contribute to future research by providing descriptive data on exposures and low back disorder health that will support development of hypotheses, methodologies, and designs for future research. In terms of epidemiology, developing statistical modeling techniques for cost-effective exposure assessment will allow for higher-quality, lower-cost, large-scale studies in the future. Poor exposure assessment is a persistent problem in prevention of low back disorders. A major outcome of this project will be the development of a parsimonious, cost-effective exposure prediction model to identify determinants of back health status during large, prospective epidemiological studies. By developing an exposure prediction model, the proposed study will determine if farmers can report farm tasks and working conditions accurately enough to develop empirical models of WBV, back posture, and manual material handling to make quantitative predictions of working exposures. For example, this model could identify a simple set of questions that are demonstrably related to exposure for a baseline exposure assessment via postal questionnaire. This would be an advance over current self-reported exposure questionnaires that have face validity but without a quantified relationship between reported and measured exposures. It should be noted that this type of model develops a relationship based on exposures measured on a specific day. However, many musculoskeletal disorders, including low back disorders, develop from long-term exposures accumulated over time. Therefore, models that rely on predictors that vary over time may be less representative on relevant long-term exposures than those predictors that are relatively fixed.

Many of the applications of the findings could be translated to other industries. For example, mining is one industry where many of the same exposures (WBV and lifting) exist. In addition, identifying the determinants of exposure will allow for better targeting of prevention efforts, because these workplace factors can be modified or controlled.

Perhaps most relevant to immediately applicable prevention efforts will be the creation of an ergonomic intervention inventory describing existing and potential farmer-initiated preventative measures. This will provide a great deal of quantitative and qualitative information to support future prevention research. In addition to identifying promising designs and strategies for exposure control, the inventory can provide insight into why these interventions are implemented, including barriers and facilitators that can predict the success of future intervention designs; this will be published on the study website. This inventory will facilitate identification of promising designs, strategies, and opportunities for future research that investigates effectiveness of interventions.

Relevance

This project directly addresses an important health issue in an understudied population with high anticipated risks for the development of low back disorders. It represents the first phase in a longer-term research program to investigate the etiology of back disorders in this group. The results of this research will ultimately provide evidence to inform policy and prevention program decisions.

Conflicts of Interest

None declared.

References

1. Deyo RA, Weinstein D. Low back pain. N Engl J Med 2001 Feb 1;344(5):363-370. [doi: 10.1056/NEJM200102013440508] [Medline: 11172169]
2. Papageorgiou PA, Croft P, Ferry S, Jayson M, Silman A. Estimating the prevalence of low back pain in the general population. Evidence from the South Manchester Back Pain Survey. Spine (Phila Pa 1976) 1995 Sep 1;20(17):1889-1894. [Medline: 8560337]
3. van Tulder M, Koes B, Bombardier C. Low back pain. Best Pract Res Clin Rheumatol 2002 Dec;16(5):761-775. [Medline: 12473272]
4. van Tulder M, Koes B, Bouter L. A cost-of-illness study of back pain in The Netherlands. Pain 1995 Aug;62(2):233-240. [Medline: 8545149]
5. Osborne OA, Blake C, Fullen B, Meredith D, Phelan J, McNamara J, et al. Prevalence of musculoskeletal disorders among farmers: A systematic review. Am J Ind Med 2012 Feb;55(2):143-158. [doi: 10.1002/ajim.21033] [Medline: 22069159]
6. Rosecrance RJ, Rodgers G, Merlino L. Low back pain and musculoskeletal symptoms among Kansas farmers. Am J Ind Med 2006 Jul;49(7):547-556. [doi: 10.1002/ajim.20324] [Medline: 16685722]
7. Walker-Bone WK, Palmer K. Musculoskeletal disorders in farmers and farm workers. Occup Med (Lond) 2002 Dec;52(8):441-450 [FREE Full text] [Medline: 12488514]

8. Guo GH, Tanaka S, Halperin W, Cameron L. Back pain prevalence in US industry and estimates of lost workdays. Am J Public Health 1999 Jul;89(7):1029-1035. [Medline: 10394311]
9. Meerding MW, IJzelenberg W, Koopmanschap MA, Severens JL, Burdorf A. Health problems lead to considerable productivity loss at work among workers with high physical load jobs. J Clin Epidemiol 2005 May;58(5):517-523. [doi: 10.1016/j.jclinepi.2004.06.016] [Medline: 15845339]
10. Whelan WS, Ruane D, McNamara J, Kinsella A, McNamara A. Disability on Irish farms--a real concern. J Agromedicine 2009;14(2):157-163. [doi: 10.1080/10599240902813078] [Medline: 19437272]
11. Park PH, Sprince N, Whitten P, Burmeister L, Zwerling C. Risk factors for back pain among male farmers: analysis of Iowa Farm Family Health and Hazard Surveillance Study. Am J Ind Med 2001 Dec;40(6):646-654. [Medline: 11757041]
12. Holmberg HS, Thelin A, Stiernstrom E, Svardsudd K. The impact of physical work exposure on musculoskeletal symptoms among farmers and rural non-farmers. Ann Agric Environ Med 2003;10(2):179-184 [FREE Full text] [Medline: 14677909]
13. Manninen MP, Riihimäk H, Heliövaara M. Incidence and risk factors of low-back pain in middle-aged farmers. Occup Med (Lond) 1995 Jun;45(3):141-146. [Medline: 7605976]
14. Kolstrup KC, Stål M, Pinzke S, Lundqvist P. Ache, pain, and discomfort: the reward for working with many cows and sows? J Agromedicine 2006;11(2):45-55. [doi: 10.1300/J096v11n02_08] [Medline: 17135142]
15. Fathallah FA, Miller BJ, Miles AJ. Low back disorders in agriculture and the role of stooped work: scope, potential interventions, and research needs. J Agric Saf Health 2008 Apr;14(2):221-245. [Medline: 18524286]
16. Hartman HE, Oude Vrielink HH, Huirne RB, Metz JH. Risk factors for sick leave due to musculoskeletal disorders among self-employed Dutch farmers: a case-control study. Am J Ind Med 2006 Mar;49(3):204-214. [doi: 10.1002/ajim.20276] [Medline: 16470545]
17. Davis DK, Kotowski S. Understanding the ergonomic risk for musculoskeletal disorders in the United States agricultural sector. Am J Ind Med 2007 Jul;50(7):501-511. [doi: 10.1002/ajim.20479] [Medline: 17506508]
18. Punnett PL, Wegman D. Work-related musculoskeletal disorders: the epidemiologic evidence and the debate. J Electromyogr Kinesiol 2004 Feb;14(1):13-23. [doi: 10.1016/j.jelekin.2003.09.015] [Medline: 14759746]
19. Burdorf BA, Rossignol M, Fathallah F, Snook S, Herrick R. Challenges in assessing risk factors in epidemiologic studies on back disorders. Am J Ind Med 1997 Aug;32(2):142-152. [Medline: 9215436]
20. Winkel WJ, Mathiassen S. Assessment of physical work load in epidemiologic studies: concepts, issues and operational considerations. Ergonomics 1994 Jun;37(6):979-988. [doi: 10.1080/00140139408963711] [Medline: 8026455]
21. Burdorf A, Sorock G. Positive and negative evidence of risk factors for back disorders. Scand J Work Environ Health 1997 Aug;23(4):243-256 [FREE Full text] [Medline: 9322815]
22. Norman NR, Wells R, Neumann P, Frank J, Shannon H, Kerr M. A comparison of peak vs cumulative physical work exposure risk factors for the reporting of low back pain in the automotive industry. Clin Biomech (Bristol, Avon) 1998 Dec;13(8):561-573. [Medline: 11415835]
23. Svendsen SS, Gelineck J, Mathiassen S, Bonde J, Frich J, Stengaard-Pedersen K, et al. Work above shoulder level and degenerative alterations of the rotator cuff tendons: a magnetic resonance imaging study. Arthritis Rheum 2004 Oct;50(10):3314-3322 [FREE Full text] [doi: 10.1002/art.20495] [Medline: 15476229]
24. Trask TC, Teschke K, Village J, Chow Y, Johnson P, Luong N, et al. Measuring low back injury risk factors in challenging work environments: an evaluation of cost and feasibility. Am J Ind Med 2007 Sep;50(9):687-696. [doi: 10.1002/ajim.20497] [Medline: 17680639]
25. Trask TC, Mathiassen S, Wahlström J, Heiden M, Regahzoli M. Modeling costs of exposure assessment in occupational settings. In: International Ergonomics Association. 2012 Presented at: 18th World Congress on Ergonomics; February 2012; Recife, Brasil.
26. Burstyn BI, Teschke K. Studying the determinants of exposure: a review of methods. Am Ind Hyg Assoc J 1999;60(1):57-72. [doi: 10.1080/00028899908984423] [Medline: 10028617]
27. Teschke K, Spierings J, Marion S, Demers P, Davies H, Kennedy S. Reducing attenuation in exposure-response relationships by exposure modeling and grouping: the relationship between wood dust exposure and lung function. Am J Ind Med 2004 Dec;46(6):663-667. [doi: 10.1002/ajim.20105] [Medline: 15551365]
28. Teschke TK, Trask C, Johnson P, Chow Y, Village J, Koehoorn M. Measuring posture for epidemiology: comparing inclinometry, observations and self-reports. Ergonomics 2009 Sep;52(9):1067-1078. [doi: 10.1080/00140130902912811] [Medline: 19787510]
29. Trask TC, Teschke K, Morrison J, Johnson P, Village J, Koehoorn M. EMG estimated mean, peak, and cumulative spinal compression of workers in five heavy industries. International Journal of Industrial Ergonomics 2010 Jul;40(4):448-454. [doi: 10.1016/j.ergon.2010.02.006]
30. Village VJ, Trask C, Chow Y, Morrison J, Koehoorn M, Teschke K. Assessing whole body vibration exposure for use in epidemiological studies of back injuries: measurements, observations and self-reports. Ergonomics 2012;55(4):415-424. [doi: 10.1080/00140139.2011.643243] [Medline: 22397358]
31. Chen CJ, Chang WR, Shih TS, Chen CJ, Chang WP, Dennerlein JT, et al. Using exposure prediction rules for exposure assessment: an example on whole-body vibration in taxi drivers. Epidemiology 2004 May;15(3):293-299. [Medline: 15097009]

32. Kirkhorn KS, Earle-Richardson G, Banks R. Ergonomic risks and musculoskeletal disorders in production agriculture: recommendations for effective research to practice. J Agromedicine 2010 Jul;15(3):281-299. [doi: 10.1080/1059924X.2010.488618] [Medline: 20665313]
33. Earle-Richardson EG, Jenkins P, Freivalds A, Burdick P, Park S, Lee C, et al. Laboratory evaluation of belt usage with apple buckets. Am J Ind Med 2006 Jan;49(1):23-29. [doi: 10.1002/ajim.20239] [Medline: 16362945]
34. Kotowski KS, Davis K, Waters T. Investigation of select ergonomic interventions for farm youth. Part 1: shovels. J Agromedicine 2009;14(1):33-43. [doi: 10.1080/10599240802612604] [Medline: 19214854]
35. Southard SS, Freeman J, Drum J, Mirka J. Ergonomic interventions for the reduction of back and shoulder biomechanical loading when weighing calves. International Journal of Industrial Ergonomics 2007 Feb;37(2):103-110. [doi: 10.1016/j.ergon.2006.10.016]
36. Earle-Richardson EG, Jenkins P, Strogatz D, Bell E, Sorensen J, May J. Orchard evaluation of ergonomically modified apple bucket. J Agromedicine 2006;11(3-4):95-105. [doi: 10.1300/J096v11n03_10] [Medline: 19274901]
37. May J, Hawkes L, Jones A, Burdick P, Ginley B, Santiago B, et al. Evaluation of a community-based effort to reduce blueberry harvesting injury. Am J Ind Med 2008 Apr;51(4):307-315. [doi: 10.1002/ajim.20554] [Medline: 18247320]
38. NIOSH N. Simple Solutions Ergonomics for Farm Workers. DHHS (NIOSH) Publication 2001:1-111.
39. van Eerd D, Cole D, Irvin E, Mahood Q, Keown K, Theberge N, et al. Process and implementation of participatory ergonomic interventions: a systematic review. Ergonomics 2010 Oct;53(10):1153-1166. [doi: 10.1080/00140139.2010.513452] [Medline: 20865600]
40. StatisticsCanada. Census of Agriculture counts 44,329 farms in Saskatchewan. 2007 Dec 07. URL: http://www.statcan.gc.ca/ca-ra2006/analysis-analyses/sask-eng.htm [accessed 2016-04-04] [WebCite Cache ID 6gWgPVSRW]
41. Voaklander D, Dosman J, Hagel L, Warsh J, Pickett W, Saskatchewan Farm Injury Cohort Study Team. Farm work exposure of older male farmers in Saskatchewan. Am J Ind Med 2010 Jul;53(7):706-715. [doi: 10.1002/ajim.20811] [Medline: 20187005]
42. Pickett W, Hagel L, Day A, Day L, Sun X, Brison R, et al. Determinants of agricultural injury: a novel application of population health theory. Inj Prev 2010 Dec;16(6):376-382. [doi: 10.1136/ip.2010.026286] [Medline: 20805619]
43. ISO. ISO 2631-1:1997. 1997. Mechanical vibration and shock -- Evaluation of human exposure to whole-body vibration URL: http://www.iso.org/iso/catalogue_detail.htm?csnumber=7612 [accessed 2016-05-23] [WebCite Cache ID 6hiJoCLQ5]
44. Kazmierczak KK, Mathiassen S, Forsman M, Winkel J. An integrated analysis of ergonomics and time consumption in Swedish 'craft-type' car disassembly. Appl Ergon 2005 May;36(3):263-273. [doi: 10.1016/j.apergo.2005.01.010] [Medline: 15854569]
45. Snook SH, Ciriello V. The design of manual handling tasks: revised tables of maximum acceptable weights and forces. Ergonomics 1991 Sep;34(9):1197-1213. [doi: 10.1080/00140139108964855] [Medline: 1743178]
46. Ayoub M, Mital M. Manual materials handling. London and New York: Taylor & Francis; 1989.
47. Wiktorin C, Vingård E, Mortimer M, Pernold G, Wigaeus-Hjelm E, Kilbom A, et al. Interview versus questionnaire for assessing physical loads in the population-based MUSIC-Norrtälje Study. Am J Ind Med 1999 May;35(5):441-455. [Medline: 10212697]
48. Hollmann HS, Klimmer F, Schmidt K, Kylian H. Validation of a questionnaire for assessing physical work load. Scand J Work Environ Health 1999 Apr;25(2):105-114 [FREE Full text] [Medline: 10360465]
49. Karasek KR, Brisson C, Kawakami N, Houtman I, Bongers P, Amick B. The Job Content Questionnaire (JCQ): an instrument for internationally comparative assessments of psychosocial job characteristics. J Occup Health Psychol 1998 Oct;3(4):322-355. [Medline: 9805280]
50. Main MC, Wood P, Hollis S, Spanswick C, Waddell G. The Distress and Risk Assessment Method. A simple patient classification to identify distress and evaluate the risk of poor outcome. Spine (Phila Pa 1976) 1992 Jan;17(1):42-52. [Medline: 1531554]
51. Fritz FJ, Irrgang J. A comparison of a modified Oswestry Low Back Pain Disability Questionnaire and the Quebec Back Pain Disability Scale. Phys Ther 2001 Feb;81(2):776-788 [FREE Full text] [Medline: 11175676]
52. Fairbank FJ, Pynsent P. The Oswestry Disability Index. Spine (Phila Pa 1976) 2000 Nov 15;25(22):2940-52; discussion 2952. [Medline: 11074683]
53. Waddell WG, Newton M, Henderson I, Somerville D, Main C. A Fear-Avoidance Beliefs Questionnaire (FABQ) and the role of fear-avoidance beliefs in chronic low back pain and disability. Pain 1993 Feb;52(2):157-168. [Medline: 8455963]
54. Goggins GR, Spielholz P, Nothstein G. Estimating the effectiveness of ergonomics interventions through case studies: implications for predictive cost-benefit analysis. J Safety Res 2008;39(3):339-344. [doi: 10.1016/j.jsr.2007.12.006] [Medline: 18571576]
55. Burdorf BA, van Riel M. Design of strategies to assess lumbar posture during work. International Journal of Industrial Ergonomics 1996 Oct;18(4):239-249. [doi: 10.1016/0169-8141(95)00035-6]
56. Trask TC, Teschke K, Morrison J, Village J, Johnson P, Koehoorn M. Using observation and self-report to predict mean, 90th percentile, and cumulative low back muscle activity in heavy industry workers. Ann Occup Hyg 2010 Jul;54(5):595-606 [FREE Full text] [doi: 10.1093/annhyg/meq011] [Medline: 20413415]

57. International Labour Office, International Ergonomics Association. Ergonomic Checkpoints In Agriculture. Geneva: ILO; 2012.
58. Mathiassen MS, Möller T, Forsman M. Variability in mechanical exposure within and between individuals performing a highly constrained industrial work task. Ergonomics 2003 Jun 20;46(8):800-824. [doi: 10.1080/0014013031000090125] [Medline: 12745980]
59. Kleinbaum KD, Kupper L, Nizam A, Rosenberg E. Regression Analysis and Multivariable Methods, 4th Edition. Pacific Grove, CA: Duxbury Press; 2007.

Abbreviations

ISO: International Organization for Standardization
NIOSH: National Institute for Occupational Safety and Health
WBV: whole-body vibration

Edited by G Eysenbach; submitted 27.01.16; peer-reviewed by A Burdorf, M Bin Homaid, MS Alhalabi; comments to author 10.03.16; revised version received 04.04.16; accepted 22.04.16; published 10.06.16.

Please cite as:
Trask C, Bath B, Johnson PW, Teschke K
Risk Factors for Low Back Disorders in Saskatchewan Farmers: Field-based Exposure Assessment to Build a Foundation for Epidemiological Studies
JMIR Res Protoc 2016;5(2):e111
URL: http://www.researchprotocols.org/2016/2/e111/
doi:10.2196/resprot.5573
PMID:27286748

Protocol

A Single Dose of Prednisolone as a Modulator of Undercarboxylated Osteocalcin and Insulin Sensitivity Post-Exercise in Healthy Young Men: A Study Protocol

Itamar Levinger[1], PhD; Tara C Brennan-Speranza[2], PhD; Nigel K Stepto[1], PhD; George Jerums[3], MBBS, MD, FRACP; Lewan Parker[1], BSpExSc(Hons); Glenn K McConell[1], PhD; Mitchell Anderson[1], MBBS, BPhysio, B.Sci, DipSurg.Anat; Andrew Garnham[4], MBBS, DipRACOG, FACSP; David L Hare[5], MBBS, FRACP, DPM; Peter R Ebeling[6], MBBS, MD, FRACP; Ego Seeman[3], MBBS, MD, FRACP

[1]Clinical Exercise Science Research Program, Institute of Sport, Exercise and Active Living (ISEAL), Victoria University, Melbourne, Australia

[2]Department of Physiology, Bosch Institute for Medical Research, University of Sydney, Sydney, Australia

[3]University of Melbourne and the Department of Endocrinology, Austin Health, Melbourne, Australia

[4]School of Exercise & Nutrition Sciences, Deakin University, Melbourne, Australia

[5]University of Melbourne and the Department of Cardiology, Austin Health, Melbourne, Australia

[6]Department of Medicine, School of Clinical Sciences,, Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, Australia

Corresponding Author:
Itamar Levinger, PhD
Clinical Exercise Science Research Program
Institute of Sport, Exercise and Active Living (ISEAL)
Victoria University
PO Box 14428
Melbourne,
Australia
Phone: 61 9919 5343
Fax: 61 9919 5532
Email: itamar.levinger@vu.edu.au

Abstract

Background: Undercarboxylated osteocalcin (ucOC) increases insulin sensitivity in mice. In humans, data are supportive, but the studies are mostly cross-sectional. Exercise increases whole-body insulin sensitivity, in part via ucOC, while acute glucocorticoid treatment suppresses ucOC in humans and mice.

Objectives: A single dose of prednisolone reduces the rise in ucOC produced by exercise, which partly accounts for the failed increase in insulin sensitivity following exercise.

Methods: Healthy young men (n=12) aged 18 to 40 years will be recruited. Initial assessments will include analysis of fasting blood, body composition, aerobic power (VO_{2peak}), and peak heart rate. Participants will then be randomly allocated, double-blind, to a single dose of 20 mg of prednisolone or placebo. The two experimental trials will involve 30 minutes of interval exercise (90%-95% peak heart rate), followed by 3 hours of recovery and 2 hours of euglycaemic- hyperinsulinaemic clamp (insulin clamp). Seven muscle biopsies and blood samples will be obtained at rest, following exercise and post-insulin clamps.

Results: The study is funded by the National Heart Foundation of Australia and Victoria University. Enrollment has already commenced and data collection will be completed in 2016.

Conclusion: If the hypothesis is confirmed, the study will provide novel insights into the potential role of ucOC in insulin sensitivity in human subjects and will elucidate pathways involved in exercise-induced insulin sensitivity.

(JMIR Res Protoc 2016;5(2):e78) doi:10.2196/resprot.5119

KEYWORDS

bone metabolism; exercise; glycaemic control; undercarboxylated osteocalcin; prednisolone

Introduction

Insulin resistance is characterized by impaired insulin action in target tissues. Skeletal muscle is a major site of glucose uptake and disposal in response to insulin and skeletal muscle can become insulin resistant in obese individuals and those with type 2 diabetes mellitus (T2DM). In mice, the skeleton is partly involved in determining insulin secretion, insulin sensitivity, and glucose tolerance via the undercarboxylated form of osteocalcin (ucOC) [1,2]. UcOC- deficient mice have insulin resistance and in obese mice recombinant ucOC treatment reduces glucose levels and increases insulin secretion and sensitivity [2,3]. Moreover, recombinant ucOC increases muscle glucose uptake post ex vivo contraction in mice [4].

In humans, ucOC may influence glycemic control but most evidence is based on cross-sectional studies [5,6]. For example, patients with T2DM have lower serum ucOC than controls. A lower serum ucOC is associated with a higher fasting glucose and fat mass, and lower insulin sensitivity [7,8]. This suggests ucOC participates in glucose homeostasis in humans; however, prospective interventional studies are required [9].

Exercise increases insulin sensitivity in nonobese and obese subjects and in patients with T2DM independent of weight loss [10] Even a single bout of exercise increases glucose handling and insulin sensitivity [11]. Acute exercise also increases ucOC, which is associated with improved glycemic control and increased insulin sensitivity post exercise [7,12,13]. Thus, ucOC may contribute to the regulation of insulin sensitivity in humans.

To explore this, we have designed a prospective study aimed at inhibiting the rise in ucOC using a single dose of a glucocorticoid (GC). GC treatment is used regularly as an anti-inflammatory and immunosuppressive agent [14,15]. Long-term GC treatment causes bone loss, obesity, insulin resistance, and T2DM[16]. The detrimental long-term effects of GC on insulin resistance are partly mediated via osteoblasts, the bone cells responsible for the production of ucOC [14,15,17]. The reduction in insulin sensitivity following short-term GC treatment is related to an acute reduction in osteoblastic function and ucOC levels and not to the GC effects on skeletal muscle or liver, at least in mice [17]. As such, we will use a single dose of a GC, prednisolone, as a tool to acutely suppress ucOC and examine the consequent effect on whole-body insulin sensitivity and muscle metabolism, including measuring GC signaling in muscle. The regulation of GC-target genes, glucocorticoid-induced leucine zipper *(Gilz)*[18] and FK506-binding protein 5 *(Fkbp5)*[19] will be analyzed by polymerase chain reaction (PCR) and Western blot from muscle biopsies of humans with and without an acute dose of prednisolone. We hypothesize that the protein levels of these GC-targets will not be altered in the short time frame, even if gene expression is altered. Other studies in mice and humans confirm a 40% to 50% reduction in circulating OC within 12 to 24 hours after the commencement of GC treatment [20]. On the other hand, 5 days of prednisone treatment had minimal effect on muscle protein synthesis, breakdown, mitochondrial function, strength, and resting energy expenditure in men [21]. Thus, evidence from mice and humans indicates that a reduction in serum OC and ucOC following GC treatment occurs prior to muscle atrophy signaling changes in skeletal muscle. We hypothesize that insulin sensitivity will be partly reduced due to changes in insulin signaling proteins subsequent to a reduction in circulating ucOC levels.

No previous research has used GC (prednisolone) as a tool to examine the effect of ucOC on insulin sensitivity post exercise. Thus, the aim of this study is to test the hypothesis that attenuation of the increase in ucOC following exercise by a single dose of prednisolone reduces insulin sensitivity post exercise, as measured by euglycaemic-hyperinsulinaemic clamp, as well as impairing skeletal muscle insulin signaling. We also hypothesize that markers of muscle damage will not be increased by a single dose of prednisolone.

Methods

Study Design and Participants

This is designed as a double-blind, randomized controlled, cross-over study. We aim to recruit 12 healthy young men. Volunteers will be recruited via several advertisement strategies including flyers, global emails to staff and students from Victoria University, and Web-based advertisements.

Criteria

Healthy young men aged 18 to 40 years, body mass index range between 19 and 27 kg/m^{2}with fasting blood glucose ≤ 5.6 mmol/L^{1}will be recruited for the study. Men with bone disease (such as osteoporosis), metabolic or cardiovascular disease, and/or those who are taking any medication known to affect bone metabolism, insulin secretion, or insulin sensitivity will be excluded. Also, those with a musculoskeletal and/or orthopedic condition (such as severe osteoarthritis) that prevents normal daily function (such as walking) will be excluded. Conversion of ucOC to OC is dependent on vitamin K [22]. As such, volunteers on warfarin therapy or vitamin K supplementation or restriction will be excluded.

Sample Size and Data Analysis

The sample size is based on our previous work where exercise significantly increased ucOC by approximately 6.5% and insulin sensitivity by approximately 35% during a euglycaemic-hyperinsulinaemic clamp (n=11) [7,12]. As such, we estimate that the sample size needed in this cross-over design (power of 80%, alpha=0.05) is 12 individuals.

Descriptive statistics will be used to describe the volunteers' characteristics as well as the study measurements. Changes from pre-to-post exercise within each trial and between trials will be analyzed by paired *t*-tests. General linear model analysis of the variance will be use to compare multiple time-points within and between interventions. Multilinear regression model will be used to determine associations between selected measurements. All data will be reported as mean ± standard error of mean and all statistical analyses will be conducted at the 95% level of significance ($P \leq .05$).

Screening

Fasting blood test: a blood sample will be collected following an overnight fast. Blood will be analyzed at Austin Health pathology using the standard hospital assay protocols for glucose, HbA1c, insulin, triglyceride, low-density lipoprotein, and high-density lipoprotein.

Body composition: dual-energy x-ray absorptiometry (DXA) will be used to assess total body fat and lean body mass. In addition, the DXA will be used to assess fat mass in the abdominal region as well as bone mineral density to exclude osteoporosis [23,24].

Aerobic power (VO_{2peak}) will be assessed during a sign and symptom-limited graded exercise test as we previously described [23]. The exercise will be performed on a cycle ergometer and $VO_2$for each 15-second interval will be measured by a gas analyzer that will be calibrated as per the manufacturer's instructions before each test. Participants will be asked to refrain from physical activity (48 hours), and alcohol and caffeine ingestion (24 hours) prior to the screening session and trial days.

Randomization and Blinding

At the conclusion of the baseline/screening assessments volunteers will be randomly allocated (block allocation) in a double-blind fashion to determine the order of the treatments (prednisolone or placebo). Randomization will be performed using sealed opaque envelopes. The person responsible for the randomization, the investigators and the participants will not be aware of the intervention (prednisolone or placebo). The code for the randomization will be held by the medical practitioner who will supervise the insulin clamp to allow medical intervention in case of adverse responses during the exercise or insulin clamps.

Intervention

Volunteers will attend our laboratory twice for the experimental trials (Figure 1). On the day prior to the first trial, participants will be asked to record their daily diet in a food diary, which will then be replicated the day prior to their second trial. The two trials (prednisolone or placebo) will be performed 1 to 3 weeks apart. This ensures that the effect of the single dose of prednisolone is "washed out" [25]. Twenty-four hours prior to the first trial day, and a minimum of 1 week after the VO_{2peak}test, a single muscle biopsy and 15 ml of blood will be obtained. To avoid an additional biopsy, data from this resting biopsy will be used as the "24 hour prior" time-point for both the placebo and prednisolone trials. Then, at 7 PM (12 hours before the trial) on the day prior to each experimental trial participants will ingest a 20-mg capsule of prednisolone or placebo orally (Avicel- microcrystalline Cellulose NF PH105) (Figure 1).

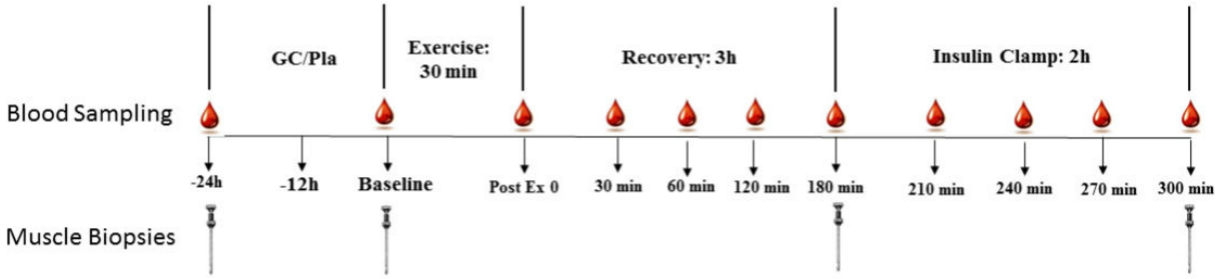
The timing of the prednisolone ingestion is based on previously published data on the suppressive effect of acute GC treatment on osteocalcin [20]. The prednisolone dose that will be used in this study is slightly higher compared with the dose used by Nielsen et al [20] (10 mg), but is lower compared with doses used in clinical practice to treat inflammatory conditions (30-70 mg/day). Both the prednisolone and placebo will be purchased from the same pharmacy and look and taste identical. Avicel is widely used as a placebo in a variety of drug trials [26].

The following day (the trial day) participants will attend our laboratory in the morning (7 AM) after an overnight fast for the experimental trial (Figure 1). The participant will lie down on a bed and a cannula will be inserted to the antecubital vein. Then a resting blood sample will be obtained. In addition, a resting muscle biopsy will be obtained from the vastus lateralis, under local anesthesia (Xylocaine 1%), using the percutaneous needle biopsy technique as previously described [12]. Exercise will commence 10 to 20 minutes after the resting muscle biopsy. The high intensity exercise will be performed as previously described and will consist of a 6-minute warm-up at 50% to 60% of peak heart rate followed by 4 × 4-minute intervals at 90% to 95% peak heart rate (HR_{peak}) and a 2-minute warm-down at 50% to 60% of peak heart. The high-intensity intervals will be separated by 2 minutes of active recovery consisting of cycling at 50% to 70% of peak intensity [12]. Peak heart rate will be defined as the highest heart rate measured during the incremental test.

After completing the exercise, participants will recover for 3 hours and blood samples will be taken immediately, 30 minutes, 1, 2, and 3 hours post exercise (Figure 1). Then, a 2-hour euglycaemic-hyperinsulinaemic clamp (insulin clamp) will be performed. During the clamp blood samples (~1-1.5 ml) will be taken every 5 minutes to monitor blood glucose levels. A 10-ml blood sample will be taken every 30 minutes during the clamp (see Figure 1) for the analysis of OC, ucOC, insulin, and other markers of bone formation and resorption (the hormones CTX and procollagen 1 N-terminal propeptide (P1NP)). Blood will be centrifuged (10 min at 3500 rpm, 4°C) and serum and plasma will be immediately stored in aliquots at −80ºc until assayed. In addition, a total of three muscle biopsies from the vastus lateralis will be undertaken in each experimental session. Muscle will be analyzed for insulin signaling proteins, markers of muscle inflammation and atrophy signaling proteins. In total, seven muscle biopsies will be obtained during the study. Four biopsies will be obtained during the first session (−24, baseline and pre and post insulin clamp) and three during the second session (baseline and pre and post insulin clamp).

A euglycemic-hyperinsulinemic clamp (insulin clamp) will be performed as previously reported [12,27,28]. Prior to the insulin clamp a single slow release tablet of potassium chloride (600 mg) will be given to reduce the risk of potassium depletion during the insulin clamp. Venous blood samples, from a heated arm vein, will be collected prior and during each session. Insulin will be infused at 40 $mU.m^{-2}$per minute for 120 minutes generating an elevated, stable insulin concentration in the last 30 minutes of the clamp. Insulin sensitivity will be assessed by the glucose infusion rate (GIR, $mg{\cdot}kg^{-1}{\cdot}min^{-1}$) during the last 30 minutes of the insulin-stimulated period and the GIR per unit of insulin (M-Value) [29]. During both euglycemic-hyperinsulinemic clamp sessions, exogenous glucose will be variably infused to achieve the target blood glucose of approximately 5 mmol/L for the duration of the clamp.

Figure 1. Experimental design. Participants will perform the protocol twice. Prednisolone (GC), or placebo (Pla) orally in a double-blind, randomized, cross-over design. The two experimental days will be separated by 1 to 3 weeks. The -24 hour biopsy will be obtained only once, prior to the first treatment. We will use the data from this biopsy for comparison across the 2 trial days.



Analysis

Total serum OC will be measured using an automated immunoassay. Serum ucOC will be measured by the same immunoassay after adsorption of carboxylated OC on 5 mg/mL hydroxyl-apatite slurry, following the method described by Gundberg et al [30]. β-isomerized C-terminal telopeptides (a bone resorption marker) and P1NP (a bone formation marker) will be analyzed at Austin pathology.

Muscle insulin signaling proteins, markers of muscle inflammation and atrophy signaling proteins (see below for details) will be measured by PCR and immunoblotting. Glucocorticoid signaling in muscle will be also monitored by quantitative reverse-transcription PCR analysis of glucocorticoid-target genes, *Gilz*and *Fkbp5*. Protein expression of the GILZ and Fkbp5 will also be analyzed by immunoblotting. Muscle mitochondrial respiration will be measured using Oxygraph O2k, to assess the effects of prednisolone and exercise on mitochondrial function.

Safety Consideration

This is an invasive study that includes seven muscle biopsies (in total), two insulin clamps, blood sampling, high intensity exercise, and administration of a single dose of prednisolone. To reduce the risk associated with the study, only healthy young individuals will participate. In addition, only those who meet the inclusion criteria (as described above) will participate. During the initial graded exercise test participants will be monitored via a 12-lead electrocardiogram (ECG) to identify cardiac abnormalities that may exclude them from the study. A 12-lead ECG will also be used during the insulin clamps. Participants will be asked to report side effects associated with the administration of prednisolone (and placebo). In case of an adverse response/event the participant will be seen by the medical practitioner involved in the study. All the participants will receive a copy of their results (blood tests, body composition, and aerobic fitness).

Ethical Considerations

This study was approved by Victoria University Human Research Ethics Committee (Application ID: HRE14-099). The trial has been registered in the Australian New Zealand Clinical Trials Registry [ANZCTR, ID ACTRN12610000943044]. The investigator, regardless of the outcome, will publish the results of the study.

Outcomes Measurements

Primary outcomes are changes in serum ucOC and changes in insulin sensitivity (glucose infusion rate per unit of insulin). Secondary outcomes are measures of skeletal muscle insulin signaling proteins for total and phosphorylated forms of protein kinase B, Akt substrate of 160 kDa, and Insulin receptor substrate 1 and 2, mitochondria function and markers of muscle inflammation including interleukin-6, tumor necrosis factor-alpha, monocyte chemotactic protein 1, interleukin 1 beta, atrogin, signal transducer and activator of transcription 3, nuclear factor kappa-light-chain-enhancer of activated B cells, forkhead box protein O1, and Muscle RING-finger protein-1. In addition, glucocorticoid-target genes, *gilz*and *Fkbp5*will be measured. G protein-coupled receptor class C group 6 member A will also be measured as it is the likely receptor for ucOC in skeletal muscle. In blood, changes in bone remodeling markers include total osteocalcin, P1NP, and beta-isomerized C-terminal telopeptides.

Discussion

Principal Findings

In mice, ucOC is a modulator of insulin sensitivity and ucOC treatment reduces the risk for type 2 diabetes [2,3]. In humans, data are supportive but are based on cross-sectional studies. If this study shows that suppression of ucOC with a single dose of prednisolone leads to suppression of insulin sensitivity post exercise, this suggests that ucOC is likely to participate in the modulation of insulin sensitivity in humans.

Insulin resistance is characterized by impaired insulin action in insulin target tissues. However, muscle glucose uptake is normal during and following exercise in patients with type 2 diabetes [31,32]. As such, understanding the mechanism/s behind the insulin sensitizing effect of exercise on muscle and whole-body glucose uptake can open the door for new therapeutic treatments for T2DM. In this study we focus on ucOC as acute exercise increases ucOC and higher ucOC correlate with an improvement in insulin sensitivity and glycemic control after exercise in obese men [7,12,13].

A single dose (10 mg) of prednisone suppresses OC and ucOC, an effect that lasts for at least 12 hours [20]. We hypothesize that prednisolone will attenuate the increase in ucOC in response to exercise and that this will coincide with reduced insulin sensitivity compared with placebo. This design will enable us to examine whether changes in ucOC levels are related to changes in insulin sensitivity in young healthy men. We also aim to determine the fraction of the observed reduction in insulin sensitivity that is modulated by ucOC in humans.

A potential limitation of the current study is that GC are known to effect several other organs/tissues and not only osteoblasts. As such, it is plausible that a reduction in insulin sensitivity following acute GC treatment may not be entirely due to the reduction in ucOC. However, in mice the reduction in ucOC and insulin sensitivity occurred prior to the GC-induced effects in muscle, liver, and adipose following short-term GC treatment suggesting that the changes in insulin sensitivity are related to the reduction in ucOC levels and not to the GC effects on skeletal muscle, fat, or liver [17]. Nevertheless, in the current study we will be able to identify if acute GC treatment has immediate effects on GC-target genes (*gilz, Fkbp5*, fatty acid binding protein 4, hydroxysteroid (11-Beta) dehydrogenase 1, peroxisome proliferator-activated receptor gamma, and CCAAT/enhancer-binding protein alpha), and any detrimental effect on skeletal muscle, as markers of muscle atrophy and degradation will also be measured.

Another limitation is that the current study will investigate young, healthy men rather than patients with T2DM. As such, it will not be possible to generalize the results to this population. Follow-up studies will be required to confirm that changes in ucOC following interventions are related to changes in insulin sensitivity in patients with T2DM.

Conclusions

Current evidence connecting ucOC to insulin sensitivity in humans is supportive, but driven by cross-sectional studies. The current dynamic study will add important knowledge concerning the role of ucOC in insulin sensitivity in humans post exercise. The project is relevant to understanding pathway/s involved in exercise-induced insulin sensitivity and the potential for using osteoblast altering drugs as a target to improve insulin sensitivity in diseases like diabetes and obesity.

Acknowledgments

Associate Professor IL is supported by Future Leader Fellowship (ID: 100040) from the National Heart Foundation of Australia, and Dr TCB-S is supported by an NHMRC Early Career Research Fellowship (ID: 1013295).

Conflicts of Interest

None declared.

References

1. Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med 2001;7:941-946. [doi: 10.1038/90984] [Medline: 11479627]
2. Lee NK, Sowa H, Hinoi E, Ferron M, Ahn JD, Confavreux C, et al. Endocrine regulation of energy metabolism by the skeleton. Cell 2007;130:456-469 [FREE Full text] [doi: 10.1016/j.cell.2007.05.047] [Medline: 17693256]
3. Ferron M, Hinoi E, Karsenty G, Ducy P. Osteocalcin differentially regulates beta cell and adipocyte gene expression and affects the development of metabolic diseases in wild-type mice. Proc Natl Acad Sci U S A 2008;105:5266-5270 [FREE Full text] [doi: 10.1073/pnas.0711119105] [Medline: 18362359]
4. Levinger I, Lin X, Zhang X, Brennan-Speranza TC, Volpato B, Hayes A, et al. The effects of muscle contraction and recombinant osteocalcin on insulin sensitivity ex vivo. Osteoporos Int 2016;27:653-663. [doi: 10.1007/s00198-015-3273-0] [Medline: 26259649]
5. Liu D, Guo X, Tong H, Tao B, Sun L, Zhao H, et al. Association between osteocalcin and glucose metabolism: a meta-analysis. Osteoporos Int 2015;26:2823-2833. [doi: 10.1007/s00198-015-3197-8] [Medline: 26089135]
6. Kunutsor SK, Apekey TA, Laukkanen JA. Association of serum total osteocalcin with type 2 diabetes and intermediate metabolic phenotypes: systematic review and meta-analysis of observational evidence. Eur J Epidemiol 2015;30:599-614. [doi: 10.1007/s10654-015-0058-x] [Medline: 26085114]
7. Levinger I, Zebaze R, Jerums G, Hare DL, Selig S, Seeman E. The effect of acute exercise on undercarboxylated osteocalcin in obese men. Osteoporos Int 2011;22:1621-1626. [doi: 10.1007/s00198-010-1370-7] [Medline: 20734028]
8. Kanazawa I, Yamaguchi T, Yamauchi M, Yamamoto M, Kurioka S, Yano S, et al. Serum undercarboxylated osteocalcin was inversely associated with plasma glucose level and fat mass in type 2 diabetes mellitus. Osteoporos Int 2011;22:187-194. [doi: 10.1007/s00198-010-1184-7] [Medline: 20165834]
9. Brennan-Speranza TC, Conigrave AD. Osteocalcin: an osteoblast-derived polypeptide hormone that modulates whole body energy metabolism. Calcif Tissue Int 2015;96:1-10. [doi: 10.1007/s00223-014-9931-y] [Medline: 25416346]
10. Duncan GE, Perri MG, Theriaque DW, Hutson AD, Eckel RH, Stacpoole PW. Exercise training, without weight loss, increases insulin sensitivity and postheparin plasma lipase activity in previously sedentary adults. Diabetes Care 2003;26:557-562. [Medline: 12610001]

11. Wojtaszewski JF, Hansen BF, Gade, Kiens B, Markuns JF, Goodyear LJ, et al. Insulin signaling and insulin sensitivity after exercise in human skeletal muscle. Diabetes 2000;49:325-331. [Medline: 10868952]
12. Levinger I, Jerums G, Stepto NK, Parker L, Serpiello FR, McConell GK, et al. The effect of acute exercise on undercarboxylated osteocalcin and insulin sensitivity in obese men. J Bone Miner Res 2014;29:2571-2576 [FREE Full text] [doi: 10.1002/jbmr.2285] [Medline: 24861730]
13. Kim Y, Nam JS, Yeo D, Kim KR, Suh S, Ahn CW. The effects of aerobic exercise training on serum osteocalcin, adipocytokines and insulin resistance on obese young males. Clin Endocrinol (Oxf) 2015;82:686-694. [doi: 10.1111/cen.12601] [Medline: 25174991]
14. Cooper MS, Seibel MJ, Zhou H. Glucocorticoids, bone and energy metabolism. Bone 2016;82:64-68. [doi: 10.1016/j.bone.2015.05.038] [Medline: 26051468]
15. Henneicke H, Gasparini SJ, Brennan-Speranza TC, Zhou H, Seibel MJ. Glucocorticoids and bone: local effects and systemic implications. Trends Endocrinol Metab 2014;25:197-211. [doi: 10.1016/j.tem.2013.12.006] [Medline: 24418120]
16. Moghadam-Kia S, Werth VP. Prevention and treatment of systemic glucocorticoid side effects. Int J Dermatol 2010;49:239-248 [FREE Full text] [doi: 10.1111/j.1365-4632.2009.04322.x] [Medline: 20465658]
17. Brennan-Speranza TC, Henneicke H, Gasparini SJ, Blankenstein KI, Heinevetter U, Cogger VC, et al. Osteoblasts mediate the adverse effects of glucocorticoids on fuel metabolism. J Clin Invest 2012;122:4172-4189 [FREE Full text] [doi: 10.1172/JCI63377] [Medline: 23093779]
18. Mittelstadt PR, Ashwell JD. Inhibition of AP-1 by the glucocorticoid-inducible protein GILZ. J Biol Chem 2001;276:29603-29610 [FREE Full text] [doi: 10.1074/jbc.M101522200] [Medline: 11397794]
19. Davies TH, Ning Y, Sánchez ER. A new first step in activation of steroid receptors: hormone-induced switching of FKBP51 and FKBP52 immunophilins. J Biol Chem 2002;277:4597-4600 [FREE Full text] [doi: 10.1074/jbc.C100531200] [Medline: 11751894]
20. Nielsen HK, Charles P, Mosekilde L. The effect of single oral doses of prednisone on the circadian rhythm of serum osteocalcin in normal subjects. J Clin Endocrinol Metab 1988;67:1025-1030. [doi: 10.1210/jcem-67-5-1025] [Medline: 3263379]
21. Short KR, Nygren J, Bigelow ML, Nair KS. Effect of short-term prednisone use on blood flow, muscle protein metabolism, and function. J Clin Endocrinol Metab 2004;89:6198-6207. [doi: 10.1210/jc.2004-0908] [Medline: 15579778]
22. Szulc P, Chapuy MC, Meunier PJ, Delmas PD. Serum undercarboxylated osteocalcin is a marker of the risk of hip fracture in elderly women. J Clin Invest 1993;91:1769-1774 [FREE Full text] [doi: 10.1172/JCI116387] [Medline: 8473517]
23. Levinger I, Goodman C, Hare DL, Jerums G, Selig S. The effect of resistance training on functional capacity and quality of life in individuals with high and low numbers of metabolic risk factors. Diabetes Care 2007;30:2205-2210. [doi: 10.2337/dc07-0841] [Medline: 17563342]
24. Levinger I, Goodman C, Matthews V, Hare DL, Jerums G, Garnham A, et al. BDNF, metabolic risk factors, and resistance training in middle-aged individuals. Med Sci Sports Exerc 2008;40:535-541. [doi: 10.1249/MSS.0b013e31815dd057] [Medline: 18379218]
25. Heuck C, Wolthers OD. A placebo-controlled study of three osteocalcin assays for assessment of prednisolone-induced suppression of bone turnover. J Endocrinol 1998;159:127-131 [FREE Full text] [Medline: 9795350]
26. Kumar N, Crocker T, Smith T, Pow-Sang J, Spiess PE, Connors S, et al. Prostate cancer chemoprevention targeting high risk populations: model for trial design and outcome measures. J Cancer Sci Ther 2012;2011 [FREE Full text] [Medline: 22422102]
27. Hutchison SK, Stepto NK, Harrison CL, Moran LJ, Strauss BJ, Teede HJ. Effects of exercise on insulin resistance and body composition in overweight and obese women with and without polycystic ovary syndrome. J Clin Endocrinol Metab 2011;96:E48-E56. [doi: 10.1210/jc.2010-0828] [Medline: 20926534]
28. Stepto NK, Cassar S, Joham AE, Hutchison SK, Harrison CL, Goldstein RF, et al. Women with polycystic ovary syndrome have intrinsic insulin resistance on euglycaemic-hyperinsulaemic clamp. Hum Reprod 2013;28:777-784 [FREE Full text] [doi: 10.1093/humrep/des463] [Medline: 23315061]
29. Howlett KF, Mathews A, Garnham A, Sakamoto K. The effect of exercise and insulin on AS160 phosphorylation and 14-3-3 binding capacity in human skeletal muscle. Am J Physiol Endocrinol Metab 2008;294:E401-E407 [FREE Full text] [doi: 10.1152/ajpendo.00542.2007] [Medline: 18042670]
30. Gundberg CM, Nieman SD, Abrams S, Rosen H. Vitamin K status and bone health: an analysis of methods for determination of undercarboxylated osteocalcin. J Clin Endocrinol Metab 1998;83:3258-3266. [doi: 10.1210/jcem.83.9.5126] [Medline: 9745439]
31. Kingwell BA, Formosa M, Muhlmann M, Bradley SJ, McConell GK. Nitric oxide synthase inhibition reduces glucose uptake during exercise in individuals with type 2 diabetes more than in control subjects. Diabetes 2002;51:2572-2580 [FREE Full text] [Medline: 12145173]
32. Devlin JT, Hirshman M, Horton ED, Horton ES. Enhanced peripheral and splanchnic insulin sensitivity in NIDDM men after single bout of exercise. Diabetes 1987;36:434-439. [Medline: 3102297]

Abbreviations

DXA: dual-energy x-ray absorptiometry
ECG: electrocardiogram
Fkbp5: FK506-binding protein 5
GC: glucocorticoid
Gilz: glucocorticoid-induced leucine zipper
GIR: glucose infusion rate
P1NP: procollagen 1 N-terminal propeptide
PCR: polymerase chain reaction
T2DM: type 2 diabetes mellitus
ucOC: undercarboxylated osteocalcin

Edited by G Eysenbach; submitted 09.09.15; peer-reviewed by N Smart; comments to author 22.01.16; revised version received 24.01.16; accepted 25.01.16; published 03.06.16.

Please cite as:
Levinger I, Brennan-Speranza TC, Stepto NK, Jerums G, Parker L, McConell GK, Anderson M, Garnham A, Hare DL, Ebeling PR, Seeman E
A Single Dose of Prednisolone as a Modulator of Undercarboxylated Osteocalcin and Insulin Sensitivity Post-Exercise in Healthy Young Men: A Study Protocol
JMIR Res Protoc 2016;5(2):e78
URL: http://www.researchprotocols.org/2016/2/e78/
doi:10.2196/resprot.5119
PMID:27259402

Proposal

Why We Belong - Exploring Membership of Healthcare Professionals in an Intensive Care Virtual Community Via Online Focus Groups: Rationale and Protocol

Kaye Rolls[1,2,3], B AppSc, RN; Margaret Hansen[4], RN, MSN, CNL, EdD, Professor; Debra Jackson[5,6,7], RN, PhD, Professor; Doug Elliott[2], RN, PhD, Professor

[1]Agency for Clinical Innovation, Intensive Care Coordination and Monitoring Unit, Chatswood, Australia

[2]University of Technology Sydney, Faculty of Health, Sydney, Australia

[3]University of Syndey, Sydney Nursing School, Sydney, Australia

[4]University of San Francisco, School of Nursing and Health Professions, San Francisco, CA, United States

[5]Oxford Brookes University, Faculty of Health and Life Sciences, Oxford, United Kingdom

[6]NHS Foundation Trust, Oxford University Hospitals Foundation Trust, Oxford, United Kingdom

[7]University of New England, School of Health, Armidale, Australia

Corresponding Author:
Kaye Rolls, B AppSc, RN
Agency for Clinical Innovation
Intensive Care Coordination and Monitoring Unit
Sage Building, Albert Avenue
Chatswood, 2067
Australia
Phone: 61 +61294644666
Fax: 61 61294644728
Email: kaye.d.rolls@student.uts.edu.au

Abstract

Background: Many current challenges of evidence-based practice are related to ineffective social networks among health care professionals. Opportunities exist for multidisciplinary virtual communities to transcend professional and organizational boundaries and facilitate important knowledge transfer. Although health care professionals have been using the Internet to form virtual communities for many years, little is known regarding "why" they join, as most research has focused on the perspective of "posters," who form a minority of members.

Objective: Our aim was to develop a comprehensive understanding of why health care professionals belong to a virtual community (VC).

Methods: A qualitative approach will be used to explore why health care professionals belong to an intensive care practice-based VC, established since 2003. Three asynchronous online focus groups will be convened using a closed secure discussion forum. Participants will be recruited directly by sending emails to the VC and a Google form used to collect consent and participant demographics. Participants will be stratified by their online posting behaviors between September 1, 2012, and August 31, 2014: (1) more than 5 posts, (2) 1-5 posts, or (3) no posts. A question guide will be used to guide participant discussion. A moderation approach based on the principles of focus group method and e-moderation has been developed. The main source of data will be discussion threads, supported by a research diary and field notes. Data analysis will be undertaken using a thematic approach and framed by the Diffusion of Innovation theory. NVivo software will be used to support analyses.

Results: At the time of writing, 29 participants agreed to participate (Focus Group 1: n=4; Focus Group 2: n=16; Focus Group 3: n=9) and data collection was complete.

Conclusions: This study will contribute to a growing body of research on the use of social media in professional health care settings. Specifically, we hope results will demonstrate an enhancement of health care professionals' social networks and how VCs may improve knowledge distribution and patient care outcomes. Additionally, the study will contribute to research methods development in this area by detailing approaches to understand the effectiveness of online focus groups as a data collection method for qualitative research methods.

(JMIR Res Protoc 2016;5(2):e99) doi:10.2196/resprot.5323

KEYWORDS

focus groups; virtual communities; social media; qualitative methods; clinicians; intensive care

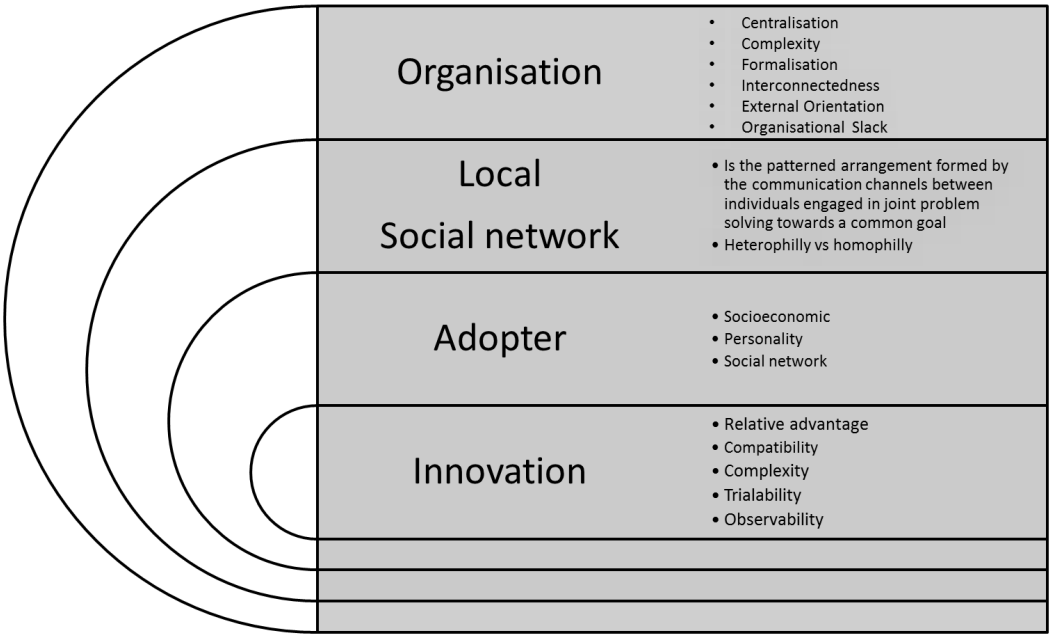
Introduction

Contemporary organizational [1] and learning theories [2] that highlight learning and behavior are influenced by social networks [3,4]. Many of the current challenges of evidence-based practice [3] are related to the ineffective social networks [5] created by professional and organizational boundaries [6,7]. While there is significant potential within multidisciplinary virtual communities (VC) to facilitate the transfer of research and best practice [6,8] and support the professional development of clinicians [9], at this time we know little of why health care professionals (HCPs) join or how they use a VC. The purpose of this paper is to present a research protocol for a study that aims to develop an understanding of why HCPs join a practice-based VC and how they use it.

Influence of Local Social Networks on Clinical Practice

For 30 years, evidence-based practices have been viewed as the gold standard. However, significant clinical practice variation and evidence-practice gaps persist [10-12]. According to Rogers' Diffusion of Innovation theory [13], the adoption of an innovation, such as new practices, research, or technologies, is mediated by characteristics of the innovation, an individual's adoption style and their social network, the broader social context, and time (see Figure 1 and Multimedia Appendix 1). Access to novel information requires a heterogeneous social network (where members may not have similar values and characteristics) where communication channels cross organizational and/or professional boundaries [14]. Furthermore, trials and final adoption decisions are strongly influenced by opinion leaders and peers [13,15-18]. However, current research suggests that the preferred information sources of many clinicians are a function of perceived credibility and ease of access [19-21] and that professional networks shape and limit clinical behaviors [4]. If clinicians do not have communication channels beyond local networks, they will not have access to novel knowledge and may be under the illusion that local practices reflect the majority [22]. Social media have the potential to improve HCP social networks by creating multidisciplinary VCs that facilitate knowledge exchange regardless of geography or time [6-8].

Figure 1. Diffusion of Innovation 5, 13.



Virtual Community Use by Health Care Professionals

Health care professionals have been using VCs since the early 1990s with long-term success stories including (1) Critical care mailing list launched in 1994 [23], (2) NurseNet founded in 1993 [24], and (3) MEDLIB started 1991 [25]. These VCs were created using early social media technologies including listserv and discussion forums [26]. The advent of Web 2.0 and the newer technologies of social networking and microblogging platforms have expanded the possibilities of professional networking and perhaps virtual communities [8]. While reasons for establishing a discrete VC vary, the most common motivation was to create a professional forum where relevant professional and academic issues may be discussed and

knowledge shared [27-39]. Unfortunately at this time, membership of many health care VCs is often homophilic (ie, the tendency to associate with individuals who share similar values and characteristics [13]) where members are commonly from a single health care discipline and usually work in a specific clinical specialty area [25,31,37,40-42]. Additionally there are limited population-based data describing how different types of HCPs are using the variety of social media platforms. In 2011, as few as 1.7% of emergency physicians were using Twitter [43] and 13.4% of Korean emergency physicians were using a Facebook page [44], whereas up to 20% of intensive care nurses [14], occupational health practitioners [45], or nurse practitioners [34] were using a professional listserv established for their use. These differences in uptake, and that each technology will be seen as an innovation, indicate a possible mediating factor related to the social medium itself [46] as well as the influence of peers [14,47].

The most common online activities undertaken by VC members are the solicitation and supply of experiential domain-specific knowledge [30,45,48]; however, 60-89% of members rarely post online [42,45,48,49]. A limited number of studies suggest that HCPs view VCs as valuable knowledge portals, enabling members to remain clinically current [50] with relevant and quality information [49,51], develop workplace resources [41], and benchmark practice [41,50]. This suggests HCPs use VCs to establish virtual professional networks [13] to enhance access to colleagues and best practice knowledge.

A reliance on readily available data and use of online observation has limited our understanding of how or why HCP use social media because this gathers data on a limited number of members. Given this, what motivates HCPs to join a VC, and what do they value that influences them to remain members? The absorption and diffusion of knowledge or innovation into and around an organization is the role of boundary spanners (eg, nursing unit managers or project officers) [52] and knowledge brokers (eg, nurses in education or advanced practice roles) [53]. Do these individuals see membership as part of personal professional development or as a tool for their substantive position, as preliminary data suggest [41]? Additionally, understanding these phenomena will assist health care leaders in understanding how to develop VC to optimally leverage social media to improve knowledge diffusion and patient care.

Online Focus Groups

Focus groups are used by researchers to gather qualitative data on specific group experiences by capitalizing on group dynamics to synergistically develop a deeper, richer understanding of a phenomenon of interest [54,55]. Moreover, the collective conversation between participants facilitates the gathering of individual and group voices, which may uncover an understanding not available via other data collection modes (eg, surveys or interviews) and democratizes the research by decentering the researcher [54]. A moderator guides participants through a discussion commonly using a guide based on the core research questions and objectives and evolves as data emerge [55]. While face-to-face focus groups are acknowledged as a strong method for gathering qualitative data [55], there can be significant logistical challenges, such as convening the focus group on a specific date and time and at a location that facilitates maximal participation. Online or virtual focus groups are becoming more common as they enable participation of geographically distributed and time-poor individuals and are less expensive to conduct [55,56]. Online focus groups have been used to examine a diverse range of health-related questions, with considerable variation in methods used across studies (see Table 1). While the term “virtual focus group” is more commonly used, we use the term “online focus group” to avoid confusion with the term “virtual community.”

Table 1. Use of virtual focus groups in health[a].

Author, year, country	Aim	Focus group + participants	Running the virtual focus group (VFG)	Data analysis
Alonzo, 2009, USA [61]	What motivates associate degree and diploma-prepared RN to pursue a baccalaureate degree through an RN-to-BSN program	4 VFG (2-6 participants); nurses; 2 weeks	Asynchronous using discussion forum and a question guide (11)	Inductive content analysis
Synnot, 2014, Australia [62]	Compare face-to-face and VFG for people with multiple sclerosis & relatives regarding needs, experiences, preferences, and values when integrating evidence-based health information into their decision making about the management of their health	4 face-to-face (27participants); 1 VFG (33 participants) over 2 months	Asynchronous using discussion forum; 10-question guide	Thematic analysis
Hanson, 2011, USA [63]	To explore fieldwork educator motivations for working with students and the kind of support needed from the academic institution (occupational therapists enrolled in master's program)	2 VFG based on stratification to pediatric & adult practice settings (10 participants); over 2 weeks; credit incentives for participation	Asynchronous using discussion forum; all questions posted at start with instructions for students to respond to each question plus 2 peer responses	Content analysis
Tates, 2009, Netherlands [64]	Determine what constitutes good quality of communication with a diagnosis of childhood cancer, in terms of participation and role delineation from their point of view	3 VFG grouped by type (7 current patients, 11 parents of these patients; 18 survivors)	Asynchronous using discussion forum; daily questions over 1 week	Not described
Harmsen, 2013, Holland [65]	Gain insight into factors that influence parents to not vaccinate their children	8 VFG; 5 non-vaccinators (n=39; 7-9); 3 partial (n=21; 7 each); running over 5 days	Asynchronous using discussion forum; predetermined topics introduced daily with open questions; anonymous	Thematic analysis
Murray, 2001, International [66]	To test method and gather data to inform interviews; part of a mixed methods study to gather data & test method	2 VFG Educators and listserv experts (N not provided); 4 weeks	Asynchronous using listserv	Not explained
Adler, 2002, USA [67]	VFG as mode of data collection; lived experience of women confined to best rest because at risk of preterm labor; value of VFG as peer support	1 FG (7); 4 weeks	Asynchronous using listserv; Question guide – 6 (semistructured, open ended)	Content analysis for thematic coding
Kenny, 2005, Australia [51]	Whether active engagement and group interaction could be captured in an online environment in an EN conversion program	1 FG with census sample	Asynchronous using Web CT starting with one question; ran for 2 months	Thematic analysis
Pechak, 2002, USA [68]	Develop recommendations for implantation of ICE in physical therapist education to promote ethical practice	1 VFG (5 participants); followed by 3 delphi rounds (19 participants)	Synchronous using Blackboard; anonymous; highly structured feedback on predetermined script	Not described
Levine, 2011, USA [69]	Involve youth of color in design of programmatic content and formats for an Internet intervention for sex education	4 synchronous FG (7,5,4,2 participants); 1 asynchronous (18 participants)	Synchronous using chat room (4 by 1 hr); switched to asynchronous due to low numbers – 7 days with daily questions (9 in total)	Not described
Brubaker, 2012, USA [70]	Gather information about women's knowledge and attitudes regarding research participation	2 FG grouped by research-experience or research-naive (12 in total); study protocol also include 14 face-to-face FG	Synchronous using semistructured discussion guides	
Tuttas, 2014, USA [71]	Capture travel nurses' perceptions of boarding experiences	4 FG (2-5 participants); registered nurses	Synchronous using Web conferencing and a question guide (5 questions); over 45-60 minutes	Qualitative content analysis

[a]BSN baccalaureate science nursing; EN enrolled nurse; FG focus group; ICE international clinical education; RN registered nurse; VFG virtual focus group.

Two modes of online focus groups are possible: synchronous and asynchronous. The synchronous mode closely matches face-to-face groups where participants meet in real time using chat rooms or discussion boards. While this mode may promote a more dynamic discussion with high levels of feedback, an individual's typing speed, connection bandwidth, and thought speed may impact users' ability to effectively participate [55]. Asynchronous groups have been conducted using either listserv or discussion forum technology, providing participants with time to consider their posts or responses, and enable posting at a time of their convenience. Other advantages of the asynchronous mode include immediate creation of a threaded discussion facilitating review by members as well as data collection and analysis [55,57]. Study credibility is enhanced

[58] by participant-controlled, real-time data collection. While the asynchronous mode may facilitate the development of more reflexive answers [56], large participant numbers may create two methodological issues: (1) the quality of interaction, and therefore data, may be limited because the volume of posts is off-putting and/or too high for participants to review properly, and (2) moderation is more challenging. A high volume of data also may make data analysis more difficult.

As noted above, considerable variation exists regarding how researchers structure online focus groups (see [55]. In addition, most VC members do not actively post online and the decision to post is complex [59,60]. Focus group participants may be more inclined to disclose their experiences and opinions where they feel they share values and beliefs with other group members and there is no group hierarchy [61]. This homogeneity along with efficient moderation can lead to effective group interactions resulting in quality data [55]. The ideal moderator understands both the context of the research and the cultural world of participants [62,63]. However, effective online moderation requires additional skills and interventions that socialize participants to the online space and encourages posting [64]. Two other important considerations are that the platform chosen is user-friendly (ie, easy to access and use and esthetically pleasing) [65] and the posts are confidential [66].

A key component of a focus group is the discussion guide that frames and focuses discussions and ensures collection of rich in-depth data [55,62]. Questions should reflect the study questions and funnel discussions through introductory, transition, and key questions to ensure consistent data where multiple groups are used and aid data analysis [67]. Introductory questions encourage participation and provide participants and researchers with an understanding of individual perspectives [55]. These are similar to activities undertaken as part of an e-moderation process to support effective online learning, including establishing an effective group, introduction of the research phenomena, and induction of participants to the online environment [64].

Focus Groups and Virtual Communities

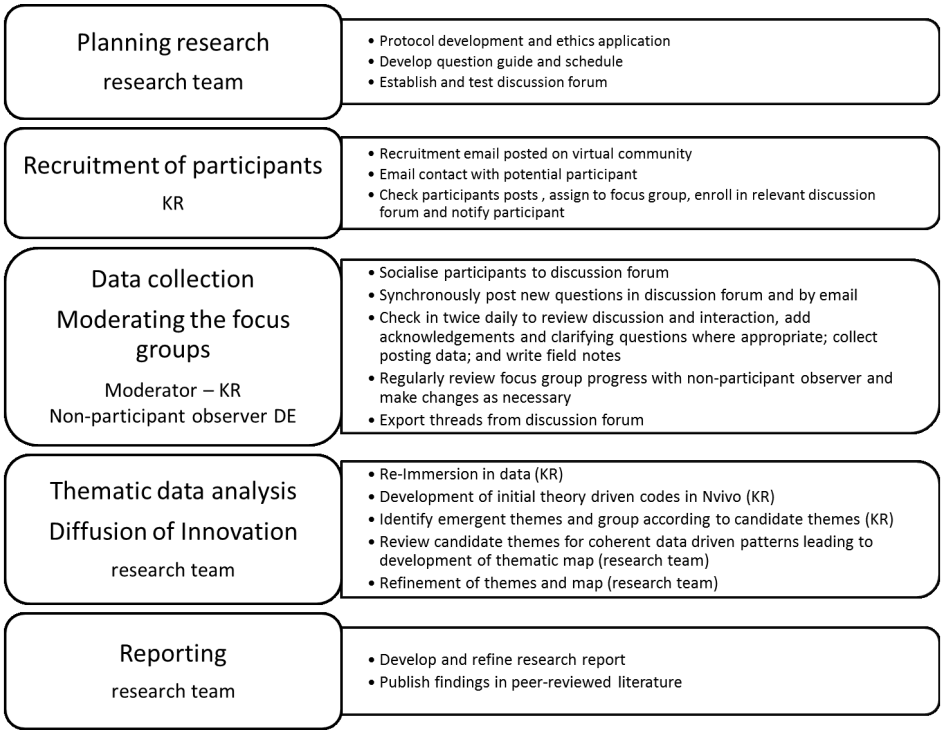
While focus groups are frequently used to collect data for qualitative or mixed-methods studies, only two studies [31,68] were identified that examined HCP experiences of virtual communities or computer-mediated communication. In a mixed-methods study exploring how and why occupational therapists used a virtual community of practice (VCoP), two face-to-face focus groups (stratified by use or not of the VCoP) were used to develop a survey instrument [31]. In earlier work [68], two online asynchronous focus groups were convened using listserv technology to explore current practice and future potential of text-based computer-mediated communication as a mechanism for qualified nurses to meet their formal and informal continuing professional development needs. In this latter study, questions were introduced at the beginning of the focus group, with the author later reflecting that this was overwhelming for some participants [69]. While listserv technology is the most straightforward and accessible of all VC platforms, it may not result in a chronologically ordered discussion thread. This may be difficult for both the participants and moderator to follow the discussion, especially those with multiple posts, and could therefore limit interaction and conversation development with probable negative effects on data. Data analysis is also more complicated because of difficulties in understanding the chronology and/or evolution of a discussion.

The aim of this study is to explore why HCPs belong to an intensive care practice-based VC. The main objectives are to (1) understand why members join and remain members, (2) identify what purpose the VC serves in in their professional lives, (3) identify how a member uses the VC, and (4) identify how they have used the knowledge or resources shared on the VC.

Methods

A qualitative approach will be used to collect data using three asynchronous online focus groups, with participants allocated to a group based on their posting behaviors in the past 2 years. The study is framed by the Diffusion of Innovations theory [13]. A summary of the protocol is provided inFigure 2.

Figure 2. Study protocol summary.



Ethics

Approval has been granted by a University Human Research Ethics Committee (UTS HREC REF NO. 2014000378). Participant confidentially will be ensured using two measures: (1) a group rule, covering non-disclosure of participant names or sharing the content of posts, will be developed and participants will be asked to agree to it on participant registration, and (2) focus groups will be convened within a secure website using a closed, password-protected discussion forum with any social media sharing function disabled. These layers are designed to protect participant anonymity and prevent forum posts from being searchable via the Web [66].

Setting

The VC is a professional listserv established in 2003 by an Australian state health department to reduce the sense of professional isolation and improve knowledge distribution between the 43 intensive care units [51]. By mid-2014, there were more than 1700 members from more than 225 health care facilities, universities, and industry partners, spread throughout several countries with most being Australian intensive care clinicians and nursing being the largest professional group. Analysis of the social network of the VC suggests that it is highly valued by members because the majority of HCP who join choose to remain members for extended periods and recommend the VC to colleagues [14]. The VC would be classified as a VC with an interdisciplinary culture and stable membership, a medium geographic distribution, and an open and voluntary enrollment [70].

Participants and Sample

A purposive sampling method will be used to recruit between 24 and 36 participants for the three focus groups. The sample size is based on recruiting 8-12 participants per group, which is the current recommendation for both traditional [55] and online [65] focus groups. Members of the VC will be invited to participate via a recruitment email posted to the VC, providing all participant information, and an invitation to contact the research team for further information, and a link to the online recruitment form (Google forms). The online recruitment form will include participant information, consent, participant demographics, and a short survey covering group rules (see Multimedia Appendix 2). Once a potential participant has completed the online registration and consent, their posting behavior will be checked, they will be assigned to a focus group, and they will be notified of the details regarding this focus group.

To develop an understanding of a range of member types, we chose to undertake three focus groups based the online activity of a VC member. Participants will be purposely assigned to a focus group based on their posting activities on the VC in the last 2 years (onlist posting) (September 1, 2012, to August 31, 2014): (1) more than five times, (2) five times or less, and (3) not posted. We will not cap the number of participants as dropouts or inabilities to participate have been identified as limitations by previous researchers [71,72]. The only exclusion criteria will be non-availability over the 3-week time frame for each focus group.

Recruitment challenges are anticipated. As the majority of VC members do not post, this reduces the number of potential candidates for the posting groups particularly for Groups 1 and 2. A review of 12 months of activity identified at least 25 members eligible for focus Groups 1 and 2. While there are a high number of potential members for the non-posting group, these members are reluctant to post for a variety of reasons, especially about how their contribution might be received by members of the virtual community. We hope that by convening focus groups where the shared characteristic is posting,

behaviors will create an online space where individual members feel comfortable and confident that their contributions will be met in a positive and supportive environment [56].

Moderation

The approach to moderation of the focus groups is based on principles from moderating traditional focus groups [55] and facilitating learning online or e-moderating [62-64]. The first author will be the moderator and is an experienced intensive care nurse and was the previous moderator of the VC. Author 4 will be a non-participant observer. To facilitate access to and understanding of the focus group platform, a "how-to" guide has been developed as an important component of providing access and motivation to post in an online forum [64].

Running the Online Focus Groups

The focus groups will be run over 3 weeks using a closed discussion forum (IPBoard version 3, Invision, Powerboard) hosted on a secure jurisdictional health department website. The focus groups will be held consecutively, which will allow for refinement of the question guide based on data from a previous group [73]. This approach was developed to enable optimal participation and interaction, safeguarding participant confidentiality, facilitating moderation and effective data collection. The host site was chosen as it was accessible and useable across fixed and mobile technologies. A discussion forum was chosen for a number of reasons. Discussion forums are asynchronous and create a chronological electronic record where participants will be able to review what has been posted, have time to consider and formulate a response, and then post at a time convenient to them [57]. This should promote a more egalitarian focus group as all participants will have the opportunity to provide input. This enhances participant control and may encourage more detailed and reflective answers, and thus potentially richer data [55]. As the discussion moves forward, a record is created providing participants with chronological discussion points and data collection is facilitated through the development of discussion threads.

Question Guide and Discussion Schedule

A question guide (see Table 2) was developed with questions based on the research questions and the theoretical framework of diffusion of innovations [13]. A schedule will be developed with new questions posted every 2-3 days depending on how the discussion is developing. To facilitate visibility of the study and new questions, an email using a standardized subject heading will be sent to participants alerting them to new content. The moderator will access the forum at least twice each day for promoting interaction (eg, reviewing posts, answering questions, or adding additional questions to clarify participants' views) [71,72], regularly thank and encourage participants, and re-inforce the value of posting [64].

Table 2. Question guide.

Type of question	Questions	Possible aspect of diffusion of innovation[a,b]
Introductory question	Please introduce yourself and tell the group about your professional role and experience.	
Transition question	You were invited to this focus group because you are a member of ICU-Connect. Could you explain what prompted you to join?	Type of adopter; homophily; influence of peers
	Do you use any other social media or online communities for professional networking and development?	Type of adopter; external orientation; interconnectedness; Innovation characteristics of social media
Key question	What do you value most about ICUConnect?	Access to colleagues (homophily), external orientation; interconnectedness; Innovation characteristics of social media
	What are the least valuable aspects of ICUConnect?	Innovation characteristics of social media
	What advantages or disadvantages does ICUConnect have over other social media?	See above
	Current research indicates that there are active users of virtual communities (individuals who post) and passive users (individuals who mainly read &/or share). How would you describe how you use ICUConnect?	Type of innovator: role of individual in local social network
	Do you share ICUConnect posts with other professional colleagues?	Role of individual in local social network; external orientation
	Is there a post in the past 3 months that has been of high relevance to you?	Knowledge (innovation) on IC-VC is credible
	Have you been able to use any posts from the last 6 months of discussions?	As above
Concluding question	Are there any other important aspects of ICUConnect that we have not discussed?	As above

[a][5,13].

[b]See Figure 1 and Multimedia Appendix 1.

Data Analyses

Study data will include (1) demographic data describing participant characteristics, (2) categorical data describing discussion forum participation, (3) discussion threads documenting focus group discussion, and (4) field notes. Discussion threads will be extracted from the Forums using NCapture (QRS International). NVivo (QRS International) will be used to manage data analyses. A research diary and field notes will be maintained to support analyses. Initial analyses will be conducted by KR, supported by scheduled reviews with the research team to evaluate progress and reach consensus regarding themes and other interpretations. Analysis of the discussion threads will be undertaken using a thematic approach [74], framed by the diffusion of innovation [13]. Thematic analysis is a 6-phase process allowing the researcher to systematically identify, analyze, and report patterns found in qualitative data [74]. During Phase 1, KR will be immersed in the data through active reading of discussion threads and looking for meanings or patterns. This familiarization will commence during data collection because of the dual role of researcher-moderator. DE also will be familiar with the data in his role as researcher-participant observer. During Phase 2, the initial codes will be generated; these codes will be theory driven and will represent the most basic element of the raw data that is meaningful. Additionally, code descriptors will be developed to ensure systematic coding. In Phase 3, we will look for themes by grouping codes into candidate themes. In Phase 4, we will refine this list of themes by reviewing the coded extracts and looking for a coherent pattern within each theme and ensure there is sufficient data to support it. Once we have achieved this, we will move on to developing the thematic map, which reflects how well the themes represent the data as a whole. Re-reading the whole dataset is essential, and some recoding may be required at this point. During Phase 5, we will define and refine the themes by identifying the essence of the theme and determining which aspect of the data it captures. This involves developing a detailed analysis of each theme and its associated subthemes. In the last phase, we will provide a written report of our analyses.

Diffusion of innovation [13] was chosen as the theoretical lens because the research team felt it was a better match for both the broad problem of inadequate social networks limiting knowledge diffusion in health care and the current gaps in the literature. While other behavioral models, including theory of reasoned action [75], theory of planned behavior [75], and technology acceptance model [46], have been used and produced important insights, they are focused on an individual's behavior.

Study Quality

Rigor in qualitative research is a contentious area [58,76,77]. The preferred terms of "trustworthiness" or "confirmability" reflect accuracy and comprehensiveness in how data were collected, analyzed, and reported. For this study, several strategies will be used. Credibility of data will be enhanced as participants have direct control over their contributions that will be recorded in real time, and by use of NVivo software as the major study file repository for the research diary, field notes, and data, thus establishing a clear audit trail [78]. A "thick" description of the research context will be provided by describing the participants (using the recruitment survey), virtual community, and research process (p. 69 [58]). Auditability will be supported by field notes, recording impressions arising from focus groups, and NVivo to manage data analyses. Data credibility will be enhanced by presenting preliminary themes to participants for early review (member checking) [56].

Field notes record what the researcher experiences during data collection and includes (1) both a description of and reflection on what occurred, (2) a reflective journal that includes personal thoughts and feelings, and (3) any insights, judgments, and interpretations made in the field [76,78]. Field notes will facilitate both data collection (eg, aid in development of elaboration and clarification questions) and analysis (eg, through the development of preliminary themes).

Researcher Bias and Relationship With Participants

The potential for bias in qualitative research may be significant when the research team fails to understand and then manage their assumptions and biases. In addition, where there is an unequal or prior relationship between the research team and participants, data collected may not reflect the reality of participant experience. In this study, KR was a long-term moderator of the VC and DE is a member. However, the other authors are not members or associated with the VC. To manage any potential for bias during data collection and analyses, a number of procedures will be implemented: (1) KR withdrew from the moderator role several months prior to VC members' being aware of the research (all stages of the study), (2) to minimize coercion in all communications, KR will describe participants in a passive research guise and will not make any direct communications with individual members, (3) KR will undergo a bracketing process prior to the first focus group, outlining the researcher position by documenting any assumptions and therefore identifying potential sources of bias [79,80], and forming part of the research diary, (4) assumptions will be revisited during data analyses, (5) during focus group moderation, the roles as researcher (KR) and non-participant observer (DE) will be explicitly described, (6) to minimize bias and enhance credibility, all researchers will be responsible for data analysis, and (7) member checking will be undertaken by posting preliminary results in the discussion forums for participants to provide feedback.

Results

At the time of writing, 29 VC community members have been recruited and the focus groups were conducted October to December 2014 with these participants. Table 3 shows focus group recruitment outcomes and professional roles of participants. There was mixed participation across the focus groups (3, 9, and 7 respectively), which may create challenges for data analyses.

Table 3. Focus group recruitment outcomes.

Type of member	Focus group 1: Frequent posters (>5)	Focus group 2: Low posters (1-5)	Focus group 3: Non posters	Total
Clinical nurse-internal[a]		4	2	6
Clinical nurse-external[b]		1	1	2
Knowledge broker nurse[c]	3	4	2	9
Clinical unit manager[d]	1	2	1	4
Academic nurse[e]		4	1	5
Physiotherapist			1	1
Physician		1		1
Bureaucrat[f]			1	1
Total	4	16	9	29
Post range	6-19	1-4 (mode 1; median 1)		

[a]Clinical nurse internal provides clinical services within a clinical unit.

[b]Clinical nurse external provides clinical services across multiple clinical unit.

[c]Knowledge broker job role could include advanced practice, education, research, or practice development.

[d]Clinical unit manager manages a defined ward or clinical area.

[e]Academic nurse is employed by a tertiary education institution.

[f]Bureaucrat is employed in a non-clinical or managerial role in health service.

Discussion

Principal Considerations

Like the rest of the community, HCPs are adopting social media platforms, although uptake varies considerably [14,34,43,44]. Despite positive attitudes towards social media, this has not translated to significant professional use [81]. There are some data suggesting this is influenced by individual characteristics [46], peers [46,82], and perceptions of the platform as an innovation [46]. At this time, however, the research base on why or how HCPs use these communities or social media is limited because online observation reveals the perspective of a minority of VC members [25,27,32,42,45,49,83] and measurement [25,36,44,49,84-87] and sample [31,49,84,88-92] bias in surveys. It has been suggested that a comprehensive understanding of VCs requires a mixed-methods approach that includes a member survey, content analysis, and social network analysis [93]. Social network analysis has revealed that members have more complex reading than posting behaviors [39]; however, this will not reveal member motivations and will be limited to platforms where these data are available.

The aim of this study is therefore to develop a comprehensive understanding of why members belong to an intensive care practice-based virtual community for HCPs. This includes understanding why they join and remain members, identifying the purpose of the VC in their professional lives, and understanding how they use the VC, and what they do or how they use the knowledge or resources obtained. By using focus groups, we will be able to examine the experiences of all types of VC members, leading to a more complete understanding of why HCPs join and use social media. By using the diffusion of innovation as a theoretical lens, we also examine the phenomena from several perspectives including social media as an innovation, the VC as an IC-VC, VC member adopter type, and VC as a social network. We hope to show that VC membership enhances the professional (social) networks of HCPs and access to valuable knowledge, to improve clinical practice, and by extension patient outcomes.

There are a number of possible benefits arising from this study. The study will provide data about participation in this VC, particularly as a method to support evidence-based practice and professional development [8] and address patient care challenges [6]. As this VC is part of a jurisdictional health department initiative, the health system and broader community may benefit by demonstrating the viability and value of social media to improve the social networks of intensive clinicians and as a knowledge diffusion and adoption initiative. Findings may also allow the development of a survey instrument to gather data from a larger sample of VC members and on other VCs. This study will also contribute understanding on the efficacy of online focus groups as a data collection method for qualitative research methods.

Strengths and Limitations

There are several strengths and limitations of this study. Two elements limit generalizability to the broader population of HCPs, namely the qualitative design using focus groups and the Australian intensive care setting. However, in the current literature, generalizability of surveys is hampered by sampling bias [31,49,84,88-92]. Our design leverages the advantages of online focus groups with learnings from virtual tertiary education [64] to facilitate participation by a broad range of members thus providing an extensive understanding of the experiences of all types of members, especially the non-posting majority. Our recruitment has been moderately successful in gaining adequate participants for the low and non-posting focus

groups but not for the high-posting group [65]. This may limit the quality and quantity of data arising from this focus group.

Conclusions

This study aims to contribute to the growing body of research on the use of social media; specifically we hope it will demonstrate this by enhancing access to social networks for HCPs. VCs may improve collegiality, data sharing, knowledge distribution, and ultimately patient care and health outcomes. Additionally, the study will contribute to qualitative research methods by evaluating the utility of online focus groups as a data collection approach.

Authors' Contributions

KR, MH, DJ, and DE conceived the study design and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Description of terms used in Diffusion of Innovations framework.

[PDF File (Adobe PDF File), 35KB - resprot_v5i2e99_app1.pdf]

Multimedia Appendix 2

Online recruitment - demographics and group rules.

[PDF File (Adobe PDF File), 34KB - resprot_v5i2e99_app2.pdf]

References

1. Drucker PF. The new society of organizations. Harvard Business Review 1992(Sept-Oct):95-104.
2. Wenger E. Communities of practicesocial learning systems. In: Starkey K, Tempest S, McKinlay A, editors. How organisations learn: Managing the search for knowledge. Thomson Learning: London; 2004:238-258.
3. Borgatti SP, Halgin DS. On Network Theory. Organization Science 2011 Oct;22(5):1168-1181. [doi: 10.1287/orsc.1100.0641]
4. Dopson S, FitzGerald L, Ferlie E, Gabbay J, Locock L. No magic targets! Changing clinical practice to become more evidence based. Health Care Manage Rev 2002;27(3):35-47. [Medline: 12146782]
5. Kyriakidou O, Bate P, Peacock R, Greenhalgh T, MacFarlane F. Diffusion of innovations in health service organisations: a systematic literature review. Malden, MA: Blackwell; 2005.
6. McGowan B. #SocialQI: simple solutions for improving your healthcare. Sioux Falls, SD: No Limit Publishing; 2012.
7. Currie G, White L. Inter-professional Barriers and Knowledge Brokering in an Organizational Context: The Case of Healthcare. Organization Studies 2012 Oct 22;33(10):1333-1361. [doi: 10.1177/0170840612457617]
8. Burrell AR, Elliott D, Hansen MM. ICT in the ICU: using Web 2.0 to enhance a community of practice for intensive care physicians. Crit Care Resusc 2009 Jun;11(2):155-159. [Medline: 19485881]
9. Barnett S, Jones SC, Bennett S, Iverson D, Bonney A. General practice training and virtual communities of practice - a review of the literature. BMC Fam Pract 2012;13:87 [FREE Full text] [doi: 10.1186/1471-2296-13-87] [Medline: 22905827]
10. Hewson-Conroy KM, Burrell AR, Elliott D, Webb SAR, Seppelt IM, Taylor C, et al. Compliance with processes of care in intensive care units in Australia and New Zealand--a point prevalence study. Anaesth Intensive Care 2011 Sep;39(5):926-935. [Medline: 21970141]
11. Melnyk BM, Fineout-Overholt E, Gallagher-Ford L, Kaplan L. The state of evidence-based practice in US nurses: critical implications for nurse leaders and educators. J Nurs Adm 2012 Sep;42(9):410-417. [doi: 10.1097/NNA.0b013e3182664e0a] [Medline: 22922750]
12. Oborn E, Barrett MG, Racko G. Knowledge translation in healthcare: a review of the literature.: Cambridge University; 2010. URL: https://www.jbs.cam.ac.uk/fileadmin/user_upload/research/workingpapers/wp1005.pdf [WebCite Cache ID 6cU9Kj12O17]
13. Rogers E. Diffusion of innovations. New York: Free Press; 2003.
14. Rolls KD, Hansen M, Jackson D, Elliott D. Analysis of the social network development of a virtual community for Australian intensive care professionals. Comput Inform Nurs 2014 Nov;32(11):536-544. [doi: 10.1097/CIN.0000000000000104] [Medline: 25310223]
15. Granovetter M. The strength of weak ties: a network theory revisited. In: Marsden P, Lin N, editors. Social Structure and Network Analysis. New York: John Wiley and Sons; 1982:105-130.
16. Fleuren M, Wiefferink K, Paulussen T. Determinants of innovation within health care organizations: literature review and Delphi study. Int J Qual Health Care 2004 Apr;16(2):107-123 [FREE Full text] [doi: 10.1093/intqhc/mzh030] [Medline: 15051705]

17. Locock L, Dopson S, Chambers D, Gabbay J. Understanding the role of opinion leaders in improving clinical effectiveness. Soc Sci Med 2001 Sep;53(6):745-757. [Medline: 11511050]
18. Valente T. Diffusion of Innovations and Policy Decision-Making. J Communication 1993 Mar;43(1):30-45. [doi: 10.1111/j.1460-2466.1993.tb01247.x]
19. Marshall AP, West SH, Aitken LM. Preferred information sources for clinical decision making: critical care nurses' perceptions of information accessibility and usefulness. Worldviews Evid Based Nurs 2011 Dec;8(4):224-235. [doi: 10.1111/j.1741-6787.2011.00221.x] [Medline: 21649854]
20. Curran JA, Murphy AL, Sinclair D, McGrath P. Factors influencing rural and urban emergency clinicians' participation in an online knowledge exchange intervention. Rural Remote Health 2013;13(1):2175 [FREE Full text] [Medline: 23374031]
21. Kostagiolas P, Korfiatis N, Kourouthanasis P, Alexias G. Work-related factors influencing doctors search behaviors and trust toward medical information resources. International Journal of Information Management 2014;34(2):80-88. [doi: 10.1016/j.ijinformgt.2013.11.009]
22. Lerman K, Yan X, Wu XZ. The Majority Illusion in Social Networks. Social and Information Networks 2015. [doi: 10.1371/journal.pone.0147617]
23. DeWitt AL, Gunn SR, Hopkins P, Streat S. Critical care medicine mailing list: growth of an online forum. BMJ 2004 May 15;328(7449):1180 [FREE Full text] [doi: 10.1136/bmj.328.7449.1180] [Medline: 15142927]
24. Murray PJ. Nurses' computer-mediated communications on NURSENET. A case study. Comput Nurs 1996;14(4):227-234. [Medline: 8718843]
25. Schoch NA, Shooshan SE. Communication on a listserv for health information professionals: uses and users of MEDLIB-L. Bull Med Libr Assoc 1997 Jan;85(1):23-32 [FREE Full text] [Medline: 9028568]
26. Paton C, Luquel L. IMIA Social Media Working Group. URL: https://imiasocialmedia.wordpress.com/about/ [accessed 2015-02-14] [WebCite Cache ID 6WKFGBTs0]
27. Berman Y. Discussion groups on the Internet as sources of information: the case of social work. Aslib Proceedings 1996 Feb;48(2):31-36. [doi: 10.1108/eb051407]
28. Roberts C, Fox N. General practitioners and the Internet: modelling a 'virtual community'. Fam Pract 1998 Jun;15(3):211-215 [FREE Full text] [Medline: 9694177]
29. Cervantez Thompson Teresa L. You've got mail: rehabilitation nurses on the RehabNurse-L LISTSERV. Rehabil Nurs 2002;27(4):146-151. [Medline: 12116527]
30. Long S, de Jonge JD, Ziviani J, Jones A. Paediatricots: Utilisation of an Australian list serve to support occupational therapists working with children. Aust Occup Ther J 2009 Feb;56(1):63-71. [doi: 10.1111/j.1440-1630.2007.00716.x] [Medline: 20854490]
31. Hoffmann T, Desha L, Verrall K. Evaluating an online occupational therapy community of practice and its role in supporting occupational therapy practice. Aust Occup Ther J 2011 Oct;58(5):337-345. [doi: 10.1111/j.1440-1630.2011.00954.x] [Medline: 21957918]
32. Thomas R, James S. Informal communications networking health professionals: a study of gp-uk. Health Informatics Journal 1999;5(2):74-81. [doi: 10.1177/146045829900500204]
33. Valaitis RK, Akhtar-Danesh N, Brooks F, Binks S, Semogas D. Online communities of practice as a communication resource for community health nurses working with homeless persons. J Adv Nurs 2011 Jun;67(6):1273-1284. [doi: 10.1111/j.1365-2648.2010.05582.x] [Medline: 21306424]
34. Widemark E. Community and Learning: A Virtual Community of Practice for Nurse Practitioners. In: Education. Ann Arbor, MI: Capella University; 2009.
35. Foong DPS, McGrouther DA. An Internet-based discussion forum as a useful resource for the discussion of clinical cases and an educational tool. Indian J Plast Surg 2010 Jul;43(2):195-197 [FREE Full text] [doi: 10.4103/0970-0358.73448] [Medline: 21217980]
36. Watson DAR. Ozbug: an email mailing list for physicians that works. Intern Med J 2003 Nov;33(11):532-534. [Medline: 14656258]
37. Smith C. A Longitudinal Study of the Culture of MEDLIB-L. J Hosp Librarianship 2004 Mar 24;4(1):29-43. [doi: 10.1300/J186v04n01_03]
38. Reutzel TJ, Patel R. Medication management problems reported by subscribers to a school nurse listserv. J Sch Nurs 2001 Jun;17(3):131-139. [Medline: 11885443]
39. Stewart SA, Abidi SSR. Applying social network analysis to understand the knowledge sharing behaviour of practitioners in a clinical online discussion forum. J Med Internet Res 2012;14(6):e170 [FREE Full text] [doi: 10.2196/jmir.1982] [Medline: 23211783]
40. Hara N, Foon Hew K. Knowledge ‐ sharing in an online community of health ‐ care professionals. Info Technology & People 2007 Aug 28;20(3):235-261. [doi: 10.1108/09593840710822859]
41. Thompson TL, Penprase B. RehabNurse-L: an analysis of the rehabilitation nursing LISTSERV experience. Rehabil Nurs 2004;29(2):56-61. [Medline: 15052747]
42. Brooks F, Scott P. Knowledge work in nursing and midwifery: an evaluation through computer-mediated communication. Int J Nurs Stud 2006 Jan;43(1):83-97. [doi: 10.1016/j.ijnurstu.2005.02.003] [Medline: 16326164]

43. Lulic I, Kovic I. Analysis of emergency physicians' Twitter accounts. Emerg Med J 2013 May;30(5):371-376. [doi: 10.1136/emermed-2012-201132] [Medline: 22634832]
44. Kim C, Kang BS, Choi HJ, Lee YJ, Kang GH, Choi WJ, et al. Nationwide online social networking for cardiovascular care in Korea using Facebook. J Am Med Inform Assoc 2014;21(1):17-22 [FREE Full text] [doi: 10.1136/amiajnl-2012-001465] [Medline: 23703828]
45. Morken T, Bull N, Moen BE. The activity on a Norwegian Occupational Health mailing list 1997-2006. Occup Med (Lond) 2009 Jan;59(1):56-58 [FREE Full text] [doi: 10.1093/occmed/kqn143] [Medline: 19001070]
46. McGowan BS, Wasko M, Vartabedian BS, Miller RS, Freiherr DD, Abdolrasulnia M. Understanding the factors that influence the adoption and meaningful use of social media by physicians to share medical information. J Med Internet Res 2012;14(5):e117 [FREE Full text] [doi: 10.2196/jmir.2138] [Medline: 23006336]
47. Gagnon M, Desmartis M, Labrecque M, Car J, Pagliari C, Pluye P, et al. Systematic review of factors influencing the adoption of information and communication technologies by healthcare professionals. J Med Syst 2012 Feb;36(1):241-277 [FREE Full text] [doi: 10.1007/s10916-010-9473-4] [Medline: 20703721]
48. Macdonald L, MacPherson DW, Gushulak BD. Online communication as a potential travel medicine research tool: analysis of messages posted on the TravelMed listserv. J Travel Med 2009;16(1):7-12. [doi: 10.1111/j.1708-8305.2008.00255.x] [Medline: 19192121]
49. Rodriguez-Recio FJ, Sendra-Portero F. Analysis of the Spanish-speaking mailing list RADIOLOGIA. Eur J Radiol 2007 Jul;63(1):136-143. [doi: 10.1016/j.ejrad.2007.01.031] [Medline: 17344009]
50. Hew KF, Hara N. An online listserv for nurse practitioners: a viable venue for continuous nursing professional development? Nurse Educ Today 2008 May;28(4):450-457. [doi: 10.1016/j.nedt.2007.07.009] [Medline: 17881096]
51. Rolls K, Kowal D, Elliott D, Burrell AR. Building a statewide knowledge network for clinicians in intensive care units: knowledge brokering and the NSW Intensive Care Coordination and Monitoring Unit (ICCMU). Aust Crit Care 2008 Feb;21(1):29-37. [doi: 10.1016/j.aucc.2007.10.003] [Medline: 18226542]
52. Long JC, Cunningham FC, Braithwaite J. Bridges, brokers and boundary spanners in collaborative networks: a systematic review. BMC Health Serv Res 2013;13:158 [FREE Full text] [doi: 10.1186/1472-6963-13-158] [Medline: 23631517]
53. Gerrish K, Guillaume L, Kirshbaum M, McDonnell A, Tod A, Nolan M. Factors influencing the contribution of advanced practice nurses to promoting evidence-based practice among front-line nurses: findings from a cross-sectional survey. J Adv Nurs 2011 May;67(5):1079-1090. [doi: 10.1111/j.1365-2648.2010.05560.x] [Medline: 21226873]
54. Denzin NK, Lincoln Y, editors. Focus Groups: Contingent articulations of Pedagogy, Politics, Inquiry. In: The SAGE Handbook of Qualitative Research. Thousand Oaks, CA: Sage Publications, Inc; 2011.
55. Liamputtong P. Focus group methodology: Principles and practice. London, UK: SAGE; 2011.
56. Williams S, Clausen M, Robertson A, Peacock S, McPherson K. Methodological Reflections on the Use of Asynchronous Online Focus Groups in Health Research. Int J Qual Methods 2012;11(4):368-383. [doi: 10.1177/160940691201100405]
57. Kenny AJ. Interaction in cyberspace: an online focus group. J Adv Nurs 2005 Feb;49(4):414-422. [doi: 10.1111/j.1365-2648.2004.03305.x] [Medline: 15701156]
58. Shenton A. Strategies for ensuring trustworthiness in qualitative research projects. Education for information 2004;22(2):63-75.
59. Edelmann N. Reviewing the definitions of “lurkers” and some implications for online research. Cyberpsychol Behav Soc Netw 2013 Sep;16(9):645-649. [doi: 10.1089/cyber.2012.0362] [Medline: 23848960]
60. Sun N, Rau P, Ma L. Understanding lurkers in online communities: A literature review. Computers in Human Behavior 2014;38:110-117. [doi: 10.1016/j.chb.2014.05.022]
61. Acocella I. The focus groups in social research: advantages and disadvantages. Qual Quant 2011 Sep 3;46(4):1125-1136. [doi: 10.1007/s11135-011-9600-4]
62. Barbour RS, Flick U, Kvale S, Angrosino MV, Banks M, Gibbs G, et al. Negotiating the coresearcher mandate - service users' experiences of doing collaborative research on mental health. In: The Sage qualitative research kit. London, UK: SAGE; 2007.
63. Bringsvor HB, Bentsen SB, Berland A. Sources of knowledge used by intensive care nurses in Norway: an exploratory study. Intensive Crit Care Nurs 2014 Jun;30(3):159-166. [doi: 10.1016/j.iccn.2013.12.001] [Medline: 24380660]
64. Salmon G. E-moderating: The Key to Teaching and Learning Online. 3rd Edition ed. New York: Routledge; 2011.
65. Hatten J, Christensen L, Liu K, Goldstone L, Thurlow M. Elements of Successful Online Asynchronous Text-Based Discussions. Chesapeake, VA: Association for the Advancement of Computing in Education (AACE); 2014 Presented at: World Conference on E-Learning in Corporate, Government, Healthcare, and Higher Education; 2014; New Orleans, LA.
66. Whitehead LC. Methodological and ethical issues in Internet-mediated research in the field of health: an integrated review of the literature. Soc Sci Med 2007 Aug;65(4):782-791. [doi: 10.1016/j.socscimed.2007.03.005] [Medline: 17512105]
67. Halcomb EJ, Gholizadeh L, DiGiacomo M, Phillips J, Davidson PM. Literature review: considerations in undertaking focus group research with culturally and linguistically diverse groups. J Clin Nurs 2007 Jun;16(6):1000-1011. [doi: 10.1111/j.1365-2702.2006.01760.x] [Medline: 17518876]

68. Murray P. Institute of Educational Technology. 2001. Subject: talk.to/reflect - reflection and practice in nurses' computer-mediated communications URL: http://www.nursing-informatics.com/PhD/PMurray.pdf [accessed 2016-05-04] [WebCite Cache ID 6hEOc4mYF]
69. Murray PJ. Using Virtual Focus Groups in Qualitative Research. Qualitative Health Research 1997 Nov 01;7(4):542-549. [doi: 10.1177/104973239700700408]
70. Hara N, Shachaf P, Stoerger S. Online communities of practice typology revisited. Journal of Information Science 2009 Aug 18;35(6):740-757. [doi: 10.1177/0165551509342361]
71. Alonzo A. Graduate Faculty.: University of Kansas; 2009. Motivational factors in registered nurses completing a baccalaureate completion program URL: http://kuscholarworks.ku.edu/dspace/bitstream/1808/5945/1/Alonzo_ku_0099D_10552_DATA_1.pdf [accessed 2016-05-03] [WebCite Cache ID 6hEOkvzAO]
72. Tates K, Zwaanswijk M, Otten R, van DS, Hoogerbrugge PM, Kamps WA, et al. Online focus groups as a tool to collect data in hard-to-include populations: examples from paediatric oncology. BMC Med Res Methodol 2009;9:15 [FREE Full text] [doi: 10.1186/1471-2288-9-15] [Medline: 19257883]
73. Turner D. Qualitative interview design: A practical guide for novice investigators. The Qualitative Report 2010;15:754-760 [FREE Full text]
74. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology 2006 Jan;3(2):77-101. [doi: 10.1191/1478088706qp063oa]
75. Lau ASM. Hospital-based nurses' perceptions of the adoption of Web 2.0 tools for knowledge sharing, learning, social interaction and the production of collective intelligence. J Med Internet Res 2011;13(4):e92 [FREE Full text] [doi: 10.2196/jmir.1398] [Medline: 22079851]
76. Borbasi S, Jackson D. Qualitative Research: the Whole Picture. In: Borbasi S, Jackson D, editors. Navigating the maze of research: enhancing nursing and midwifery practice. Chatswood, Australia: Mosby; 2012:123-145.
77. Porter S. Validity, trustworthiness and rigour: reasserting realism in qualitative research. J Adv Nurs 2007 Oct;60(1):79-86. [doi: 10.1111/j.1365-2648.2007.04360.x] [Medline: 17824942]
78. Noble H, Smith J. Issues of validity and reliability in qualitative research. Evid Based Nurs 2015 Apr;18(2):34-35. [doi: 10.1136/eb-2015-102054] [Medline: 25653237]
79. Ahern KJ. Ten Tips for Reflexive Bracketing. Qualitative Health Research 1999 May 01;9(3):407-411. [doi: 10.1177/104973239900900309]
80. Hanson DJ. The Perspectives of Fieldwork Educators Regarding Level II Fieldwork Students. Occup Ther Health Care 2011;25(2-3):164-177. [doi: 10.3109/07380577.2011.561420] [Medline: 23899033]
81. McCrea J. Current use, future trends and opportunties in public sector social media. 2012. URL: http://www.jbmccrea.com/publisher.kc/J%20B%20McCrea%20Knowledge%20Centre/cogitamus_report_Aug2012.pdf [accessed 2016-02-06] [WebCite Cache ID 6f5K4k6r8]
82. Archambault PM, Bilodeau A, Gagnon M, Aubin K, Lavoie A, Lapointe J, et al. Health care professionals' beliefs about using wiki-based reminders to promote best practices in trauma care. J Med Internet Res 2012;14(2):e49 [FREE Full text] [doi: 10.2196/jmir.1983] [Medline: 22515985]
83. Brooks F, Scott P. Exploring knowledge work and leadership in online midwifery communication. J Adv Nurs 2006 Aug;55(4):510-520. [doi: 10.1111/j.1365-2648.2006.03937.x] [Medline: 16866846]
84. Cook-Craig PG, Sabah Y. The Role of Virtual Communities of Practice in Supporting Collaborative Learning among Social Workers. British Journal of Social Work 2009 May 12;39(4):725-739. [doi: 10.1093/bjsw/bcp048]
85. Hughes B, Joshi I, Lemonde H, Wareham J. Junior physician's use of Web 2.0 for information seeking and medical education: a qualitative study. Int J Med Inform 2009 Oct;78(10):645-655. [doi: 10.1016/j.ijmedinf.2009.04.008] [Medline: 19501017]
86. Fuoco M, Leveridge MJ. Early adopters or laggards? Attitudes toward and use of social media among urologists. BJU Int 2015 Mar;115(3):491-497 [FREE Full text] [doi: 10.1111/bju.12855] [Medline: 24981237]
87. Frisch N, Atherton P, Borycki E, Mickelson G, Cordeiro J, Novak LH, et al. Growing a professional network to over 3000 members in less than 4 years: evaluation of InspireNet, British Columbia's virtual nursing health services research network. J Med Internet Res 2014;16(2):e49 [FREE Full text] [doi: 10.2196/jmir.3018] [Medline: 24566806]
88. Burg MA, Adorno G, Hidalgo J. An analysis of Social Work Oncology Network Listserv Postings on the Commission of Cancer's distress screening guidelines. J Psychosoc Oncol 2012;30(6):636-651. [doi: 10.1080/07347332.2012.721484] [Medline: 23101548]
89. Kukreja P, Heck SA, Riggins J. Use of social media by pharmacy preceptors. Am J Pharm Educ 2011 Nov 10;75(9):176 [FREE Full text] [doi: 10.5688/ajpe759176] [Medline: 22171104]
90. Usher WT. Australian health professionals' social media (Web 2.0) adoption trends: early 21st century health care delivery and practice promotion. Aust J Prim Health 2012;18(1):31-41. [doi: 10.1071/PY10084] [Medline: 22394660]
91. Stewart S, Sidebotham M, Davis D. International networking: connecting midwives through social media. Int Nurs Rev 2012 Sep;59(3):431-434. [doi: 10.1111/j.1466-7657.2012.00990.x] [Medline: 22897197]
92. Apostolakis I, Koulierakis G, Berler A, Chryssanthou A, Varlamis I. Use of social media by healthcare professionals in Greece: an exploratory study. Int J Electron Healthc 2012;7(2):105-124. [doi: 10.1504/IJEH.2012.049873] [Medline: 23079026]

93. Li X, Gray K, Chang S, Elliott K, Barnett S. A conceptual model for analysing informal learning in online social networks for health professionals. Stud Health Technol Inform 2014;204:80-85. [Medline: 25087531]

Abbreviations

HCP: health care professionals
VC: virtual communities
VFG: virtual focus group

Edited by G Eysenbach; submitted 04.11.15; peer-reviewed by M Aebersold, WC Su; comments to author 10.12.15; revised version received 06.02.16; accepted 24.03.16; published 13.06.16.

Please cite as:
Rolls K, Hansen M, Jackson D, Elliott D
Why We Belong - Exploring Membership of Healthcare Professionals in an Intensive Care Virtual Community Via Online Focus Groups: Rationale and Protocol
JMIR Res Protoc 2016;5(2):e99
URL: http://www.researchprotocols.org/2016/2/e99/
doi:10.2196/resprot.5323
PMID:27296929

Proposal

A Mixed-Method Study to Determine the Benefits of Periconceptional Folic Acid Supplementation and Effects of Folic Acid Deficiency in Mothers on Birth Outcomes

Gudlavalleti Venkata S Murthy[1]; Sunanda Reddy Kolli[2]; Sutapa B Neogi[3]; Samiksha Singh[1]; Komal Preet Allagh[1]; Neena John[1]; Srinivas N.[4]; Sudha Ramani[5]; BR Shamanna[6]; Pat Doyle[7]; Sanjay Kinra[8]; Andy Ness[9]; Dinesh Raj Pallepogula[1]; Hira B Pant[1]; Smiksha Babbar[3]; Raghunath Reddy[10]; Rachna Singh[10]

[1]Indian Institute of Public Health, Hyderabad, India

[2]Centre for Applied Research and Education on Neurodevelopmental impairments and Disability-related health initiatives (CARENIDHI), New delhi, India

[3]Indian Institute of Public Health, Delhi, Delhi, India

[4]Indian Institute of Public Health, Bhubaneswar, Bhubaneswar, India

[5]Indian Institute of Public Health- Bangalore, Bangalore, India

[6]University of Hyderabad, School of Medical Sciences, Hyderabad, India

[7]London School of Hygiene and Tropical Medicine, London, United Kingdom

[8]London School of Hygiene & Tropical Medicine, London, United Kingdom

[9]University of Bristol, Bristol, United Kingdom

[10]Indian Institute of Public Health, Delhi, India

Corresponding Author:
Komal Preet Allagh
Indian Institute of Public Health
Plot no 1, ANV Archade, Amar co-op society, Kavuri hills, Madhapur
Hyderabad, 500033
India
Phone: 91 4049006003
Fax: 91 4049006000
Email: komal.allagh@gmail.com

Abstract

Background: Evidence from high income countries shows mothers who are supplemented with folic acid in their periconceptional period and early pregnancy have significantly reduced adverse outcomes like birth defects. However, in India there is a paucity of data on association of birth defects and folic acid supplementation. We identified a few important questions to be answered using separate scientific methods and then planned to triangulate the information.

Objective: In this paper, we describe the protocol of our study that aims to determine the association of folic acid and pregnancy outcomes like neural tube defects (NTDs) and orofacial clefts (OFCs). We decided to fill the gaps in knowledge from India to determine public health consequences of folic acid deficiency and factors influencing dietary and periconceptional consumption of folic acid.

Methods: The proposed study will be carried out in five stages and will examine the questions related to folic acid deficiency across selected locations in South and North India. The study will be carried out over a period of 4 years through the hierarchical evidence-based approach. At first a systematic review was conducted to pool the current birth prevalence of NTDs and orofacial clefts OFCs in India. To investigate the population prevalence, we plan to use the key informant method to determine prevalence of NTDs and OFCs. To determine the normal serum estimates of folic acid, iron, and vitamin B12 among Indian women (15-35 years), we will conduct a population-based, cross-sectional study. We will further strengthen the evidence of association between OFCs and folic acid by conducting a hospital-based, case-control study across three locations of India. Lastly, using qualitative methods we will understand community and health workers perspective on factors that decide the intake of folic acid supplements.

Results: This study will provide evidence on the community prevalence of birth defects and prevalence folic acid and vitamin B12 deficiency in the community. The case-control study will help understand the association of folic acid deficiency with OFCs.

Conclusions: The results from this study are intended to strengthen the evidence base in childhood disability for planning and policy initiatives.

(JMIR Res Protoc 2016;5(2):e129) doi:10.2196/resprot.5722

KEYWORDS

folic acid; neural tube defects; orofacial clefts; periconceptional folic supplement; key informant method

Introduction

Background

Folic acid is a micronutrient with a vital role during human reproduction and in a variety of physiological processes [1,2]. A report from the World Health Organization [3] indicated that the percentage of pregnant women with a serum folic acid level less than 3 ng/mL was highest among pregnant women in Sri Lanka (57%), followed by India (41.6%). Poor serum folic acid levels are linked with negative health outcomes in pregnancy like abruptio placentae, preeclampsia, spontaneous abortion, congenital heart defects, stillbirth, preterm delivery, low birth weight, and serious birth defects of the brain and spine [4]. Studies from developed countries have shown folic acid deficiency is strongly associated with birth defects, particularly neural tube defects (NTDs) and orofacial clefts (OFCs) [1,5]. Evidence from some countries shows that mothers who are supplemented with folic acid in their periconceptional period and early pregnancy have significantly reduced adverse outcomes compared with mothers who are not similarly supplemented [6].

The review of the 4th Millennium development goal (reduce child mortality) shows that the global under-5 child mortality has drastically dropped by more than half [7]. In India, the current under-5 child mortality is estimated to be 48 per 1000 live births, a little over the set target [8]. However, this decline is attributed to a fall in the number of deaths from infectious diseases and malnutrition; while the mortality attributed to birth defects remains constant [9]. The most common birth defects in India are NTDs [8]. OFCs are also an important birth defect in India.

There are currently no large studies from India that report the normal folate levels among Indian women and periconceptional dietary consumption or supplementation of folic acid. The periconceptional folic acid supplementation is challenging to incorporate in the national programs. In the absence of baseline evidence, planning and monitoring will be difficult. There are no large studies on knowledge of folic acid and its importance among laypersons in India. Only one small study demonstrates that the awareness is poor, 10 of 50 women knew of folic acid, and none of them linked it with birth defects [10]. Studies have also shown that awareness among health providers about periconceptional supplements is inadequate [11,12], while many physicians were generally aware of the linkage between folic acid and birth defects, their knowledge of timing and dosage was found to be lacking.

India also does not have evidence for population prevalence of NTDs or OFCs and association of low folic acid levels and birth defects. India is one of the many countries of the world where population estimates of the prevalence of birth defects are not routinely collected [13]. Currently, there is no national registry for birth defects. Hospital-based surveys or studies are the most common source of information on birth defects like NTDs and OFCs in India. These studies have reported inconsistent results. We conducted a systematic review to determine the current birth prevalence of NTDs and OFCs in India [14]. Our review revealed that there was just one population-based study reporting prevalence of NTDs from a rural district of North India [15]. There have been no population-based, high-quality studies reporting prevalence of NTDs and OFCs from South India. The review also pointed out significant regional differences in pooled prevalence of both NTDs and OFCs [14].

The only population-based prevalence study from North India used the door-to-door survey method to identify cases of NTDs [15]. A door-to-door survey is time consuming and expensive [16]. The key informant method (KIM) [17] may be a faster and more cost-effective method to estimate population prevalence's. KIM has been successfully used in the past in identifying children with disabilities in various low- and middle-income countries like Bangladesh, China, Ethiopia, Iran, Malawi, and Nigeria [18-26]. In India, only a few studies have considered Integrated Child Development Service (Anganwadi) workers and other community-based personnel as key informants (KIs) to identify childhood disability [27,28].

We decided to fill the gaps in knowledge from India to determine public health consequences of folic acid deficiency and factors influencing dietary and periconceptional consumption of folic acid. We identified a few important questions to be answered using separate scientific methods and then we plan to triangulate the information. To investigate the population prevalence and to capture regional differences, we plan to carry out a population-based prevalence study of birth defects (NTDs and OFCs) in a rural community of South India and urban community from North India using KIM. As a part of the prevalence study, we will elicit history of specific dietary practices and folic acid intake during the affected pregnancy. This will provide evidence on association between dietary folic acid and birth defects. We will also conduct a population-based, cross-sectional study among women in the reproductive age group (15-35 years) in South India, to determine normal serum estimates of folic acid, iron, and vitamin B12.

A review of literature on association of folic acid and OFCs shows there is some suggestive evidence for the role of folic acid in prevention of OFCs [29]. However, the observational case-control studies conducted so far have limitations of recall bias and biased report of use based on the pregnancy outcome of OFCs [29]. Yet, many studies have shown that knowledge about consuming folic acid periconceptionally among women is poor [30-34]. To build on the evidence gathered in our study,

we will conduct a hospital-based, case-control study to look at the association between folic acid deficiency during pregnancy and OFCs. We are not including NTDs in the case-control study as the child survival until 4 months of age is very low [35]. In order to prevent recall bias, we will be eliciting history of folic acid intake and dietary practices among cases within 4 months of birth and from controls within 48 hours of birth. One case-control study has been previously conducted in India, and shows no significant association between the serum folate levels of mothers of children with or without clefts [36]. However, in this study, cases were included until the age of 14 months, by which time the maternal folate levels would have fluctuated as well as recall bias would have set in. The sample size of this study was very small with just 28 cases of nonsyndromic clefts.

In order to triangulate the information, we will conduct a qualitative study to determine the community and the health provider's perspective to the factors that decide the intake of folic acid supplements, and the health-seeking behavior among pregnant women in the community.

Study Aim

The aim of this study is to determine the public health consequences of folic acid deficiency among mothers in India. Also, to study the association of folic acid deficiency with pregnancy outcomes especially NTDs and OFCs.

Ethical Approval

The ethics committee of the Public Health Foundation of India (TRC-IEC-117/11) has granted favorable ethical approval for this study. Ethical approval was obtained in June 2012.

Methods

Design

The research proposed in five stages will examine the questions related to folic acid deficiency across selected locations in South and North India and its related consequences through the hierarchical evidence-based approach. The overall study duration will be 4 years. All data will be archived in an anonymized format at the end of the study and will be password protected to ensure that access is restricted to the investigators. Table 1 shows an overview of the five stages of this study with the expected outcome and analysis plan.

Table 1. Overview of study stages.

Stage	Study method	Study location	Tools used	Expected outcome	Analysis plan
Stage 1	Systematic review	India	Review manager	Birth prevalence of NTDs and OFCs in India	Meta-analysis using Review manager. Random and fixed- effect model to calculate pooled prevalence
Stage 2	Quantitative/ prevalence study	Mahbubnagar district, Telangana and North east Delhi	Flip book for training KIs[a], KI profile, line listing format, and semistructured questionnaire for cases on: sociodemography, antenatal, intrapartum history, and life style behavior	Population prevalence of NTDs[b], OFCs[c], microcephaly, hydrocephalus, visual impairment, hearing impairment, motor impairments and intellectual impairments among children less than 6 years of age Prevalence of stillbirths in the community Descriptive statistics	Database will be developed in MS Access. STATA 14.0 will be used for analysis
Stage 3	Estimation of serum folic acid, ferritin and vitamin B12 levels	Mahbubnagar district, Telangana	Semistructured questionnaire on sociodemographic and reproductive history, and blood samples; anthropometric measurements	Normative values for serum folic acid, ferritin and vitamin B-12 among women in 15 to 35 years age group Body mass index of women in the age group 15 to 35 years Prevalence of folic acid and Vitamin B12 deficiency Hemoglobin estimation	Analysis of blood sample by solid phase radioimmunoassay method
Stage 4	Qualitative study	Mahbubnagar district, Telangana	Topic guide for focus group discussions, semistructured questionnaire for case studies, and interview schedule for in-depth interviews	Community perspectives on NTDs and OFCs Sociocultural factors that affect the uptake of folic acid supplements Health-seeking behavior during pregnancy Attitudes on periconceptional folic acid supplementation National Program and policy perspectives from experts	Computer assisted thematic analysis (Atlas-Ti software)
Stage 5	Case control study- hospital based	Hyderabad Bangalore and Delhi	Semistructured questionnaire on sociodemographics, reproductive, medical, occupational history and consumption of periconceptional folic acid supplements	Association between folic acid supplementation and OFCs	STATA 14.0 will be used for analysis, and calculation of odds ratio

[a]Key informants.

[b]Neural tube defects.

[c]Orofacial clefts.

Stage 1: Systematic Review

At the outset, a systematic review was conducted to summarize the existing research evidence on the prevalence of NTDs and OFCs among live births and stillbirths in India using data from all available community- and hospital-based observational studies [14]. A comprehensive literature search for observational studies was conducted on MEDLINE and EMBASE databases using medical subject heading terms (neural tube defects OR cleft lip OR cleft palate AND prevalence AND India). We included all hospital- or community-based studies determining the birth prevalence of OFCs or NTDs. Nineteen studies met our inclusion criteria, with only one community-based study. Subgroup analysis was performed for region, time period, consanguinity, and gender of newborn.

Meta-analysis was performed using Review Manager software. We obtained a pooled birth prevalence of 4.5 per 1000 total births (95% confidence interval [CI] 4.2-4.9) for NTDs and 1.3 per 1000 total births (95% CI 1.1-1.5) for OFCs using the random-effect model. There was a significant variation in the prevalence of both NTD and OFCs across regions of India [14].

Stage 2: Population Prevalence study (KIM)

Objectives

1. To estimate the prevalence of specific birth defects: NTDs, OFCs, microcephaly, hydrocephalus, visual impairment, hearing impairment, motor impairment (cerebral palsy, club foot, muscular dystrophy, poliomyelitis, phocomelia), and still births among children less than 6 years of age in the community using the KIs and health workers in Mahbubnagar district (Telangana) and Northeast Delhi (Delhi)

2. To determine the proportion of disability caused by OFCs and NTDs among all the specified birth defects in children less than 6 years in Mahbubnagar district (Telangana) and Northeast Delhi (Delhi)

3. To assess whether key informants can identify birth defects that are visible to the naked eye

4. To describe epidemiological characteristics (maternal characteristics such as age, parity, consumption of folic acid supplements, residence, etc) of specified birth defects in Mahbubnagar district (Telangana) and Northeast Delhi (Delhi).

Study Population

Children in the age group 0 to 6 years (born between 2008 and 2013), both live and stillbirths with any birth defect will be recruited in the study. The respondent will be the mother of the child. If she is not present (unavailable inspite of three visits or dead), the child will be included in prevalence but will not be recruited for eliciting the detailed history.

Sample Size and Study Sites

We used a combined prevalence of NTDs and OFCs of 10 per 10,000 births [37,38], 20% precision and alpha of 0.1 to estimate the sample size. We calculated a total sample size of 44,824 for the study. We plan to include two regions of India to conduct the community-based prevalence study. One site is in North India (Delhi) and the other in South India (Telangana).

Purposive sampling has been used to identify our study sites within the two states. In Telangana, we have included seven rural mandals (smallest administrative unit) of Mahbubnagar district (Addakal, Bhoothpur, Bijinapalle, Jadcherla, Ghanpur, Mahbubnagar (rural), and Thimmajipet). As per Census 2011, the total population of these seven mandals is 355,043 [39] and the population of children aged 0 to 6 years is 48,016 [40].

In Delhi, we have included seven urban regions from Northeast Delhi (Shahadra, Seemapuri, Seelampur, Babarpur, Gautam vihar, Wazirabad, and Anand mansarovar). The total population from these seven regions is 335,805 [39] and the population of children aged 0 to 6 years is 38,407 [41].

Study Design

The KIM [17] will be used to identify children (0-6 years) with birth defects in the community. The KIs will be Anganwadi workers, Accredited Social Health Activist, members of Disabled Peoples Organization, and self-help groups from within the study sites. We will recruit one KI for every 1000 population. The KIs will undergo a 1-day training on identification of specific birth defects among children: NTDs, OFCs, microcephaly, congenital hydrocephalus, visual impairment, hearing impairment, motor impairment (cerebral palsy, clubfoot, muscular dystrophy, poliomyelitis, and phocomelia), and intellectual impairment. Using a flipbook and a PowerPoint presentation, our research team will conduct the training. We are training the KIs on identifying birth defects other than NTDs and OFCs so that we can determine the proportion of children with NTDs and OFCs among all the visible birth defects in the community.

The flipbook consists of 60 images depicting the various birth defects mentioned above. The flipbook also consists of images depicting foods rich in folic acid, images of folic acid tablets and ways to prevent NTDs, OFCs, and other birth defects. From each administrative region (approximately 100,000 population), two to three batches of 20 to 22 KIs will be trained. The flipbook has been pretested in the community and changes incorporated in the images to make it culturally appropriate. The flipbook is for training purposes only and will not be given to KIs for use in the field. The pictures in the flipbook are thought to be disturbing if showed to the layman in the field. However, sketches of all the disabilities will be provided in a handout for their reference in the field.

The KIs will do line listing for the 1000 population in which she usually caters her community services too. The KIs will be given 2 weeks to complete listing of cases of birth defects and stillbirths from their specified population, after the training is completed. The completed line listing forms will be handed over to the field investigator, who will confirm and verify the addresses of all the children listed. After the listing is completed, a trained medical doctor will visit each of these children's homes and examine them to confirm the diagnosis. Written informed consent will be obtained from the mother for examining the child. For all the confirmed cases of specified birth defects, the field investigator will document sociodemographic-, pregnancy-, and birth-related history and risk factors using a prestructured questionnaire from the mother of the affected child.

The mother of each child identified with birth defects will also be asked if she is aware of any other child with a similar birth defect in the vicinity. This will help in identifying any case, which may have been missed by the KI. In order to triangulate the data, a list of children with birth defects will be obtained from the Society for Elimination of Rural Poverty in Telangana and Smile Train Project. This will be used to compare and identify the missed cases if any.

Prevalence will be calculated as the number of cases of birth defect identified in the district using the KIM divided by the estimated number of children (0-6 years) alive in that district as per the Census data.

Statistical Analysis

A database will be developed in MS ACCESS. STATA 14.0 will be used for data analysis.

Stage 3: Estimation of Serum Folic Acid, Ferritin, and Vitamin B-12

This study is being conducted in association with National Institute of Nutrition (NIN) at Hyderabad. It is part of a

concurrent study at NIN looking at the nutritional status of women in the age group 15 to 35 years of age in Mahbubnagar district of Telangana.

Objective

1. To estimate normative values of serum folic acid, ferritin, and vitamin B12 among women in the age group 15 to 35 years in Mahbubnagar district, Telangana

2. To estimate the prevalence of folic acid and vitamin B-12 deficiency among 15 to 35 years women in the community (Mahbubnagar district, Telangana).

Sample Size and Study Site

For calculating the sample size, we used unpublished data from NIN on mean folic acid levels and standard error for women in the reproductive age group. Using the mean folic acid level of 10 ng/mL and standard error of 1.1, and a precision of 0.1 and 0.05 alpha, we calculated a sample size of 465. Thus, for this study, we will recruit 500 women in the reproductive age (15-35 years) from Mahbubnagar district, Telangana.

Study Design

This is a community-based, cross-sectional study. Women in the age group 15 to 35 years, irrespective of their marital, pregnancy, and lactation status, will be recruited in the study. Written informed consent will be obtained from the participants before registering and conducting any interview or blood examination. Any woman who is seriously ill or refuses to participate will be excluded from the study. A multistage, stratified, two-stage, random sampling method will be used. To get a representative sample, we will randomly select one mandal from each revenue division of the Mahbubnagar district. Thus, five mandals will be randomly selected. From each mandal, three villages will be randomly selected. Within each selected village, we will randomly select 30 to 35 households with women 15 to 35 years. From each household, only one woman will be randomly selected for the study.

The field investigator will administer a semistructured questionnaire eliciting sociodemographic and reproductive history and take anthropometric measurements. A trained lab technician will then draw 5 to 10 mL of blood from the participants under aseptic conditions. The blood sample will be centrifuged in the field, within 6 hours and stored at −20° C in a laboratory in the mandal. The samples will be transported to NIN, Hyderabad thrice a week for analysis.

At NIN, plasma levels of vitamin B12 and folic acid will be measured by solid phase radioimmunoassay method using a commercially available kit designed for simultaneous measurement of vitamin B12, ferritin and folic acid [42]. Hemoglobin estimation will be done. We will estimate the prevalence of folic acid and vitamin B12 deficiency among the women.

Statistical Analysis

The data will be analyzed using SPSS and a normogram will be plotted. The mean and median level of folic acid, ferritin, and vitamin B12 levels will be ascertained. Appropriate adjustments for potential confounder effects will be made.

Stage 4: Community and Program Perspectives on NTDS, OFCs, and Periconceptional Folic Acid Supplementation

Objectives

1. To explore community perspectives among both men and women, on birth defects like NTDs and OFCs, using case studies and focus group discussions (FGDs) in Mahbubnagar district, Telangana

2. To examine sociocultural factors and their effect on uptake of folic acid supplementation during the periconceptional period by using interviews with health care staff in Mahbubnagar district, Telangana

3. To examine program perspectives on periconceptional folic acid supplementation by using in-depth interviews (IDIs) among personnel working in National program against anemia.

Study Design

This is a qualitative study. Data for this aspect of the study will be collected through a mix of qualitative data collection tools such as FGDs, IDIs, and case studies. In order to get a holistic picture of the knowledge and perceptions of NTDs and OFCs and the link of these with folic acid, data will be collected from the community as well the health system. Then the results will then be triangulated.

Study Site

The study will be conducted in the four Mandals of Mahbubnagar district of Telangana. These mandals have been purposively chosen to cover a diverse population that is depictive of the natural setting in this region: Bijinapalle (majority population is Scheduled caste and tribes), Jadcherla (majority tribal population), Mahbubnagar (predominantly Muslim population with easy access to health care), and Ghanpur (predominantly Muslim population with poor access to health care).

Sampling and Data Collection Methods

For objectives 1 and 2, data will be collected from the community using FGDs and case studies. Because some of the themes are gender-sensitive, FGDs will be conducted separately with men and women. The FGDs are intended to elicit community perceptions on local ideas of causation, prevention, and treatment of NTDs and OFCs. FGDs with women also include themes on practices during pregnancy and childbirth that might have repercussions on NTDs/OFCs.

The composition of persons participating in the FGDs will be purposively selected. The study population we cover includes a mix of scheduled castes, tribes, Muslim minorities, and persons who reside in the semiurban regions. We intend to conduct discussions with each of these four groups. An indicative number of FGDs in each of the mandals is given in Table 2. The principle of data saturation will be used to guide the actual number of FGDs conducted.

In addition to the FGDs with the community, we will be doing individual interviews (case studies) with families having affected children and with affected adults. Here, we chose to do

interviews because we felt that responses to certain questions such as stigma, testing, and ways through which the disease affects their life, may be personal and people may be hesitant to share such ideas in a group. The participants for case studies will also be purposively chosen so as to elicit rich and illustrative perspectives on themes such as living with OFCs, coping with a child having NTDs/OFCs, stigma in different stages of live, gender differences in coping, and access to care. We intend to do approximately 10 to 15 case studies in the four mandals.

For objective 2, we will be collecting data through IDIs with health system staff including doctors, nurses, auxiliary nurse midwife (ANM), and other community level workers. These interviews will help us understand issues pertinent to the knowledge of NTDs/OFCs among health workers and issues with the supply of folic acid and its supplementation. Here, we choose the interview method over FGDs due to the logistic difficulties in getting health system staff together in one place. We will supplement this information with data from interviews with personnel working in the National program against anemia (objective 3). Overall, this set of interviews will help us envisage barriers to the supplementation of folic acid from the perspective of the health system; and the feasibility of a periconceptional folic acid program in India. All interviews will be conducted in the local language (Telugu and Deccani Hindi). Table 2 gives an indicative number of the number of interviews to be conducted within the health system; the concept of data saturation will be used to guide the actual numbers.

Table 2. Data collection for qualitative study (indicative numbers).

		In-depth interviews	In-depth interviews	Focus group discussions	Focus group discussions	Case Studies
Type of population						
		Health system	Experts and personnel in National anemia program	Community (General)	Community (women in reproductive age group)	Families with affected children/Adults with NTD[a]/OFC[b]
Name of mandal						
	Bijinapalle	Doctor -3 Nurse-3 ANM[c]/ASHA[d]- 6		Scheduled Tribe- 1 Scheduled Caste-2	Scheduled Tribe -1 Scheduled Caste -2	
	Jadcherla	Doctor -1 Nurse-1 ANM/ASHA- 2		Scheduled Tribe -2	Scheduled Tribe-2	
	Mahbubnagar	Doctor -1 Nurse-1 ANM/ASHA- 2		Muslim-1 Semiurban-2	Muslim-1 Semiurban-2	
	Ghanpur	Doctor -2 Nurse-2 ANM/ASHA- 4		Muslim-1	Muslim-1	
Total						
		Doctor -7 Nurse-7 ANM/ASHA- 14	As required (5-10)	8 FGDs	8 FGDs	To choose depending on number/ type of cases from the KI[e] study –approximately 10-15

[a]Neural tube defects.

[b]Orofacial cleft.

[c]Auxiliary nurse midwife.

[d]Accredited social health activist.

[e]Key informant.

Data Analysis

Data analysis for this study will be initiated concurrently with the data collection process, so as to allow the team to refine the questions, develop hypothesis, and pursue emerging avenues of inquiry for IDIs subsequently. All the FGDs, case studies, and IDIs will be translated into English and transcribed. Generic thematic analysis techniques will be used for the study. Analyses will be initiated with a list of predefined themes and new themes will be incorporated as these emerge. For data reduction, the qualitative analysis software ATLAS-TI will be used.

Stage 5: Case Control Study (Hospital-Based)

Objectives

The objective is to determine if mothers of children with OFCs are more likely to have folic acid deficiency during the periconceptional period and early pregnancy (first trimester) in

hospital-based settings in Delhi, Hyderabad, and Bangalore. In order to prevent recall bias among the respondents, we will be eliciting history of folic acid intake and dietary practices among cases within 4 months of birth and from controls within 48 hours of birth. In this study, we did not include NTDs, as it was not logistically feasible to capture cases at the time of birth. If we increased the case population to less than 4-months old then due to high mortality of NTDs we will not get the required sample size.

Sample Size and Study Site

In terms of power and sample size, it is estimated with 90% power assumed to detect a 50% increase in risk (odds ratio=1.5) associated with a risk factor (periconceptional folic acid intake) present in the controls group at a prevalence of approximately 20% and assuming nonresponse rate of 5%. The required sample size would be 150 cases and 600 controls. Hence, this total sample size will be recruited cumulatively from three sites.

Study Design (Recruitment of Cases and Controls)

This is a hospital-based case control study that will be conducted simultaneously in three cities of India: Hyderabad, Delhi, and Bangalore. From each city, we will select two treatment centers and two delivery centers (hospitals). The cases and controls will be recruited over a period of 6 months from each site.

Any child with cleft lip with or without cleft palate or only cleft palate visiting the hospital for treatment (treatment center) within 4 months of birth will be recruited in the study. Clefts may occur in the lip, the roof of the mouth (hard palate), or the tissue at the back of the mouth (soft palate). The mother of this child will be considered as a case. Cases will be recruited only if they belong to the catchment area of the hospital. We will define the catchment area of the hospital by reviewing the statistics of the previous years. Controls will be matched based on the parity of the mother (primigravida or multigravida).

Controls will be recruited from the maternity hospitals (delivery centers) nearby to the treatment centers with a delivery load of 10,000 deliveries. Also, district level tertiary hospitals (government) will be considered for recruitment of controls. Controls will be recruited and interviewed within 48 hours of the birth of the baby.

A researcher will be stationed round the clock at the treatment and recruitment centers in all the three cities. They will recruit a case only after the physician has confirmed the diagnosis.

Textbox 1. Inclusion and exclusion criteria for the selection of cases.

Inclusion criteria

- Mothers of babies born with nonsyndromic OFCs
- Mothers of babies visiting the treatment center within 4 months of birth of baby and from the center's catchment area

Exclusion criteria

- Not belonging to treatment center's catchment area
- Syndromic cases of OFCs
- Mothers who are currently a part of another ongoing research study receiving any intervention

Textbox 2. Inclusion and exclusion criteria for the selection of controls.

Inclusion criteria

- Mother of babies born at the delivery center and from the same geographical location
- Mother of a live birth without any birth defect

Exclusion criteria

- Mothers who are currently a part of any other ongoing research study receiving any intervention
- Any maternal complication that requires immediate emergency care

Study Tool

A semistructured questionnaire will be administered to cases and controls by our research team. This will gather details on sociodemographic aspects and details of reproductive, medical, and occupational history.

The primary exposure for the study is folic acid consumption in the periconceptional period in a mother. History of intake of folic acid tablets during the periconceptional period and dietary history would help elicit the exposure status. Other exposures likely to be associated with OFCs, such as intake of drugs during pregnancy, sex selection practices, and exposure to pesticides would be elicited from history.

Statistical Analysis

A database will be developed in MS Access. Data analysis will be done using STATA 14.0. Descriptive and inferential statistics output will be generated. The prevalence of exposure will be compared between cases and controls using logistic regression, adjusting for potential confounder effects as appropriate.

Results

This research was supported by a Wellcome Trust Capacity Strengthening Strategic Award to the Public Health Foundation of India and a consortium of United Kingdom universities. The results from the individual studies will be available between 2016 and 2017.

Discussion

Trial Implications

This paper outlines the rationale and design of a multistage study including a systematic review determining the current trends in birth prevalence of OFCs and NTDs across India, followed by a cross-sectional, population-based study to determine prevalence of specified birth defects and deficiency of folic acid and vitamin B12 in the community and by a case control study to study association of folic acid deficiency with OFCs. The outcomes from this study will help inform the research community about the feasibility of involving grass root level functionaries for screening cases of OFCs and NTDs.

We anticipate certain challenges in conducting this study. Identification of some of these is likely to be an intermediate outcome of this study as well as help in addressing the challenges involved in implementation of national programmes for early identification and early intervention.

Challenges

Birth defects being considered a social taboo in India, we may have difficulty in getting mothers to participate in the study. Also, the prevalence of some of the specified birth defects is low and it may be difficult to identify these children in the community. For the case control study, it may be very difficult to get cooperation from the cases, as they may want to tend to the child. The deliverables and the outcomes from this research will drive strategies in minimizing the adverse public health consequences of folic acid deficiency among mothers in India and strengthen the evidence base in childhood disability for planning and policy initiatives.

Acknowledgments

This research was supported by a Wellcome Trust Capacity Strengthening Strategic Award to the Public Health Foundation of India and a consortium of United Kingdom universities.

Authors' Contributions

GVSM, SRK, SBN, SS, PD, AN, SK, NJ, SN, SR conceived and designed the study. GVSM is the principal investigator. SRK, SBN, SS, KPA, NJ, SN, BRS, PD, SK, AN, DRP, HBP, SB, RR, RS are the coinvestigators. KPA and DRP have drafted the manuscript. All authors reviewed, gave feedback, and approved the final version of the manuscript.

Conflicts of Interest

None declared.

References

1. Molloy AM, Kirke PN, Brody LC, Scott JM, Mills JL. Effects of folate and vitamin B12 deficiencies during pregnancy on fetal, infant, and child development. Food Nutr Bull 2008;29(Suppl):S101-S111; discussion S112. [Medline: 18709885]
2. Matherly LH, Goldman DI. Membrane transport of folates. Vitam Horm 2003;66:403-456. [Medline: 12852262]
3. Bhutta ZB. Periconceptional Supplementation With Folate and/or Multivitamins for Preventing Neural Tube Defects: RHL Commentary (last revisedJanuary. Geneva: World Health Organization; 2002.
4. WHO. Guideline: Optimal Serum and Red Blood Cell Folate Concentrations in Women of Reproductive Age for Prevention of Neural Tube Defects. Geneva: World Health Organization; 2015.
5. Botto L, Moore C, Khoury MJ, Erickson JD. Medical progress: neural tube defects. N Eng J Med 1999;341:1509-1519. [doi: 10.1056/NEJM199911113412006]
6. Barua S, Kuizon S, Junaid MA. Folic acid supplementation in pregnancy and implications in health and disease. J Biomed Sci 2014;21:77 [FREE Full text] [doi: 10.1186/s12929-014-0077-z] [Medline: 25135350]
7. United Nations. Millennium Development Goals and Beyond 2015 URL: http://www.un.org/millenniumgoals/childhealth.shtml [accessed 2016-06-04] [WebCite Cache ID 6i0x4HLQ5]
8. Ministry of StatisticsProgramme Implementation, Government Of India. India Country Report. 2015. Millennium Development Goals URL: http://mospi.nic.in/Mospi_New/upload/mdg_26feb15.pdf [accessed 2016-06-04] [WebCite Cache ID 6i0x8nawL]
9. World Health Organisation. Strategic Framework. Prevention and Control of Birth Defects in Southeast Asia Region URL: http://apps.searo.who.int/PDS_DOCS/B4941.pdf [accessed 2016-06-04] [WebCite Cache ID 6i0xMLBVm]
10. Piyush G. Awareness regarding use of folic acid for prevention of congenital neural tube defects. NMIJ 2000;13(2).
11. Kondo A, Yamamoto S, Inoue H, Watanabe J, Tada K, Yoshimoto N. Folic acid in the prevention of neural tube defects: awareness among laywomen and healthcare providers in Japan. Congenit Anom (Kyoto) 2009;49:97-101. [doi: 10.1111/j.1741-4520.2009.00232.x] [Medline: 20002900]

12. Aggarwal A, Kumhar GD, Harit D, Faridi MMA. Role of folic acid supplementation in prevention of neural tube defects: physicians yet unaware!. J Prev Med Hyg 2010;51:131-132. [Medline: 21361119]
13. Mossey P, Little J. Addressing the challenges of cleft lip and palate research in India. Indian J Plast Surg 2009;42 Suppl:S9-S18 [FREE Full text] [doi: 10.4103/0970-0358.57182] [Medline: 19884687]
14. Allagh KP, Shamanna BR, Murthy GVS, Ness AR, Doyle P, Neogi SB, Wellcome Trust- PHFI Folic Acid project team. Birth prevalence of neural tube defects and orofacial clefts in India: a systematic review and meta-analysis. PLoS One 2015;10:e0118961 [FREE Full text] [doi: 10.1371/journal.pone.0118961] [Medline: 25768737]
15. Cherian A, Seena S, Bullock R, Antony A. Incidence of neural tube defects in the least-developed area of India: a population-based study. Lancet 2005;366:930-931. [doi: 10.1016/S0140-6736(05)67319-9] [Medline: 16154020]
16. Mactaggart I, Murthy GVS. The key informant child disability project in Bangladesh and Pakistan. International Centre for Evidence in Disability 2013.
17. Using the Key Informant Method to Identify Children with Disabilities: A Working Guide. 2015. URL: http://blogs.lshtm.ac.uk/disabilitycentre/files/2015/03/KIM-Working-Guide.pdf [accessed 2016-06-04] [WebCite Cache ID 6i0xqBdmC]
18. Demissie B, Solomon A. Magnitude and causes of childhood blindness and severe visual impairment in Sekoru District, Southwest Ethiopia: a survey using the key informant method. Trans R Soc Trop Med Hyg 2011;105:507-511. [doi: 10.1016/j.trstmh.2011.04.007] [Medline: 21621807]
19. Kalua K, Ng'ongola RT, Mbewe F, Gilbert C. Using primary health care (PHC) workers and key informants for community based detection of blindness in children in Southern Malawi. Hum Resour Health 2012;10:37 [FREE Full text] [doi: 10.1186/1478-4491-10-37] [Medline: 23017106]
20. Tataryn M, Chokotho L, Mulwafu W, Kayange P, Polack S, Lavy C. The Malawi Key Informant Child Disability Project - Summary Report. URL: http://www.ndorms.ox.ac.uk/downloads/kim_malawi.summary.pdf [accessed 2016-06-04] [WebCite Cache ID 6i8pcZ3NM]
21. Razavi H, Kuper H, Rezvan F, Amelie K, Mahboobi-Pur H, Oladi M, et al. Prevalence and causes of severe visual impairment and blindness among children in the lorestan province of iran, using the key informant method. Ophthalmic Epidemiol 2010;17:95-102. [doi: 10.3109/09286581003624954] [Medline: 20302431]
22. Muhit MA, Shah S, Gilbert C, Hartley S, Foster A. The key informant method: a novel means of ascertaining blind children in Bangladesh. Br J Ophthalmol 2007;91:995-999 [FREE Full text] [doi: 10.1136/bjo.2006.108027] [Medline: 17431019]
23. Kalua K, Patel D, Muhit M, Courtright P. Productivity of key informants for identifying blind children: evidence from a pilot study in Malawi. Eye (Lond) 2009;23:7-9. [doi: 10.1038/eye.2008.49] [Medline: 18344959]
24. Muhammad N, Maishanu N, Jabo A, Rabiu M. Tracing children with blindness and visual impairment using the key informant survey in a district of north-Western Nigeria. Middle East Afr J Ophthalmol 2010;17:330-334 [FREE Full text] [doi: 10.4103/0974-9233.71601] [Medline: 21180434]
25. Husain L. Using the key informant method to investigate childhood blindness related to vitamin A deficiency disorder in six rural sub-districts in Bangladesh. Community Eye Health 2007;20:7-8 [FREE Full text] [Medline: 17637851]
26. Xiao B, Fan J, Deng Y, Ding Y, Muhit M, Kuper H. Using key informant method to assess the prevalence and causes of childhood blindness in Xiu'shui County, Jiangxi Province, Southeast China. Ophthalmic Epidemiol 2011;18:30-35. [doi: 10.3109/09286586.2010.528138] [Medline: 21117893]
27. Kumar R, Singh A, Kumar V. Survey of village informants--an alternate method to estimate paralytic poliomyelitis prevalence in rural area. Indian J Pediatr 1991;58:239-243. [Medline: 1879905]
28. Mathur G, Mathur S, Singh Y, Kushwaha K, Lele S. Detection and prevention of childhood disability with the help of Anganwadi workers. Indian Pediatr 1995;32:773-777. [Medline: 8617553]
29. Wehby G, Murray JC. Folic acid and orofacial clefts: a review of the evidence. Oral Dis 2010;16:11-19 [FREE Full text] [doi: 10.1111/j.1601-0825.2009.01587.x] [Medline: 20331806]
30. Bener A, Al Maadid MGA, Al-Bast DAE, Al-Marri S. Maternal knowledge, attitude and practice on folic acid intake among Arabian Qatari women. Reprod Toxicol 2006;21:21-25. [doi: 10.1016/j.reprotox.2005.07.004] [Medline: 16112540]
31. Nawapun K, Phupong V. Awareness of the benefits of folic acid and prevalence of the use of folic acid supplements to prevent neural tube defects among Thai women. Arch Gynecol Obstet 2007;276:53-57. [doi: 10.1007/s00404-006-0305-1] [Medline: 17186253]
32. Coll O, Pisa S, Palacio M, Quintó L, Cararach V. Awareness of the use of folic acid to prevent neural tube defects in a Mediterranean area. Eur J Obstet Gynecol Reprod Biol 2004;115:173-177. [doi: 10.1016/j.ejogrb.2003.12.009] [Medline: 15262351]
33. Ren A, Zhang L, Li Z, Hao L, Tian Y, Li Z. Awareness and use of folic acid, and blood folate concentrations among pregnant women in northern China--an area with a high prevalence of neural tube defects. Reprod Toxicol 2006;22:431-436. [doi: 10.1016/j.reprotox.2006.02.003] [Medline: 16549319]
34. Eghwrudjakpor PO, Amadi CE, Amusan EO. Evaluation of the level of awareness of the role of folic acid in the prevention of neural tube defects amongst women of reproductive age in a tertiary health institution. Niger J Med 2011;20:207-212. [Medline: 21970229]
35. March of Dimes. Birth Defects URL: http://www.marchofdimes.org/baby/neural-tube-defects.aspx [accessed 2016-06-04] [WebCite Cache ID 6i0y7MgN2]

36. Ajila V, Babu G, Gopakumar R, Harini K, Hegde S, Reema B. Serum folate levels among mothers of children with and without cleft lip and palate: A comparative biochemical study. J Cleft Lip Palate Craniofac Anomal 2014;1:93. [doi: 10.4103/2348-2125.137898]
37. Reddy SG, Reddy RR, Bronkhorst EM, Prasad R, Ettema AM, Sailer HF, et al. Incidence of cleft lip and palate in the state of Andhra Pradesh, South India. Indian J Plast Surg 2010;43:184-189 [FREE Full text] [doi: 10.4103/0970-0358.73443] [Medline: 21217978]
38. Bhide P, Sagoo GS, Moorthie S, Burton H, Kar A. Systematic review of birth prevalence of neural tube defects in India. Birth Defects Res A Clin Mol Teratol 2013;97:437-443. [doi: 10.1002/bdra.23153] [Medline: 23873811]
39. Census of India. Ministry of Home Affairs, Government of India. 2011. C.D. Block Wise Primary Census Abstract Data (PCA) URL: http://censusindia.gov.in/pca/cdb_pca_census/Houselisting-housing-AP.html [accessed 2016-06-04] [WebCite Cache ID 6i0yH06BG]
40. Census of India. Ministry of Home Affairs, Government of India. 2011. C-13 Single Year Age Returns by Residence and Sex URL: http://www.censusindia.gov.in/2011census/C-series/C-13.html [accessed 2016-06-04] [WebCite Cache ID 6i0yHeVrO]
41. Department of Women and Child Development. Integrated Child Development Services (ICDS) URL: http://wcddel.in/icds.html [accessed 2016-06-04] [WebCite Cache ID 6i0y9KV8K]
42. Siemens Healthineers. Anemia Assay Menu. 2015. URL: http://usa.healthcare.siemens.com/clinical-specialities/anemia/anemia-assay-menu [accessed 2016-06-04] [WebCite Cache ID 6i0xsQNEO]

Abbreviations

ANM: auxiliary nurse midwives
FGD: focus group discussion
IDI: in-depth interview
KI: key informant
KIM: Key informant method
NIN: National institute of Nutrition
NTDs: neural tube defects
OFCs: orofacial clefts

Edited by G Eysenbach; submitted 07.03.16; peer-reviewed by YB Nisar; comments to author 03.04.16; revised version received 13.04.16; accepted 15.04.16; published 23.06.16.

Please cite as:
Murthy GVS, Kolli SR, Neogi SB, Singh S, Allagh KP, John N, N. S, Ramani S, Shamanna BR, Doyle P, Kinra S, Ness A, Pallepogula DR, Pant HB, Babbar S, Reddy R, Singh R
A Mixed-Method Study to Determine the Benefits of Periconceptional Folic Acid Supplementation and Effects of Folic Acid Deficiency in Mothers on Birth Outcomes
JMIR Res Protoc 2016;5(2):e129
URL: http://www.researchprotocols.org/2016/2/e129/
doi:10.2196/resprot.5722
PMID:27339656

Protocol

Using an Electronic Decision Support Tool to Reduce Inappropriate Polypharmacy and Optimize Medicines: Rationale and Methods

Amber Young[1], BPharm, PGCertPharm, PGCertGPP; June Tordoff[1], BPharm (Hons), MPharm, PhD; Susan Dovey[2], MPH, PhD; David Reith[3], PhD, FRACP; Hywel Lloyd[2,4], MB, ChB; Murray Tilyard[2,4], BSc, MB ChB, DipObst, MD; Alesha Smith[1,4], BSc, MSc, PhD

[1]New Zealand's National School of Pharmacy, University of Otago, Dunedin, New Zealand

[2]Department of General Practice and Rural Health, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand

[3]Dunedin School of Medicine, University of Otago, Dunedin, New Zealand

[4]Best Practice Advocacy Centre (BPAC), Dunedin, New Zealand

Corresponding Author:
Amber Young, BPharm, PGCertPharm, PGCertGPP
New Zealand's National School of Pharmacy
University of Otago
PO Box 56
Dunedin, 9054
New Zealand
Phone: 64 34797321
Fax: 64 3 479 7034
Email: amber.young@otago.ac.nz

Abstract

Background: Polypharmacy and inappropriate continuation of medicines can lead to a significant risk of adverse drug events and drug interactions with patient harm and escalating health care costs as a result. Thorough review of patients' medications focusing on the need for each drug can reduce the potential for harm. Limitations in performing effective medicine reviews in practice include consultation time constraints and funding for pharmacy services. We will aim to overcome these problems by designing an automatic electronic decision support tool (the medicines optimization/review and evaluation (MORE) module) that is embedded in general practice electronic records systems. The tool will focus on medicines optimization and reducing polypharmacy to aid prescribers in reviewing medicines and improve patient outcomes.

Objective: The objectives of this study are: (1) to develop an electronic decision support tool to assist prescribers in performing clinical medication reviews with a particular focus on patients experiencing multimorbidity and polypharmacy, and (2) evaluate and assess the use of the electronic decision support tool, providing pilot data on its usefulness in supporting prescribers during consultations with patients.

Methods: The first three study phases involve development of clinical rules outlining clinical interventions and the creation and validation of the MORE decision support tool. Phase four is a community-based, single-blind, prospective, 6-month controlled trial involving two interventions and two control general practices, matched for practice demographics. We will be measuring the number of times prescribers engage with the tool, total number of interventions suggested by the tool, and total number of times prescribers change medicines in response to recommendations. There will also be prospective follow-up of patients in the intervention group to examine whether changes to medications are upheld, and to determine the number of hospitalizations or emergency department visits within 6 months of a medicine intervention. Comparisons between control and intervention practices will measure the changes in proportions of patients with polypharmacy and inappropriately prescribed medicines before and after the introduction of the electronic decision support tool, proportions of patients receiving appropriate treatment in each practice, and changed, maintained, or improved health status, hospitalizations, and deaths in the study year. Initiation rates of inappropriately prescribed medicines will be measured as a secondary outcome. As well as external assessment of the extent of use and application of the tool, prescribers will receive monthly practice progress reports detailing the proportion of their patients experiencing polypharmacy and taking inappropriately prescribed medicines identified for review.

Results: Phase one has now been completed and the decision support tool is under development. Final data analysis is expected to be available in December 2016.

Conclusions: This study will establish whether the MORE decision support tool stands up to real world conditions and promotes changes in prescribing practice.

(JMIR Res Protoc 2016;5(2):e105) doi:10.2196/resprot.5543

KEYWORDS

polypharmacy; decision support systems; clinical, drug-related side effects and adverse reactions; drug interactions; primary health care; inappropriate prescribing; medication therapy management

Introduction

Background

As the New Zealand population is rapidly ageing, there are increasing numbers of patients with more long-term conditions and taking more medicines. With declining organ function and introduction of comorbidities, increasing age may also influence the suitability of a patient's long-term medications. Periodic assessment of patients' medications should be undertaken, keeping in mind their remaining life expectancy, time until benefit of treatment, treatment targets, and goals of care [1].

Polypharmacy can be defined as the concurrent use of five or more medicines, and excessive polypharmacy, the use of 10 or more concurrent medicines [2]. Inappropriate polypharmacy occurs when more medicines are prescribed than are clinically indicated or when medicines are inappropriately continued [3]. Increasing the number of prescribed medicines greatly increases the risk of drug interactions and adverse drug events, resulting in iatrogenic patient morbidity [3-5]. The medical mantra of 'First do no harm' is at risk when patients' are in danger of multimorbidity from cumulative prescribing of inappropriate medicines, particularly when this is compounded with altered pharmacodynamics from declining renal and hepatic function with age. Overall, there is a danger that patients' medication regimens may begin to pose more risks than benefits to their health [5]. Between 2013 and 2014, 8.5% of the New Zealand population received five or more medicines and 2.6% received 11 or more medicines [2]. These proportions of the population with polypharmacy and hyperpolypharmacy are increasing in all age groups every year [2], particularly for 40- to 60-year olds [6].

Thorough review of patients' medications focusing on the need for each drug can reduce the potential for harm [5,7]. A 2014 Cochrane review found that interventions to improve appropriate polypharmacy are beneficial in reducing inappropriate prescribing [3]. Despite the evidence, most people taking multiple medicines do not receive an annual comprehensive medicines review due to general practitioners' limited consultation times. Tools exist to assist a review but are infrequently used due to being complex and time-consuming [8,9]. A scheme for collaborative medications reviews involving pharmacists exists in New Zealand (Medicines Therapy Assessment) but is funded in few regions. This deficiency is similar worldwide as many international models of primary care do not promote intensive medication reviews by a clinical pharmacist.

This study will attempt to overcome the problems in completing medication reviews by designing an automatic electronic decision support tool. These tools have been shown to influence prescriber performance, improve quality of care and patient outcomes [10], and reduce inappropriate prescribing [3]. The medicines optimization/review and evaluation (MORE) decision support tool will focus on medicines optimization to aid prescribers in reviewing medicines and improve patient outcomes while reducing inappropriate polypharmacy. The electronic decision support software will also provide continuous and reproducible medication reviews [11].

Recent studies have demonstrated benefits of electronic decision support tools, but the technology itself can become a burden on physicians' time and patient management [12-15]. For successful implementation, decision support tools must be fast, reliable, and able to integrate into existing systems used in practice.

The 2012 review by Clyne et al [12] demonstrated that clinical decision support has potential to improve safe and effective prescribing in many different health care settings. Likewise, the review by Topinkova et al [16] from the same year found that decision support reduces prescribing errors. However, they also concluded that the real effect of these systems requires further study, focusing on health outcomes such as overall health care cost and patient morbidity and mortality. Further research is required to evaluate the acceptability of alerts to prescribers' [16]. The 2014 Cochrane review, examined studies using specific validated screening tools or instruments, but did not include research on how doctors interact with the specific interventions, and based their recommendations for implementation of change on the recommendations presented to them [3].

This study will use an electronic decision support platform currently available in over 80% of New Zealand general practices and compatible with the most common patient management system in use. We expect that prescribers' familiarity with the decision support platform will enable immediate uptake and application of the MORE tool. We will also investigate the interaction of the doctor with the decision support tool to evaluate its' effectiveness and usefulness in practice.

In summary, the significance of this study is the development of a new decision support tool that uses each patient's medical information to automatically undertake a medicines review and assist prescribers with patient management. Personalized medicine management strategies help ensure that patients receive the most appropriate care and avoids the risk of 'alert fatigue'. Broad use of our tool is intended to improve clinical outcomes, and reduce health care use and cost. The evaluation and review of users' feedback will enable the production of a practical and efficient decision support tool.

Research Aims

The purpose of this study is to develop and test an electronic decision support tool (the MORE module) designed to assist prescribers in performing clinical medication reviews for patients experiencing multimorbidity and polypharmacy. The study will (1) provide pilot data on its usefulness in supporting prescribers during consultations with patients, and (2) test the hypothesis that there is no difference in the identification and management of patients with multiple medicines between the practices implementing the MORE decision support tool and usual care practices.

Methods

Phase One: The Development of the Clinical Rules for the MORE Decision Support Tool

Phase one involved the development of the intervention components to be incorporated into the MORE decision support tool. Literature reviews, internationally validated tools, and prescribing resources were used to identify possible intervention components (see Figure 1). A clinical advisory group was set up to provide expert opinion and direction for the development of the intervention components. This group consisted of 10 clinicians.

The intervention components focused on specific areas for change, including:

1. Reducing polypharmacy by targeting medicines with limited effectiveness, such as long-term use of benzodiazepines for insomnia, or antipsychotics in dementia

2. Stopping duplicate medication classes, such as duplicate antidepressant therapy

3. Reviewing doses and monitoring certain medications such as proton pump inhibitors, anticoagulants, and analgesia

To prioritize the list of interventions, medicines dispensing data were reviewed using the Pharmaceutical Collection, a national database of all community pharmacy dispensed medicines. Possible interventions for medicines not dispensed in large numbers (<5000 dispensing's a year nationally) were excluded. Possible interventions remaining were reviewed by the clinical advisory group to determine the appropriateness of the recommendations for the New Zealand context. The group assessed the importance of each medicine intervention using a list of references provided and their own clinical expertise. International specialist opinion was also sought. Descriptions of the interventions were modified following comments by the group, and the proposed medicine interventions with the greatest consensus of agreement were selected as the final intervention components.

These final medicine intervention components are expected to have the most impact on patient care and polypharmacy, and were used to form the clinical rules of the MORE decision support tool. See Figure 1 for an outline of the intervention development process.

Phase Two: Development of the MORE Decision Support Tool

Decision support programmers (from BPAC Inc) will use the medicine intervention components generated in phase one to create the clinical rules in the MORE decision support tool. This tool will automatically interact with the prescribing component of general practice electronic records systems and access individual patients' demographic and clinical information to make recommendations to prescribers. The program developers have previously built the Best Practice Advocacy Centre (BPAC) decision support tools, ensuring that the look, feel, and function of the MORE tool are similar to that of the current BPAC decision support tools that are in widespread use in New Zealand. These tools are also currently in use in Australia and soon to be introduced into the United Kingdom.

The decision support architecture will be using open electronic health record (open EHR) for the patient object model, which is an open international standard. This allows for the inclusion of any coding system from any underlying patient management system (PMS) to be integrated into the patient object model. The patient object model also allows for integration with any PMS application program interface (API), allowing for rapid international roll out. Interoperability is also enabled through the mapping of drug codes, medical classification, laboratory codes, and measurement parameters to the systematized nomenclature of medicine clinical terminology (SNOMED CT) using an in-house ontology service. Furthermore, the clinical rules driving the prescribing advice reside in a rules engine, allowing additional rules and functionality to be added independently of any programming interfaces. Figure 2 shows the platform architecture of the decision support module. Not all components will be used for this study, such as the SMS text messaging (short message service, SMS) function, but will be available for future roll out. This platform architecture enables rapid scalability.

The MORE decision support tool will alert prescribers through the patient prompt: this analyses patient records at the time of consultation, notifying clinicians of any areas where action may be required. Recommendations will be based on individual patients' data and therefore are specific for each patient.

Simple representation of targeted advice and prescribing alternatives is more effective than highlighting a medicine that may be inappropriate [17]. Therefore, this decision support tool will alert prescribers to medicines within patient records that are potentially inappropriate with suggested action based on each patient's individual data. There will also be a link to electronic information supporting recommended actions, where relevant. The decision support tool will also allow linking to patient information and advice that can be printed.

Figure 1. Development of the clinical rules for the MORE decision support tool.

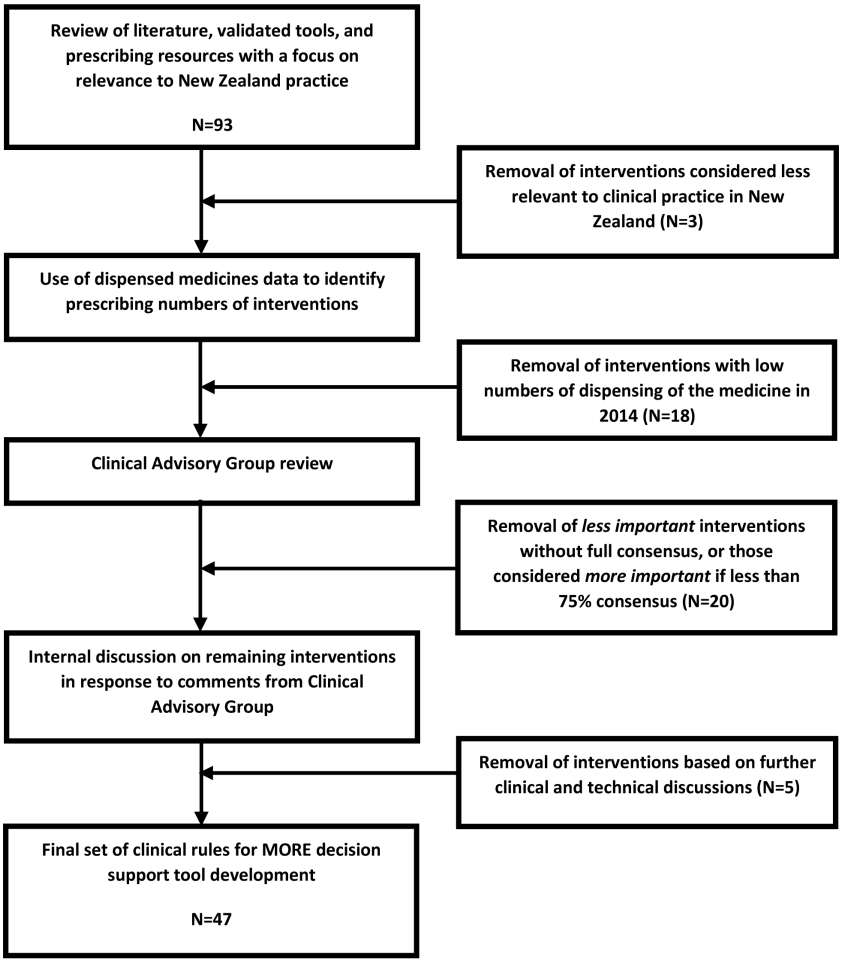
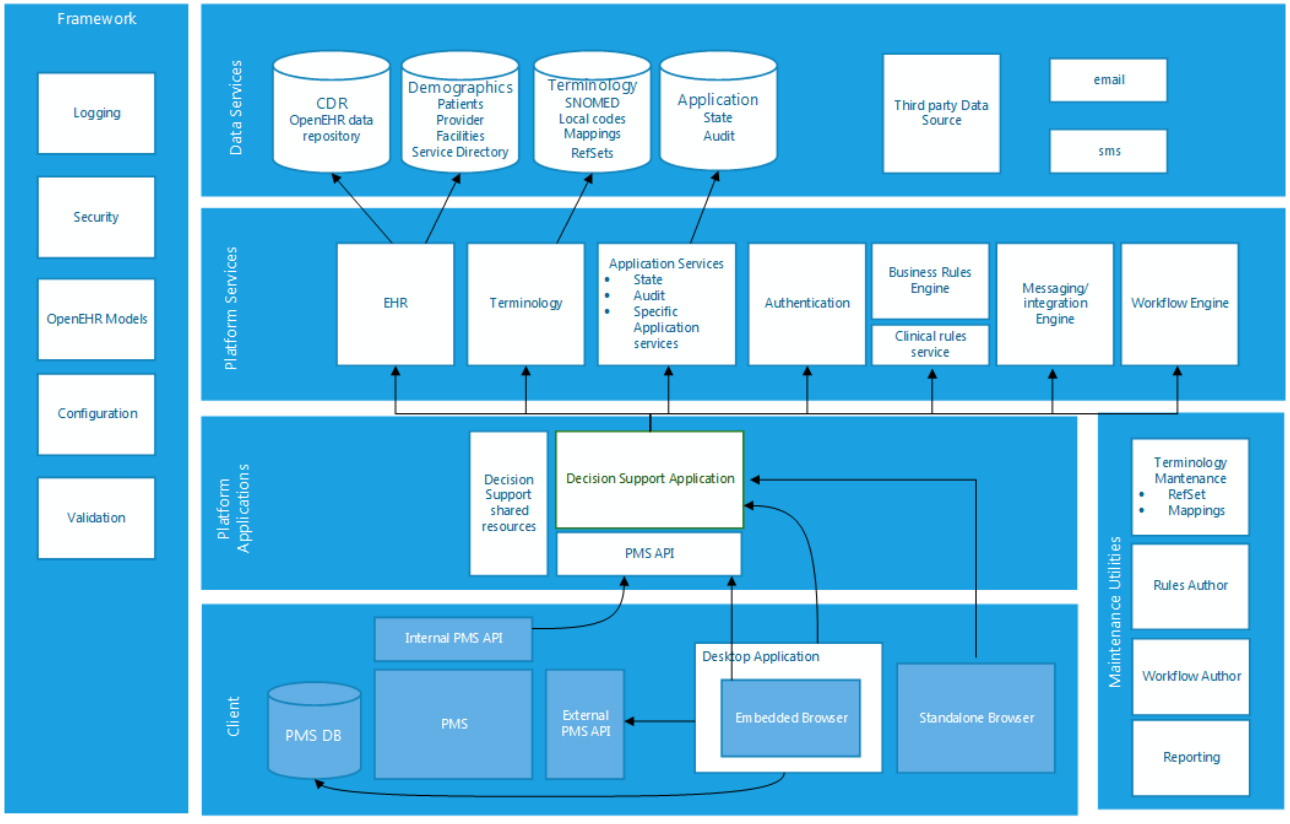


Figure 2. Platform architecture of the decision support tool.



Phase Three: Validation of the MORE Decision Support Tool

The MORE decision support tool will be validated by challenging it with data from a de-identified historical database. This will ensure that the clinical rule set is working correctly. The decision support tool will be applied to a variety of patients in the database (patients with ≥10 medicines and patients with only a few medicines) to confirm that patient data are autopopulated into the decision support tool correctly and whether an alert is triggered by the appropriate information. This phase will also allow technical checks such as the linking to external information and printing functionality. Personal practitioner progress reports will also be generated to ensure this functionality works correctly.

Phase Four: Application of the MORE Decision Support Tool

Phase four is the feasibility study of the MORE decision support tool using MORE care versus usual care to reduce unnecessary or inappropriate prescribing. The MORE decision support tool will be piloted for 6 months in two intervention general practices. A comparison in prescribing behavior and outcomes will be made between the practices and two matched control practices. This will establish whether the decision support tool stands up to real world conditions and causes a change in prescribing practices.

During the 6 months that the MORE decision support tool is active, prescribers will receive individual monthly progress reports that have been extracted remotely by BPAC analysts using the MORE decision support tool. The reports will detail the proportion of patients at their practice experiencing polypharmacy, and patients taking prescribed medicines identified for review.

This information will include patient demographics and the total number of times prescribers in the practice have engaged with the MORE decision support tool with resulting changes they may have implemented. They will also be informed of the clinical rules that, following the alert, have resulted in changes to patients' therapy the most and the least number of times.

As the study progresses the reports will depict the changes in these variables over time. Using the decision support tool query builder, prescribers will also be able to access lists of patients experiencing polypharmacy and those taking prescribed medicines identified for review, any time during the project.

Study Setting

The MORE decision support tool will be provided to two intervention general practices recruited by invitation. In order for a practice to be considered for inclusion, it must be using the MedTech software, which is in use in over 80% of New Zealand practices. Practices will be excluded from the study if they are specialist practices (eg, a sexual health clinic, student health clinic), or if they have less than 1500 registered patients. Of the practices wishing to participate, two will be randomly assigned as the MORE decision support practices and two control practices will be matched according to practice patient demographics (mean age, gender, ethnicity, and geography (urban/rural)).

The MORE decision support tool will be added to the intervention and control practices' suite of BPAC decision support tools, although in the control practices, the alerts will not be revealed at point-of-care. Instead, the type and frequency of the alerts that would have been shown will be recorded for comparison against those in the intervention group. The decision support tool can be added to the decision support platform remotely because it is a Web-based system that allows upgrades or revisions to existing decision support tools to be implemented through one centralized server. This will minimize disruption to the daily activities of study general practices.

Sample Size

Between 2013 and 2014, 11% of the New Zealand population used five or more medicines [2]. A sample size of 367 patients for each arm (the intervention and the control) will have 80% power to detect a difference in patients with polypharmacy of 20% at the 5% level of significance.

We intend to recruit four practices with 1500 or more registered patients. The average number of patients per practice in New Zealand is approximately 4000 [18], so our goal of practices with 1500 or more registered patients is achievable. Ethical approval has been obtained from the Health and Disability ethics committee (16/STH/7).

Measures

This study will test the hypothesis that there is no difference between the practices using the MORE decision support tool and usual care practices in the identification of patients with polypharmacy and the identification and review of patients who have inappropriately prescribed medicines.

Due to the nature of the study, it is not possible to blind the general practices to the intervention. However, the data retrieval from the general practices is through an automated Web-based system and a blinded analysis of the measures comparing intervention and control groups will be undertaken. This allows for unbiased assessment of these outcomes.

We plan to assess the use of the MORE decision support tool by seeing how often general practitioners use the tool and follow its recommendations. We will calculate how often the alert for review was raised and compare this with changes in prescribing. The number of patients experiencing inappropriate medicines (as defined by the clinical rules in the decision support tool) and polypharmacy before and after the study will also be reviewed, as a proxy measure of effectiveness of the intervention. See Table 1 for detailed descriptions of study measures and timeframes.

Table 1. Study Outcomes and How They Will be Measured.

Outcomes	How this will be measured	Timeframe will this be measured
Practitioners use the tool	The number of times prescribers engage with the MORE decision support tool in the intervention practices (how many times prescribers choose to look at possible interventions)	Every month during the 6-month pilot phase
	The total number of interventions suggested by the MORE decision support tool in the intervention practices (how many instances of unnecessary or inappropriate medicines)	Every month during the 6-month pilot phase
	Interview and questionnaire containing the standardized System Usability Scale and qualitative questions on usability and usefulness	After completion of pilot phase
Practitioners follow the recommendations	The total number of times prescribers change medicines in response to the MORE decision support tool in the intervention practices (ie, remove unnecessary or inappropriate medicines)	Every month during the 6-month pilot phase
	The number of changes sustained or reverted to original prescribing methods within 6 months of the intervention in the intervention practices	Six months after completion of pilot phase
	The difference in number of laboratory tests ordered between intervention and control practices in line with suggestions from the MORE decision support tool	Every month during the 6-month pilot phase
Reduction in inappropriate prescribing and polypharmacy	The change in the proportion of patients with inappropriately prescribed medicines[a] before and after the introduction of the decision support tool (adjusted for age and comorbidities) between intervention and control practices. Specifically:	At baseline and at end of the 6-month pilot phase
	1. The number and proportion of patients with hyperpolypharmacy (more than nine medicines [2]) before and after intervention	
	2. The number and proportion of patients with polypharmacy (more than four medicines [2]) before and after intervention	
	3. The average number of medicines per patient before and after intervention	
	The percentage of patients receiving appropriate treatment based on the developed clinical rules in each practice between intervention and control practices	At baseline and at end of the 6-month pilot phase
	Initiation rates of inappropriately prescribed medicines based on the developed clinical rules in each practice between intervention and control practices	Every month during the 6-month pilot phase
	Initiation rates of appropriately prescribed medicines according to the developed clinical rules in each practice between intervention and control practices	Every month during the 6-month pilot phase
Improvement in patient health	Changed, maintained, or improved health status measured by number of patient visits to general practices and hospital or emergency department admissions between intervention and control practices	From 6 months before study enrolment to 6 months after completion of the pilot phase
	Deaths in the study year between intervention and control practices	From 6 months before study enrolment to 6 months after completion of the pilot phase
	The number of related referrals, emergency department visits or hospitalizations within 6 months of the intervention in the intervention practices	During the 6-month pilot phase and for 6 months after completion of the pilot phase

[a]This assumes that on consideration of the MORE decision support tool guidance, only inappropriately prescribed medicines will be stopped (therefore, a decrease in inappropriate polypharmacy will occur).

Cost Analysis

Potential cost savings through analysis of reduced hospitalizations, emergency department visits, and visits to the general practitioner following implementation of the decision support tool will be calculated after 6 months. The costs associated with stopping or starting medicines as recommended by the MORE decision support tool during the study period will also be evaluated. This will be balanced against any consultation slow down's due to using the tool. There will also be an estimation of the time saved using the MORE decision support tool compared with alternative methods of medicine review.

Interviews

The intervention group will be interviewed to elicit feedback on the usefulness of the decision support tool and its usability and presentation. This will provide the basis for future improvements for the decision support tool. During the interview a questionnaire will be completed containing the system usability scale, a validated tool for measuring a systems usability [19], to elicit participants' satisfaction with the decision support tool. Reasons for and against following the decision support tool's interventions and the differences in managing patients with multiple medicines before and during the use of the MORE decision support tool will also be explored. This will determine whether the decision support tool improves identification of patients with polypharmacy and those who have inappropriately prescribed medicines.

The control group will also be interviewed to understand how they regularly identify and manage patients with polypharmacy. Also, to see who has inappropriately prescribed medicines, what percentage of their patients they estimate belong to these groups, and how often they would undertake a medicine review in an average week.

Results

Phase one has now been completed and the decision support tool is under development. See Textbox 1 for the clinical rules to be built into the decision support tool. Phases two and three are expected to be finalized early 2016 with implementation and analysis of the decision support tool by October 2016. Results will be reported in December 2016.

Discussion

Reducing Inappropriate Polypharmacy

New Zealand general practice is facing increasing challenges in caring for a growing number of patients with long-term conditions. This increases the complexity of primary care interactions and makes high quality medicines review more difficult to achieve within available consultation time frames. It is well recognized that the quality use of medicines leads to decreased medicine interactions, reduced health care use (including hospitalizations), and improved quality of life [72,73]. Therefore, the individualized approach to medicine review undertaken in this study will promote a safe and effective means of practicing.

The premise of optimizing medicines and the reduction of inappropriate polypharmacy is about finding the best available medication at the right dosage and for the shortest possible duration on a case-by-case basis. This decision support tool will assist prescribers in achieving these goals by collating relevant patient information automatically using the prescribing patient management system and making individual recommendations for these complex patients. This will reduce the need for manual processing, the gold standard for reviewing medicines, which is a costly and timely enterprise.

The project partnership with BPAC Inc will allow the transfer of this study from evidence to practice as, if successful, the electronic decision support decision support tool could be directly rolled out to most general practices in New Zealand, through existing BPAC systems and networks. If the MORE module is successful in achieving its goals, the clinical rules could be applied across primary care settings, internationally.

Study Strengths and Limitations

Using a full range of clinical rules rather than focusing on one condition or drug class is a strength of this study. It allows for inclusion of rules applicable to the whole population and for a wide variety of therapeutic interventions. It also enables further development of the tool without restriction to a singular therapeutic condition. Using real-world locations ensures clinical relevance and applicability of the tool.

This is a fully automated and prepopulated tool. There is no manual data entry required by general practitioners and the patient management system will be one they are currently using in their practice. This will ensure minimal time for setup and the practitioners' time can be focused on the clinical interventions rather than the technical aspect of inputting data. Moreover, training of practitioners will not need to be extensive and they will already have working knowledge of how this type of alert works.

An extra strength and uniqueness of the study is the content of the tool. It will provide suggested actions for prescribers rather than just highlighting a potentially inappropriate medicine. It is believed this will improve the use of the clinical rules by giving prescribers evidence-based guidance on how these rules should be applied to their patients. The tool will also contain links to patient information and options for printing patient information sheets.

One limitation is the inability to blind the clinicians to the intervention. However, because the analysis of the data will be blinded, objective assessment of results will be possible and is an additional strength.

A further limitation of the study is that the tool is being designed for use with a specific PMS in New Zealand. However, our patient object model allows integration with any PMS API, allowing for the solution to be rolled out internationally. If international roll out is an outcome of this pilot study, further usability studies will be necessary for users of different systems.

The measures of effectiveness are not able to capture the reasons why an alert may be dismissed by a practitioner at the time of consultation. It is hoped that the main reasons alerts are being

ignored will be captured through feedback and the user survey. The initial results will help shape the questionnaire and interview of the practitioners so these issues can be explored.

It will be difficult to specify patient deaths and hospital admissions that are not related to the intervention. However, we can investigate the causes of deaths and admission to hospital for those with a medicine-related diagnosis for the purposes of the study.

There is a risk of alert fatigue, particularly if a patient with extensive polypharmacy is triggering many alerts. We have tried to minimize this by ensuring alerts are specific to patients' characteristics. Furthermore, we will investigate complaints of this nature highlighted in the user feedback reports and work to reduce or eliminate them.

Conclusions

Optimizing medicines use is not necessarily about reducing the number of medicines below an agreed threshold, but about finding the best available medication at the right dosage and for the shortest possible duration on a case-by-case basis. Measuring reductions in the number of patients experiencing polypharmacy and the average number of medicines per patient will indicate removal of unnecessary medicines and the 'inappropriate polypharmacy' from their regimen. This study will establish whether the MORE decision support tool stands up to real world conditions and promotes changes in prescribing practice.

Textbox 1. Clinical Rules to be Built Into the Decision Support Tool.

Duplicate therapy [8]

Stop if duplication of drug class or therapy:

- H_2-receptor antagonists with proton pump inhibitors
- Duplication of benzodiazepines
- Duplication of antipsychotics
- Duplication of selective serotonin receptor antagonists

Gastroprotectants [7,8,20,21]

- Stop proton pump inhibitors if they were prescribed for gastroprotection with nonsteroidal anti-inflammatory drugs, aspirin, or corticosteroid therapy, which has now been stopped
- Consider stopping or reducing dose of proton pump inhibitors prescribed for uncomplicated peptic ulcer disease or erosive peptic esophagitis for >8 weeks

Chronic constipation [8,9,22]

In patients with chronic constipation, stop drugs likely to cause constipation if nonconstipating alternatives are appropriate

Antiplatelets and anticoagulants [8,9,23-28]

Stop vitamin K antagonist, direct thrombin inhibitor, or factor Xa inhibitors:

- if prescribed for first deep venous thrombosis without continuing provoking risk factors for >6 months
- if prescribed for first pulmonary embolus without continuing provoking risk factors for >12 months

Stop aspirin if taken for primary prevention of cardiovascular disease if risk is <20% and there is no personal history of cardiovascular disease (ie, angina, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, transient ischemic attack, ischemic stroke, or peripheral vascular disease)

Medicines in the elderly [8,9,29-37]

- Stop long-term treatment with loop diuretics treating gravitational edema (unrelated to congestive heart failure) in the elderly. If pharmacological treatment necessary, prescribe as required
- Reduce spironolactone if >25-mg daily in elderly patients with congestive heart failure or with creatinine clearance less than 30 mL/min
- Review patients >85 years taking statins for >5 years for primary cardiovascular prevention
- Stop benzodiazepines or zopiclone if taken for treatment of insomnia, agitation, or delirium in adults aged >65 years
- Stop antipsychotics for behavioral problems of dementia unless nonpharmacological options have failed, and patient is a threat to themselves or others
- Stop first-generation antihistamines in patients >75 years
- Stop orphenadrine in patients >75 years

Antipsychotics, antidepressants, and hypnotics [8,9,27,31,38-40]

- Stop all antipsychotics (except for quetiapine and clozapine), metoclopramide, prochlorperazine, and promethazine in patients with Parkinson's disease
- Reduce citalopram doses 40-mg daily
- Stop benzodiazepines or zopiclone if taken for ≥4 weeks (unless for seizure disorders, rapid eye movement sleep disorders, benzodiazepine withdrawal, alcohol withdrawal, severe generalized anxiety disorder, periprocedural anesthesia, end-of-life care)

Analgesics [31,41-47]

- Review opioids if being prescribed long term (>3 months) for nonmalignant pain
- Stop two different types of long-acting opioid
- Stop codeine or tramadol if prescribed with a strong opioid
- Stop combination paracetamol and codeine products and prescribe individual components based on the World Health Organization pain ladder

Nonsteroidal anti-inflammatory drugs [8,9,27,48,49]

- Review stopping nonsteroidal anti-inflammatory drugs:

- if used for 3 months in patients over 75 years
- if used for 3 months in patients for symptom relief of osteoarthritis pain where paracetamol has not been tried

- Stop nonsteroidal anti-inflammatory drugs:
  - if prescribed with concurrent antiplatelet or prescribe proton pump inhibitor prophylaxis
  - in patients with heart failure
  - in patients being treated with a diuretic or an Angiotensin Converting Enzyme inhibitor or Angiotensin Receptor Blocker
  - if patients already taking a nonsteroidal anti-inflammatory drug (ie, duplicate therapy)

Gout [8,50-52]

- Prescribe allopurinol for patients with a history of recurrent episodes of gout (recurrent nonsteroidal anti-inflammatory drug or colchicine prescriptions), or a suitable alternative if allopurinol contraindicated
- Alert if patient is on allopurinol and no uric acid levels or renal function tests for >1 year
- Maximize dose of allopurinol or add additional therapy if uric acid not 0.36 mmol/L

Bisphosphonates [8,53,54]

- Consider stopping bisphosphonate treatment or a ‘drug holiday’ after continuous use for >5 years (for treatment or prevention of osteoporosis) if bone mineral density stabilized
- Consider initiating bisphosphonates in patients taking long-term systemic corticosteroid therapy

Metformin [31,55]

Adjust dose of metformin in renal impairment

Seasonal influenza vaccine [8,56-59]

Recommend an annual seasonal influenza vaccine to:

- patients ≥65 years of age
- patients with ischemic heart disease
- patients with congestive heart failure
- patients with rheumatic heart disease
- patients with Transient Ischemic Attack/Stroke
- patients with asthma, if on a regular preventative therapy
- patients with chronic obstructive pulmonary disorder
- patients with diabetes
- patients with any cancer, excluding basal and squamous skin cancers if not invasive
- patients with human immune deficiency virus
- transplant recipients
- pre and post splenectomy patients
- pregnant patients

Interactions [8,27,31,60-64]

Alert for the following interactions:

- Tricyclic antidepressants and selective serotonin receptor blockers
- Beta-blocker with verapamil or diltiazem
- Concomitant use of two or more antimuscarinics
- Concomitant drugs that prolong the QT-interval

Monitoring [8,65-71]

- Monitor potassium levels if not done >6 months in patients taking spironolactone with potassium sparing drugs
-

Stop potassium supplements if serum potassium >4.0 mmol/L and if cause of hypokalemia resolved. Consider follow up potassium levels after cessation

- Alert if on lithium and no thyroid function tests, renal function tests, serum lithium levels, or sodium levels for >6 months, or no calcium levels or electrocardiogram undertaken for >1 year
- Alert if on an Angiotensin Converting Enzyme inhibitor and no renal function or serum potassium for >1 year
- Alert if on an atypical antipsychotic for schizophrenia and no CV assessment, full blood count, urea and electrolytes, liver function tests, lipid profile, weight measurement, fasting blood glucose, or prolactin levels for >1 year

Acknowledgments

This work was supported by the Health Research Council of New Zealand grant number 14/730.

With thanks to the Clinical Advisory Group: Murray Tilyard, Sharon Leitch, Sharyn Willis, Hywel Lloyd, Lalitha Raman-Wilms, Howard Wilson, Tobias Dreischulte, Bruce Guthrie, Rupert Payne, Chris Leathart, and Marcus Hawkins.

Authors' Contributions

AY had primary responsibility for the manuscript. AS conceived the study, wrote the original protocol, and assisted with development of the manuscript. JT assisted in developing the protocol and read and revised the final manuscript. SD, HL, and MT gave feedback on various medical and technical issues, contributed to refinement of the study protocol, and revised the manuscript.

Conflicts of Interest

Professor Murray Tilyard is Chief Executive of BPAC Inc, the organization that will develop the MORE decision support software.

Multimedia Appendix 1

Grant agency peer-review reports.

[PDF File (Adobe PDF File), 576KB - resprot_v5i2e105_app1.pdf]

References

1. Holmes HM, Hayley DC, Alexander GC, Sachs GA. Reconsidering medication appropriateness for patients late in life. Arch Intern Med 2006;166:605-609. [doi: 10.1001/archinte.166.6.605] [Medline: 16567597]
2. BPAC. Polypharmacy Report. 2014. URL: http://www.bpac.org.nz/Report/2014/November/polypharmacy.aspx [accessed 2016-01-05] [WebCite Cache ID 6eISpgHXk]
3. Patterson SM, Cadogan CA, Kerse N, Cardwell CR, Bradley MC, Ryan C, et al. Interventions to improve the appropriate use of polypharmacy for older people. Cochrane Database Syst Rev 2014;10:CD008165. [doi: 10.1002/14651858.CD008165.pub3] [Medline: 25288041]
4. Goldberg RM, Mabee J, Chan L, Wong S. Drug-drug and drug-disease interactions in the ED: analysis of a high-risk population. Am J Emerg Med 1996;14:447-450. [doi: 10.1016/S0735-6757(96)90147-3] [Medline: 8765105]
5. BPAC. Best Practice Journal. 2010. A Practical Guide to Stopping Medicines in Older People URL: http://www.bpac.org.nz/BPJ/2010/April/stopguide.aspx [accessed 2016-05-12] [WebCite Cache ID 6hSafxiLB]
6. Smith A, Dovey S, Lloyd H, Tilyard M. The prevalence of chronic conditions in New Zealand primary care patients. Surry Hills: NPS MedicineWise; 2014 Presented at: National Medicines Symposium; 21-23 May 2014; Brisbane, Australia.
7. Garfinkel D, Mangin D. Feasibility study of a systematic approach for discontinuation of multiple medications in older adults: addressing polypharmacy. Arch Intern Med 2010;170:1648-1654. [doi: 10.1001/archinternmed.2010.355] [Medline: 20937924]
8. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing 2015;44:213-218 [FREE Full text] [doi: 10.1093/ageing/afu145] [Medline: 25324330]
9. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2012;60:616-631 [FREE Full text] [doi: 10.1111/j.1532-5415.2012.03923.x] [Medline: 22376048]
10. BPAC. Best Practice Journal. 2013. Five Tips for Getting the Most out of Your Practice Management System URL: http://www.bpac.org.nz/BPJ/2013/November/tips.aspx [accessed 2016-05-12] [WebCite Cache ID 6hSbBfLPK]

11. de Wit HA, Mestres GC, Hurkens KP, Mulder WJ, Janknegt R, Verhey FR, et al. Development of a computer system to support medication reviews in nursing homes. Int J Clin Pharm 2013;35:668-672. [doi: 10.1007/s11096-013-9827-3] [Medline: 23888346]
12. Clyne B, Bradley MC, Hughes C, Fahey T, Lapane KL. Electronic prescribing and other forms of technology to reduce inappropriate medication use and polypharmacy in older people: a review of current evidence. Clin Geriatr Med 2012;28:301-322. [doi: 10.1016/j.cger.2012.01.009] [Medline: 22500545]
13. Hecht T, Bundscherer AC, Lassen CL, Lindenberg N, Graf BM, Ittner K, et al. The expenditure of computer-related worktime using clinical decision support systems in chronic pain therapy. BMC Anesthesiol 2015;15:113 [FREE Full text] [doi: 10.1186/s12871-015-0094-9] [Medline: 26231078]
14. Meulendijk MC, Spruit MR, Drenth-van Maanen AC, Numans ME, Brinkkemper S, Jansen PA, et al. Computerized decision support improves medication review effectiveness: an experiment evaluating the STRIP assistant's usability. Drugs Aging 2015;32:495-503 [FREE Full text] [doi: 10.1007/s40266-015-0270-0] [Medline: 26025118]
15. Tamblyn R, Huang A, Perreault R, Jacques A, Roy D, Hanley J, et al. The medical office of the 21st century (MOXXI): effectiveness of computerized decision-making support in reducing inappropriate prescribing in primary care. CMAJ 2003;169(6):549-556. [Medline: 12975221]
16. Topinková E, Baeyens JP, Michel J, Lang P. Evidence-based strategies for the optimization of pharmacotherapy in older people. Drugs Aging 2012;29:477-494. [doi: 10.2165/11632400-000000000-00000] [Medline: 22642782]
17. Ranta A, Dovey S, Weatherall M, O'Dea D. Efficacy and safety of a TIA/stroke electronic support tool (FASTEST) trial: study protocol. Implement Sci 2012;7:107 [FREE Full text] [doi: 10.1186/1748-5908-7-107] [Medline: 23114224]
18. Ministry Of Health. Primary Health Organisation Enrolment Collection. 2012. URL: http://www.health.govt.nz/nz-health-statistics/national-collections-and-surveys/collections/primary-health-organisation-enrolment-collection [accessed 2016-01-05] [WebCite Cache ID 6eJpDtH4Q]
19. U.S. Department of Health & Human Services. System Usability Scale (SUS). 2016. URL: http://www.usability.gov/how-to-and-tools/methods/system-usability-scale.html [accessed 2016-02-29] [WebCite Cache ID 6ffVzh2Aq]
20. BPAC. Best Practice Journal. 2011. Managing Dyspepsia and Heartburn in General Practice - An Update URL: http://www.bpac.org.nz/BPJ/2011/february/dyspepsia.aspx [accessed 2016-05-12] [WebCite Cache ID 6hSbQPYzN]
21. Farrell BPK, Thompson W, Boghossian T, Pizzola L, Rashid J, Rojas-Fernandez C, et al. Evidence-Based Clinical Practice Guideline for Deprescribing Proton Pump Inhibitors. 2015. URL: http://www.open-pharmacy-research.ca/wordpress/wp-content/uploads/ppi-deprescribing-algorithm-cc.pdf [accessed 2016-01-05] [WebCite Cache ID 6eJpdUwwr]
22. Waitemata District Health Board (WDHB). SafeRx. 2014. Clozapine - Safe Prescribing - We are Counting on You URL: http://www.saferx.co.nz/full%5Cclozapine.pdf [accessed 2016-01-05] [WebCite Cache ID 6eJpvJfDc]
23. Keeling D, Baglin T, Tait C, Watson H, Perry D, Baglin C, British Committee for Standards in Haematology. Guidelines on oral anticoagulation with warfarin - fourth edition. Br J Haematol 2011;154:311-324. [doi: 10.1111/j.1365-2141.2011.08753.x] [Medline: 21671894]
24. New Zealand Guidelines Group. New Zealand Primary Care handbook. 2012. Cardiovascular Disease Risk Assessment (Updated 2013) URL: https://www.health.govt.nz/system/files/documents/publications/cardiovascular-disease-risk-assessment-updated-2013-dec13.pdf [accessed 2016-01-05] [WebCite Cache ID 6eJq7WnuD]
25. Antithrombotic Trialists' (ATT) Collaboration, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;373:1849-1860 [FREE Full text] [doi: 10.1016/S0140-6736(09)60503-1] [Medline: 19482214]
26. Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Erqou S, Sattar N, et al. Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials. Arch Intern Med 2012;172:209-216. [doi: 10.1001/archinternmed.2011.628] [Medline: 22231610]
27. Avery AJ, Dex GM, Mulvaney C, Serumaga B, Spencer R, Lester HE, et al. Development of prescribing-safety indicators for GPs using the RAND Appropriateness Method. Br J Gen Pract 2011;61:e526 [FREE Full text] [doi: 10.3399/bjgp11X588501] [Medline: 21801572]
28. BPAC. Best Practice Journal. 2011. The Use of Antithrombotic Medicines in General Practice: A Consensus Statement URL: http://www.bpac.org.nz/BPJ/2011/october/antithrombotic.aspx [accessed 2016-05-12] [WebCite Cache ID 6hSbnjKG6]
29. Kolbach DN, Sandbrink MW, Hamulyak K, Neumann HA, Prins MH. Non-pharmaceutical measures for prevention of post-thrombotic syndrome. Cochrane Database Syst Rev 2004:CD004174. [doi: 10.1002/14651858.CD004174.pub2] [Medline: 14974060]
30. Simon C. Prescribing for the elderly. InnovAiT 2008;1:813-819. [doi: 10.1093/innovait/inn141]
31. New Zealand Formulary (NZF). New Zealand Formulary Release 43. 2016. URL: http://nzf.org.nz/home/noaccess [accessed 2016-01-05] [WebCite Cache ID 6eJqNJycA]
32. Tidy C. Patient. 2014. Prescribing for the Older Patient URL: http://m.patient.media/pdf/241.pdf?v=635737391117055516 [accessed 2016-01-05] [WebCite Cache ID 6eJqrHVNI]
33. Holmes HM, Min LC, Yee M, Varadhan R, Basran J, Dale W, et al. Rationalizing prescribing for older patients with multimorbidity: considering time to benefit. Drugs Aging 2013;30:655-666 [FREE Full text] [doi: 10.1007/s40266-013-0095-7] [Medline: 23749475]

34. Waitemata District Health Board (WDHB). SafeRx. 2015. Simvastatin - Safe Prescribing -Time to Chew the Fat URL: http://www.saferx.co.nz/full%5Csimvastatin.pdf [accessed 2016-01-05] [WebCite Cache ID 6eJr0NhLj]
35. RANZCP Faculty of Psychiatry of Old Age (New Zealand). The Use of Antipsychotics in Residential Aged Care. Clinical Recommendations Developed by the RANZCP Faculty of Psychiatry of Old Age (New Zealand). 2008. URL: http://www.bpac.org.nz/a4d/resources/docs/RANZCP_Clinical_recommendations.pdf [accessed 2016-01-05] [WebCite Cache ID 6eJrKBJqV]
36. Ballard C, Lana MM, Theodoulou M, Douglas S, McShane R, Jacoby R, Investigators DART AD. A randomised, blinded, placebo-controlled trial in dementia patients continuing or stopping neuroleptics (the DART-AD trial). PLoS Med 2008;5:e76 [FREE Full text] [doi: 10.1371/journal.pmed.0050076] [Medline: 18384230]
37. Ballard CG, Thomas A, Fossey J, Lee L, Jacoby R, Lana MM, et al. A 3-month, randomized, placebo-controlled, neuroleptic discontinuation study in 100 people with dementia: the neuropsychiatric inventory median cutoff is a predictor of clinical outcome. J Clin Psychiatry 2004;65:114-119. [Medline: 14744180]
38. Waitemata District Health Board (WDHB). SafeRx. 2013. Citalopram and Escitalopram - Same but Different URL: http://www.saferx.co.nz/full/citalopram_escitalopram.pdf [accessed 2016-01-05] [WebCite Cache ID 6eJrsGNfU]
39. BPAC. Best Practice Journal. 2008. Managing Insomnia URL: http://www.bpac.org.nz/BPJ/2008/June/insomnia.aspx [accessed 2016-05-12] [WebCite Cache ID 6hScaRlD1]
40. Waitemata District Health Board (WDHB). SafeRx. 2012. Hypnotics - Safe Prescribing - Dying for a Good Sleep? URL: http://www.saferx.co.nz/full%5CHypnotics.pdf [accessed 2016-01-05] [WebCite Cache ID 6eJs2Ezck]
41. BPAC. Best Practice Journal. 2014. Helping Patients Cope With Chronic Non-Malignant Pain: It's Not About the Opioids URL: http://www.bpac.org.nz/BPJ/2014/September/chronicpain.aspx [accessed 2016-05-12] [WebCite Cache ID 6hScgMTyY]
42. BPAC. Best Practice Journal. 2014. Identifying and Managing Addiction to Opioids URL: http://www.bpac.org.nz/BPJ/2014/October/opioid-addiction.aspx [accessed 2016-05-12] [WebCite Cache ID 6hScjxlfA]
43. Murnion BP. Australian Prescriber. 2010. Combination Analgesics in Adults URL: http://www.australianprescriber.com/magazine/33/4/113/5 [accessed 2016-05-12] [WebCite Cache ID 6hSdJCMm0]
44. de Craen J, Di GG, Lampe-Schoenmaeckers JE, Kessels AG, Kleijnen J. Analgesic efficacy and safety of paracetamol-codeine combinations versus paracetamol alone: a systematic review. BMJ 1996;313:321-325 [FREE Full text] [Medline: 8760737]
45. Arora S, Herbert ME. Myth: codeine is a powerful and effective analgesic. West J Med 2001;174:428 [FREE Full text] [Medline: 11381016]
46. Toms L, Derry S, Moore RA, McQuay HJ. Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults. Cochrane Database Syst Rev 2009(1):CD001547 [FREE Full text] [doi: 10.1002/14651858.CD001547.pub2] [Medline: 19160199]
47. Hunter Integrated Pain Service. NSW Agency for Clinical Innovation. 2014. Reconsidering Opioid Therapy - A Hunter New England perspective URL: http://www.aci.health.nsw.gov.au/__data/assets/pdf_file/0015/212226/Reconsidering_Opioid_Therapy_1.pdf [WebCite Cache ID 6eJsC0TlM]
48. Dreischulte T, Grant A, Donnan P, McCowan C, Davey P, Petrie D, et al. A cluster randomised stepped wedge trial to evaluate the effectiveness of a multifaceted information technology-based intervention in reducing high-risk prescribing of non-steroidal anti-inflammatory drugs and antiplatelets in primary medical care: the DQIP study protocol. Implement Sci 2012;7:24 [FREE Full text] [doi: 10.1186/1748-5908-7-24] [Medline: 22444945]
49. Waitemata District Health Board (WDHB). SafeRx. 2014. The Triple Whammy - Safe Prescribing - A Dangerous Trio URL: http://www.saferx.co.nz/triplewhammy.pdf [accessed 2016-01-05] [WebCite Cache ID 6eJsn2mX8]
50. BPAC. Best Practice Journal. 2013. An Update on the Management of Gout URL: http://www.bpac.org.nz/BPJ/2013/March/managing-gout.aspx [accessed 2016-05-12] [WebCite Cache ID 6hSdWLNDY]
51. BPAC. Best Practice Journal. 2011. The Medical Management of Gout Revisited URL: http://www.bpac.org.nz/BPJ/2011/august/gout.aspx [accessed 2016-05-12] [WebCite Cache ID 6hSdavLwc]
52. Waitemata District Health Board (WDHB). SafeRx. 2015. Allopurinol - Safe Prescribing - Dose Up URL: http://www.saferx.co.nz/full/allopurinol.pdf [accessed 2016-01-05] [WebCite Cache ID 6eJstz9a5]
53. Brown JP, Morin S, Leslie W, Papaioannou A, Cheung AM, Davison KS, et al. Bisphosphonates for treatment of osteoporosis: expected benefits, potential harms, and drug holidays. Can Fam Physician 2014;60:324-333 [FREE Full text] [Medline: 24733321]
54. Diab DL, Watts NB. Bisphosphonate drug holiday: who, when and how long. Ther Adv Musculoskelet Dis 2013;5:107-111 [FREE Full text] [doi: 10.1177/1759720X13477714] [Medline: 23858334]
55. Waitemata District Health Board (WDHB). SafeRx. 2013. Metformin - Safe Prescribing - First-Line URL: http://www.saferx.co.nz/full/Metformin.pdf [accessed 2016-01-05] [WebCite Cache ID 6eJt10kOJ]
56. National Influenza Specialist Group. Fightflu. 2015. Can I Get a Free flu Vaccine? URL: http://www.fightflu.co.nz/ [accessed 2016-01-05] [WebCite Cache ID 6eJtCKQno]
57. Gross PA, Hermogenes AW, Sacks HS, Lau J, Levandowski RA. The efficacy of influenza vaccine in elderly persons. A meta-analysis and review of the literature. Ann Intern Med 1995;123:518-527. [Medline: 7661497]

58. Nichol KL, Nordin J, Mullooly J, Lask R, Fillbrandt K, Iwane M. Influenza vaccination and reduction in hospitalizations for cardiac disease and stroke among the elderly. N Engl J Med 2003;348:1322-1332. [doi: 10.1056/NEJMoa025028] [Medline: 12672859]
59. Pharmaceutical Management Agency. PHARMAC. 2016. Online Pharmaceutical Schedule - Vaccinations URL: http://www.pharmac.govt.nz/patients/PharmaceuticalSchedule/Schedule?osq=influenz [accessed 2016-01-05] [WebCite Cache ID 6eJtRAwm8]
60. Baxter K, Preston CL, editors. Stockley's Drug Interactions. 10th edition. London: Pharmaceutical Press; 2013.
61. Rohan J, Pramesh K. Australian Prescriber. 2002. Drugs and the QTc interval URL: http://www.australianprescriber.com/magazine/25/3/63/5 [accessed 2016-05-12] [WebCite Cache ID 6hSebChNR]
62. Fazio G, Vernuccio F, Grutta G, Re GL. Drugs to be avoided in patients with long QT syndrome: Focus on the anaesthesiological management. World J Cardiol 2013;5:87-93 [FREE Full text] [doi: 10.4330/wjc.v5.i4.87] [Medline: 23675554]
63. Medsafe Pharmacovigilance Team. Prescriber Update Publications. 2010. Drug-Induced QT Prolongation and Torsades de Pointes - The Facts URL: http://www.medsafe.govt.nz/profs/PUArticles/DrugInducedQTProlongation.htm [accessed 2016-01-05] [WebCite Cache ID 6eJtsYVeT]
64. Medsafe Pharmacovigilance Team. Prescriber Update Publications. 2013. Update: QT Prolongation With Antidepressants URL: http://www.medsafe.govt.nz/profs/PUArticles/December2013QTProlongationAndAntidepressants.htm [accessed 2016-01-05] [WebCite Cache ID 6eJu3ck8T]
65. Garfinkel D, Zur-Gil S, Ben-Israel J. The war against polypharmacy: a new cost-effective geriatric-palliative approach for improving drug therapy in disabled elderly people. Isr Med Assoc J 2007;9:430-434 [FREE Full text] [Medline: 17642388]
66. BPAC. Best Tests. 2011. A Primary Care Approach to Sodium and Potassium Imbalance URL: http://www.bpac.org.nz/BT/2011/September/imbalance.aspx [accessed 2016-05-12] [WebCite Cache ID 6hSepBKal]
67. BPAC. Best Practice Journal. 2014. Bipolar Disorder: Identifying and Supporting Patients in Primary Care URL: http://www.bpac.org.nz/BPJ/2014/July/bipolar.aspx [accessed 2016-05-12] [WebCite Cache ID 6hSetG1dL]
68. Malhi GS, Tanious M, Bargh D, Das P, Berk M. Australian Prescriber. 2013. Safe and Effective Use of Lithium URL: http://www.australianprescriber.com/magazine/36/1/18/21 [accessed 2016-05-12] [WebCite Cache ID 6hSeyOyHd]
69. Hunt SA, American College of Cardiology, American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the EvaluationManagement of Heart Failure). ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol 2005;46:e1-e82 [FREE Full text] [doi: 10.1016/j.jacc.2005.08.022] [Medline: 16168273]
70. Douglas Pharmaceuticals Ltd. Medsafe. 2014. Lithium Carbonate 250 mg Capsule Data Sheet URL: http://www.medsafe.govt.nz/profs/datasheet/l/Lithiumcarbonatecap.pdf [accessed 2016-01-05] [WebCite Cache ID 6eJuB0ws4]
71. Waitemata District Health Board (WDHB). SafeRx. 2014. Atypical Antipsychotics - Safe Prescribing - Better, but not Perfect URL: http://www.saferx.co.nz/full/atypical_antipsychotics.pdf [accessed 2016-01-05] [WebCite Cache ID 6eJuMO9zD]
72. Roughead EE, Barratt JD, Ramsay E, Pratt N, Ryan P, Peck R, et al. The effectiveness of collaborative medicine reviews in delaying time to next hospitalization for patients with heart failure in the practice setting: results of a cohort study. Circ Heart Fail 2009;2:424-428 [FREE Full text] [doi: 10.1161/CIRCHEARTFAILURE.109.861013] [Medline: 19808372]
73. Roughead EE, Barratt JD, Ramsay E, Pratt N, Ryan P, Peck R, et al. Collaborative home medicines review delays time to next hospitalization for warfarin associated bleeding in Australian war veterans. J Clin Pharm Ther 2011;36:27-32. [doi: 10.1111/j.1365-2710.2009.01149.x] [Medline: 21108651]

Abbreviations

API: application program interface
BPAC: Best Practice Advocacy Centre
EHR: electronic health record
MORE: medicines optimization/review and evaluation
PMS: patient management system
SNOMED CT: systematized nomenclature of medicine clinical terminology

Edited by G Eysenbach; submitted 19.01.16; peer-reviewed by M Numans, A Billis, T Irizarry; comments to author 18.02.16; revised version received 15.03.16; accepted 30.03.16; published 10.06.16.

Please cite as:
Young A, Tordoff J, Dovey S, Reith D, Lloyd H, Tilyard M, Smith A
Using an Electronic Decision Support Tool to Reduce Inappropriate Polypharmacy and Optimize Medicines: Rationale and Methods
JMIR Res Protoc 2016;5(2):e105
URL: http://www.researchprotocols.org/2016/2/e105/
doi:10.2196/resprot.5543
PMID:27288200

Protocol

eHealth Use Among First-Generation Immigrants From Pakistan in the Oslo Area, Norway, With Focus on Diabetes: Survey Protocol

Naoe Tatara[1], PhD; Marte Karoline Råberg Kjøllesdal[2], PhD; Jelena Mirkovic[3], PhD; Hege Kristin Andreassen[4], PhD

[1]Department of Computer Science, Faculty of Technology, Art and Design, Oslo and Akershus University College of Applied Sciences, Oslo, Norway
[2]Department of Community Medicine, Institute of Health and Society, Faculty of Medicine, University of Oslo, Oslo, Norway
[3]Center for Shared Desision Making and Collaborative Care Research, Oslo University Hospital HF Division of Medicine, Oslo, Norway
[4]Norwegian Centre for eHealth Research, University Hospital of North Norway, Tromsø, Norway

Corresponding Author:
Naoe Tatara, PhD
Department of Computer Science
Faculty of Technology, Art and Design
Oslo and Akershus University College of Applied Sciences
P.O.Box 4 St. Olavs plass
Oslo, 0130
Norway
Phone: 47 67238679
Fax: 47 22453205
Email: naoe.tatara@hioa.no

Abstract

Background: A variety of eHealth services are available and commonly used by the general public. eHealth has the potential to engage and empower people with managing their health. The prerequisite is, however, that eHealth services are adapted to the sociocultural heterogeneity of the user base and are available in a language and with contents that fit the users' preference, skills, and abilities. Pakistani immigrants in the Oslo area, Norway, have a much higher risk of Type-2 diabetes (T2D) than their Norwegian counterparts do. In spite of having access to information and communication technology (ICT) and the Internet, ICT skills in this population are reported to be relatively low. Further, there is insufficient information about their use of and attitudes toward eHealth services, necessitating investigation of this group in particular.

Objective: This study targets first-generation immigrants from Pakistan living in the Oslo area and examines their use of and attitudes toward eHealth services, specifically: information searches, communication using ICT, and use of ICT for self-management or decision making, all concerning T2D.

Methods: Due to a high prevalence of low literacy among the target population, we employed questionnaire-based individual interviews. The questionnaire was developed by implementing potentially relevant theoretical constructs (technology acceptance model (TAM) and health belief model (HBM)) as measures. To explore issues around language, culture, and general ICT skills, we also implemented questions that we assume were particularly relevant in the context studied but do not appear in any theoretical frameworks. The questionnaire was revised to reflect results of a pilot study involving 10 participants. We employed culturally sensitive sampling methods to reach informants who could otherwise fail to be included in the survey.

Results: This paper presents a survey protocol. The data collection is ongoing. The aim is to collect 200 responses in total by March 2016.

Conclusions: For eHealth to become an influential social innovation, equal access to eHealth services regardless of users' language, culture, and ICT skills is a prerequisite. Results from this study will be of importance for understanding how people who may not maximally benefit from eHealth services today could be targeted in the future.

(JMIR Res Protoc 2016;5(2):e79) doi:10.2196/resprot.5468

KEYWORDS

immigrants; diabetes; information-seeking behavior; inequality

Introduction

Use of eHealth as a Common Practice

In light of the rapidly increasing number of people having access to Internet and mobile-broadband subscriptions [1], eHealth has a great potential to be a platform for social innovation that mitigates social disparity. eHealth is defined as "all kinds of information and communication technology used for supporting health care and promoting a sense of well-being" [2]. Today, massive amounts of information about health care and well-being are available via the Internet, from multiple sources and in many languages. Studies have shown that using the Internet to seek information relevant to health care and wellness is a widespread practice [3-7]. In Norway, 96% of the population (between 9- and 79-years old) had access to the Internet, 98% to a mobile phone, and 80% to a smartphone in 2014 [8]. In 2015, 62% of the Norwegian population (16- to 79-years old) had sought the Internet for health-related information during the last 3 months [6]. Health-related use of the Internet was highest in the age group 25 to 34, where it reached up to 79%.

Included in eHealth is technology supporting self-care, or "what people do for themselves to establish and maintain health, prevent and deal with illness" [9]. In addition to health-related information searches, the use of information and communication technology (ICT) for the purpose of self-care includes communication with health care providers, peer-to-peer support, self-management by recording and tracking relevant data, and decision making. It is not yet so common to use ICT for these purposes as a Web-based health information search [7,10-12]. However, eHealth for self-care has been gaining increased attention from both the academic research field and consumer health market, especially for chronic diseases, such as diabetes [13-16].

Immigrants from Pakistan in the Oslo Area – Diabetes and ICT Experiences

One of the advantages of eHealth is that each user can actively choose the eHealth services that best fit their individual needs. eHealth services in the user's primary language, adapted to cultural preferences, thus appear to be helpful tools. This advantage applies in particular to ethnic minority populations, such as immigrants, to supplement other health services where language and cultural barriers can be of note. In Norway, the number of immigrants has been steadily increasing over the last 40 years. At the beginning of 2015 [17], immigrants and Norwegians born to immigrant parents comprised 15.6% of the whole population. Of those, more than one-half (8.7% of the entire population) originated from Asia, Africa, Latin America, Oceania (except Australia and New Zealand), and Europe (except the European Union) and European Economic Area. Oslo municipality has the largest proportion of immigrants (first-generation immigrants and those born to first-generation immigrant parents) in the country (32%). For example, of first-generation immigrants from Pakistan in Norway, 69.5% live in Oslo [18]. Suburbs of Oslo also have higher proportions of immigrants than the country average [18,19].

A study among four immigrant groups in the Oslo area [20] showed that Pakistanis had the highest prevalence rates of diabetes (women: 26.4%, men: 20.0%). These rates are alarmingly high and much higher than the rates of ethnic Norwegians (women: 2.7%, men: 6.4%). Most of the diabetes cases are Type 2 diabetes (T2D), where leading a healthy lifestyle, including diet and physical activity, plays an important role in self-care. For Pakistani immigrants, barriers to being physically active [21] and maintaining a healthy diet [22] are different from those of ethnic Norwegians. They have also reported experiences of problems in communication with health care providers regarding dietary advice, both due to language barriers and to cultural differences in food traditions [23]. Culturally adapted interventions to the population have been shown to have a positive effect on reducing levels of T2D risk factors [21,24,25].

To date, there is no sufficient information available about the extent to which immigrants with Pakistani background in the Oslo area are using or benefiting from eHealth resources for self-care of T2D, and what their preferences are. Knowledge is scarce regarding their access to and usage of ICT devices and the Internet in general as well. A survey of digital skills and access to ICT among five immigrant groups (Pakistani, Polish, Iraqi, Somali, and Vietnamese) in 2010 [26] showed that 74% of the respondents with a Pakistani background used a personal computer (PC), and 69% also used the Internet. Pakistanis scored lowest among the five immigrant groups surveyed regarding ICT skills. This survey also showed that among Pakistanis, being female, aged over 40, or having an education from only primary school or less were associated with significant reduction in ICT skills scores. Among Pakistani respondents, 56% had an education from primary school or less. Also, the survey report identified that the barriers to strengthening ICT skills were mostly related to knowledge about ICT and lack of available courses, while access to ICT devices or the Internet was little mentioned by the survey participants.

These results suggest that many individuals among immigrants with a Pakistani background may not have been able to benefit from using eHealth services, despite having ICT devices and access to the Internet. Because of a high proportion of the Pakistani population with low educational level [3,19], information written in Urdu may also be inaccessible or difficult to read. We speculate that even those with sufficient ICT skills may have experienced that eHealth services fitting their context are limited compared with those for the ethnic Norwegian population living in the same area. Providing eHealth services that meet the ability and needs of this population, combined with specific training in ICT use, may trigger the motivation for using ICT in general, as well as for health purposes. As Townsend et al [27] argue, "access alone, if not accompanied by services, support, and resources designed to reach and appeal to diverse populations, will not automatically improve an individual's eHealth use, or their health outcomes" and "issues of equity need to be considered regarding disparity in access to skills, education, and opportunities to develop them."

The existing knowledge so far [18,26,28] implies that the Pakistani immigrant population is highly heterogeneous when it comes to, among many other factors, ICT skills, literacy levels

in their native language, attainment of Norwegian language, attachment to the culture of origin, and acculturation to the environment of Norway. We need to identify subgroups of this demographic group that would benefit most from eHealth use for self-care of T2D and support.

Aim of the Study and Research Questions

Today there is a digital divide that goes beyond access to ICT resources among Pakistani immigrants in Norway. This gap needs to be addressed to realize the potential in eHealth to mitigate social disparity.

This study aims to provide new insights into the use of and attitudes toward relevant eHealth services to self-care of T2D in this group. Types of eHealth use studied are information searches, communication using ICT, and use of ICT for self-care or decision making. Information searches include using search engines by entering search terms, visiting specific websites to read relevant information, and use of look-up applications. Communication using ICT includes closed communication such as voice or video conversation as well as text messaging, use of social network services, and online consultation to peers or health care professionals. ICT for self-care or decision making includes applications and similar to either record and track data of oneself, such as diet, physical activity, or blood glucose level, or assess user's health condition or risk based on input data.

The following research questions will be addressed:

1. What are the traits of informants concerning the use of and attitudes toward eHealth for their self-care of T2D?
2. How do informants describe barriers and facilitators of using eHealth services for their self-care of T2D in general?
3. What are their experiences of eHealth services for their self-care of T2D concerning their language and culture?

The survey will help us to break down the problem areas and provide a necessary overview of the status quo in eHealth use for self-care of T2D and attitudes among the target population. Once complete, the study will contribute to defining target users, their requirements and experiences with eHealth services for self-care of T2D.

Theoretical Framework

It is important to use theoretical frameworks when designing studies on predicting factors of technology use [29]. We, therefore, based our work on well-established theoretical frameworks relevant to ICT use and health behaviors. Many recent studies [30-36] have used technology acceptance model (TAM) [37] and its derivatives [38,39] as a basis to analyze the general public's or the users' acceptance of eHealth. TAM has been very well documented and widely used to analyze users' acceptance of ICT-based tools. TAM predicts users' acceptance of technology by behavioral intention (BI) to use the technology. BI is explained by users' perceived ease of use (PEOU) and perceived usefulness (PU). PU is partly explained by PEOU. The studies using TAM to analyze acceptance of eHealth typically attempt to extend TAM to find out antecedent factors of BI, PEOU, and PU or combine with other models.

Tested antecedent factors on the user side are mainly categorized into personal factors, organizational factors, and social factors. Personal factors include factors related to being a patient (or ones relevant to the purpose of using eHealth), to being an ICT user, and factors potentially related to both issues such as sociodemographic variables. Organizational factors include users' relationship with health care personnel or institute, users' satisfaction with them and available support in using technology. Social factors mostly refer to extrinsic motivation by others.

Given that use of eHealth has the potential to enhance or trigger positive health behaviors, if not improve health condition or prevent diseases by itself, it is reasonable to assess eHealth use as a component of relevant health behavior theories (HBTs). A well-known model of individual health behavior is the Health Belief Model (HBM) [40]. In HBM, individual behaviors are predicted by individual beliefs and triggered by cues to those behaviors. For example, it is reasonable to see searching the Internet for health information as a health behavior in HBM because it increases health knowledge. An integrated model of TAM and HBM has been tested and proven to be able to predict Internet use for health purpose by working women living in an urban area of Malaysia [35].

In this study, we do not intend to suggest a new model of eHealth acceptance or to test the applicability of existing models to our settings. Instead, we use relevant established theories as a framework to investigate eHealth use and to identify users' background traits depending on eHealth use and attitudes to it. Therefore, we implemented questions that supplement measures in the theoretical frameworks to explore areas that those frameworks do not cover. Such questions are especially concentrated on cultural and language oriented traits of the target population.

Methods

Sample and Recruitment

We are particularly interested in how language barriers and cultural background of the target population are associated with their eHealth use for self-care of T2D. Due to this focus, we employ purposive sampling and use culturally adopted recruiting methods to assure inclusion of otherwise "hard-to-reach" informants. The following inclusion criteria were set: (1) immigrated from Pakistan after the age of 18 and living in the Oslo area, (2) speak Urdu (the official language of Pakistan) as the primary language in their private life, (3) are aged between 25 and 59, (4) have access to or interest in ICT-tools (PC, tablet, or smartphone), connected to the Internet in daily life, and (5) are motivated for and capable of activities for self-management or prevention of T2D.

Before finalizing the inclusion criteria and the questionnaire to use, we carried out a pilot testing with 10 informants who satisfied all the inclusion criteria above but "after the age of 18" in the first criterion. The pilot testing included two informants who immigrated to Norway at an early age. Although they claimed that their primary language was Urdu, they had received primary educations in Norway and did not have any difficulties in using ICT and eHealth in the Norwegian language. Given the fact that many Pakistani people immigrate by marriage to Pakistani-Norwegians [18], we decided to add age at the time

of immigration to 18 and above. The lower age limit in the third criterion aligns inclusion criteria employed in previous intervention studies for prevention of T2D among the Norwegian-Pakistani population. [21,22,24,25].

The upper age limit and the last two inclusion criteria are set to highlight issues of language barriers and cultural differences beyond the access to ICT by eliminating common issues between the target population and the ethnic Norwegian population. Figures from 2010 show a significant drop in the percentage of the Norwegian population over the age of 55 that use the Internet to seek health-related information [6]. The proportion of the population using the Internet for such purpose among those aged between 55 and 64 increased by 20 percentage points in 2013, so upper age limit of 59 in 2015 and 2016 is reasonable.

Regarding the last criterion, activities in concern include having a healthy diet and being physically active. We employ a question asking about informant's intention to change lifestyle for self-care of T2D used in a relevant study [25]. The question is related to trans theoretical model [41]. We include those who consider changing behavior or already have done so as informants. Although we use this question as an inclusion criterion, an answer to it corresponds to a stage of lifestyle change and is an important personal factor related to his/her health. Therefore, we will include a given answer to this question in the analysis of results.

For recruitment, we follow multirecruitment strategies recommended from the experience of difficulties in recruiting South-Asian people [42]. Intervention studies among the Norwegian-Pakistani population also used these strategies [21,22,24,25]. Two research assistants who have an established connection to the Norwegian-Pakistani community in the Oslo area will be in charge of recruitment. Due to expected low literacy level, recruitment is done verbally, by phone calls and house visits in areas with high proportions of Pakistani immigrants (mainly southeast of the Oslo area [18]). A written invitation is used additionally. The recruitment strategy includes snowball sampling [43] where people who are invited to the study also contribute to disseminate the study through their networks.

We aim to recruit 200 informants in total for the survey. We consider this sample size is reasonable given the project budget and the following reasons. Sample sizes varied a lot in relevant studies that quantitatively assessed acceptance of an eHealth service using theoretical frameworks: 101 [34], 132 [32], 163 [30], 250 [31], 293 [35], and 1071 [33]. Besides two studies [30,34] where informants were selected among all the individuals having access to the eHealth service of their interest, justification of sample size was not shown. Sampling methods also varied among these studies. A study of users' perception of social media as a part of chronic disease management also found the situation similar and set the aim of its sample size as 200 to 250 [44]. The informants will receive compensation of a gift card with a value of 500 Norwegian Krone (approximately US$60) at the completion of the survey.

Data Collection – Survey by Questionnaire-Based Interview

We collect data in the form of questionnaire-based structured individual interviews. One research assistant asks questions orally, and the other assistant fills out the orally given answers on an answer sheet. Answers to open questions are written down in English by one assistant, and the other assistant assures the expression in English is reasonable.

The primary reason for using individual interview was that low-literacy and -education level is prevalent among the target population. This method has the potential to increase response rate as well as provides possibilities to explain questions and alternative answers for closed questions to assure the quality of data. To keep the condition of data collection consistent, we decided to use only the form of individual interview for all the informants regardless of their literacy levels.

Survey Questions

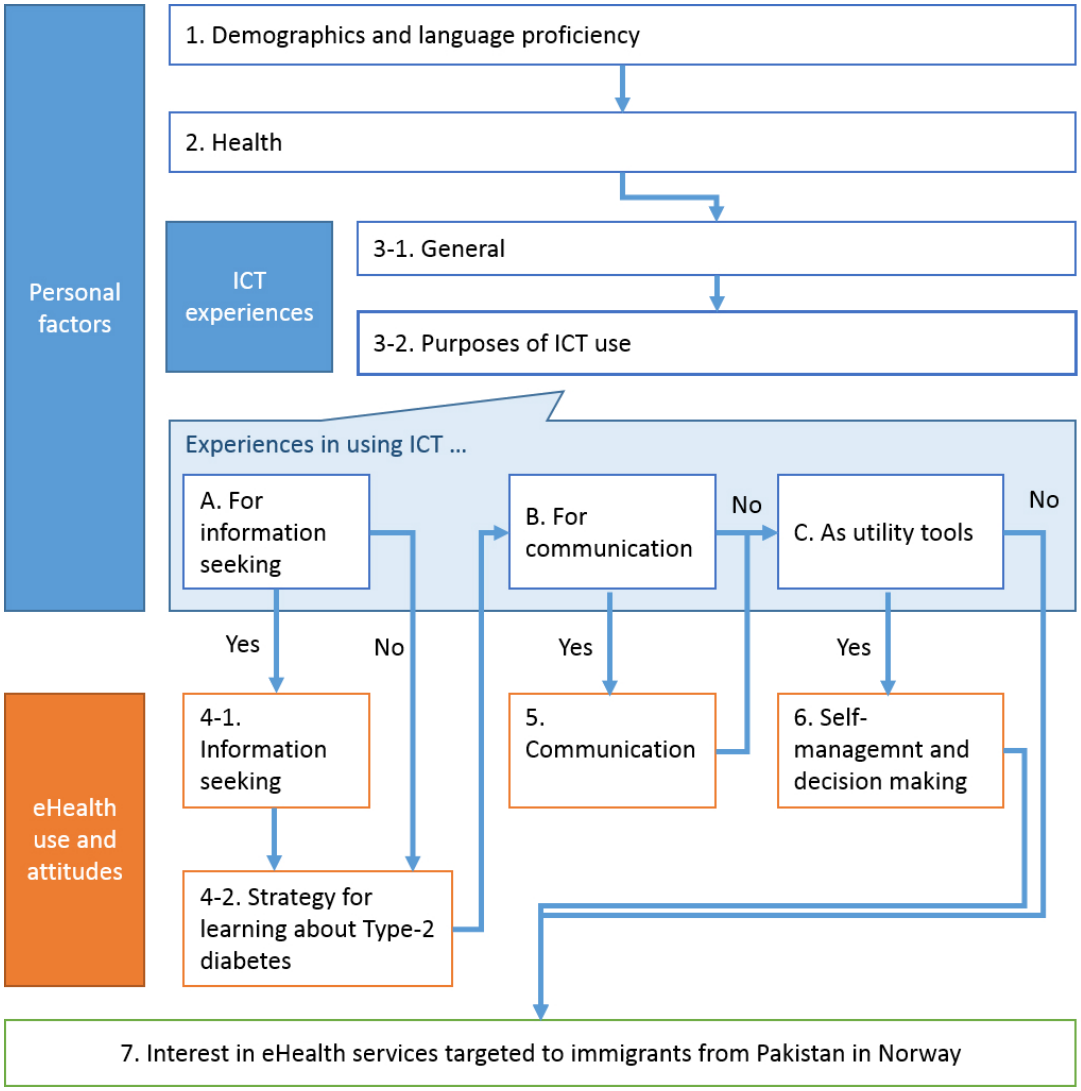
Figure 1 shows the structure of the designed survey questionnaire. They are divided into three broad categories: personal factors (sections 1-3 in Figure 1), experiences of using eHealth services and attitudes toward them (sections 4-6 in Figure 1), and interests in eHealth services targeted to immigrants from Pakistan in Norway (section 7 in Figure 1).

Questions were first formulated in English by the research members. Our approach to developing the questions in the Urdu language was concept driven [45]. We had a workshop where research members and the research assistants who are fluent in both English and Urdu confirmed concepts of questions. After the workshop, the two assistants independently developed questions in Urdu. They confirmed consistency of expression of questions in Urdu language or discussed until they reach consistent results.

In the pilot testing, we tested the questions expressed in the Urdu language and the agreed procedure of the survey. We iteratively improved the questions and the question structure. By the sixth informant in the pilot testing, the questions and the question structure were finalized.

Multimedia Appendix 1 shows the entire set of the survey questions. The final version of the questionnaire consists of seven sections and 102 main questions in total. The number of questions an informant will answer is fewer due to the logic tree structure. All the questions asked by Likert-scale employed a 5-point scale. This decision reflects the feedback from the pilot study and Dawes' study [46] showing that there is very little difference in data characteristics between 7- and 5-point Likert scales.

Figure 1. Structure of the questions to use in the survey.



Personal Factors

Questions under this category are divided into three sections corresponding to three subcategories: demographics and language proficiency (section 1), health (section 2), and ICT experiences (section 3).

The “demographics and language proficiency” subcategory includes an educational level in both Pakistan and Norway, the period of being in Norway and their confidence in writing and reading in Urdu script, Roman Urdu, and Norwegian. Roman Urdu is the Urdu language written in Roman letters. We included Roman Urdu because the pilot study revealed that Roman Urdu is often used among the target population, especially for text communication using ICT devices.

The “health” subcategory includes measurement items for theoretical constructs within relevant HBTs. We considered various validated measures used in relevant studies [24,30,33-35,38,47-49] and agreed on employing measures of theoretical constructs that were shown to predict BI of the studied eHealth service directly or indirectly. Included measures are; self-efficacy (adopted from [49]), perceived health risk, and health consciousness (adopted from [35]), health anxiety and optimism (adopted from [33]), and health knowledge scale (adopted from [30]). For knowledge about risk factors, we based our questions on an intervention study to the Pakistani-immigrant women at a high risk of T2D in the Oslo area [24]. Besides them, we have employed measures concerning their relationship with health care providers from [50] as organizational factor explained in the “theoretical framework” section above.

The “ICT experiences” subcategory is further divided into two parts. The first part, subsection 3-1, consists of questions asking about access to ICT in general including indirect access. Here, indirect access means that another person operates ICT devices on behalf of an informant. The second part, subsection 3-2, consists of questions asking informant’s experience in using ICT for different types of purpose that correspond to the types of eHealth services in this study. Therefore, these questions serve as a filter to ask further questions about the use of eHealth service.

eHealth Use and Attitudes

This category is divided into three sections corresponding to the three types of eHealth services the study is addressing (information searches (section 4), communication using ICT (section 5), and use of ICT for self-management or decision

making (section 6)). All the questions asking about experiences of using ICT include subquestions asking which languages informants use for each purpose. The informants in the pilot testing used a variety of methods for both text typing/input and reading. Therefore, we implemented subquestions asking about methods to use for each purpose of ICT use of our interest. To those who have experiences of using the specific types of eHealth services, we prepared an open question to ask about the experiences in detail. For each open question, we prepared a series of keywords and phrases as hints to make it easier for informants to remember the experiences. The key words and phrases include among others content fitness to informants' culture, lifestyle, language, gender, and age, concern about information security and privacy, and trustworthiness of services. We employed this way to explore any relevant issues to their eHealth use originating from their personal background rather than increasing the number of questions to ask informants about potentially irrelevant issues. During the pilot study, we identified several cases that theoretical constructs within TAM and its derivatives were not applicable to explain not using eHealth services. Thus, we also included questions asking reasons for not using each type of eHealth services as well as their attitudes toward using the eHealth services.

For section 4, the subcategory of information searches, we added a group of questions (subsection 4-2) that ask about informants' strategy for learning about T2D regardless of using ICT. These questions will be asked regardless of the experience of ICT use for any information searches in general.

Interest in eHealth Services Targeted to Immigrants from Pakistan in Norway

Section 7 includes measurement items for theoretical constructs within TAM and its derivatives. These measure are BI, PEOU (adopted from [33]), PU (adopted from PU2, PU3, and PU4 in [38]), subjective norms (adopted from SN1 in [38]) and intrinsic motivation (adopted from [33]), and image (adopted from IMG2 in [38]). The technologies in concern for these measures are the three types of currently available eHealth services for self-care of T2D. Due to the difficulty in differentiating expressions in Urdu language and the reported frustration of being asked very similar questions more than once in the pilot testing, we decided to ask one question for a measure of BI, subjective norms, and image. While we employed open questions to ask the reasons for no experience of using eHealth services in the previous sections, we implemented an open question to ask what would make them interested in using each type of eHealth service in a constructive manner. Also, we designed two questions that ask level of their interest in eHealth services designed for the target population in this study and in being involved in the design process of such services. Finally, we set questions asking their awareness of the Norwegian Diabetes association's services provided in the Urdu language including eHealth services and the level of their interest.

Analysis

The data analysis process will start by examining the validity of measurement models and measurements by using confirmatory factor analysis. Due to a potential for high heterogeneity of given answers and the inclusion of originally formulated questions, we will primarily employ a qualitative approach in data analysis and corroborate with results of quantitative data analysis. We will use descriptive statistics first to find out central tendencies. We will carefully examine the distribution of data for applicability of parametric analysis. If a parametric analysis is not suitable, we will use a nonparametric analysis. Because it is very likely that informants' backgrounds vary a lot, we expect that answers given to open questions will provide hints of unforeseen factors that may partly explain theoretical constructs. Thus, we will follow the framework of thematic analysis proposed by Braun and Clarke [51] to identify repeatedly emerging themes at the semantic level.

Ethical Approval

This study collects sensitive data such as diagnosis of T2D and educational levels in Pakistan and Norway. Even though the study does not collect any directly identifiable personal data, a relatively small sample size in a limited area of Norway and the inclusion criteria may compromise their anonymity. Ranges rather than exact values were used to record information regarding the informants' age and the period of being in Norway.

At the recruitment, the research assistants explain informants the purpose of this study, what types of questions are included in the survey, that the data is handled anonymously and kept in secured storage, who will attend the interview, and who will have access to the anonymized data. Informants will receive this information in a written format as well at the beginning of an interview. Informed consent is given verbally, which is allowed by the institutional review board, the Norwegian Social Science Data Services (NSD) [52]. The project protocol including the ethics of sampling and recruitment procedures was approved by NSD in June 2015 (project number: 43549).

Results

This paper is a protocol paper and data collection from the main survey is still in progress at the time of submission. The main survey started in September 2015. By the end of November, we collected responses from 103 informants. The expected time to complete data collection is the end of February 2016.

Discussion

Challenges to Include Immigrant Populations

This paper presents the protocol of a survey on eHealth use concerning T2D among first-generation immigrants from Pakistan in the Oslo area. Our focus is on their eHealth experience in relevance with language barriers and cultural differences. Although eHealth has a great potential for immigrant populations for easy access to culturally sensitive health information, knowledge on status-quo of eHealth use in immigrant populations is scarce [7,12,53-56]. Also, such knowledge cannot be generalized because of the diversity of immigrants, including the combination of their country of origin and the country they immigrated to. Failure in involving immigrant populations in research studies is not limited to surveys, which often requires literacy in the language of the survey, but is also common in clinical intervention studies in general unless they specifically target such populations [42,57].

Ensuring inclusion of immigrant populations requires culturally sensitive methods regarding recruitment and data collection. We have adopted such a strategy, aiming especially to include those who may be excluded or may feel reluctant to participate if we took other methods, such as a Web- or paper-based survey with probability sampling and invitation by letter only [58,59]. However, our chosen methods have the challenges and limitations.

First of all, the methods for recruiting and data collection are time-consuming and resource-demanding. Due to the language, the methods rely on the Urdu-speaking research assistants who recruit informants and collect data. One interview takes 1 to 1.5 hours, so the number of interviews per day is limited.

Secondly, informants' background variables, such as gender and age range, potentially have a skewed distribution. This challenge is not only related to chosen methods, but to general challenges in the group and other. From very early phases of the study design, we were aware of a potential challenge for recruiting male participants. Our research assistants have relevant experiences from an intervention study to prevent T2D among women with Pakistani background in the Oslo area (InnvaDiab study) [25,60]. Thus, their connection to the female society is strong but they have a weak connection to male society. Further, we were informed of a general tendency that Pakistani men do not feel comfortable being asked personal questions and talking about their health. A large proportion of Pakistani men are engaged in shift-time work in transportation service [18], work extraordinarily many hours, and have little flexibility. We will try to overcome such challenges by offering interviews at various times of the day as well as on weekends. A higher response rate by female than male informants is observed in other studies with similar context as well [12,30,44,61]. This gender unbalance may be an interesting finding by itself for further discussion, especially in the light of reported lower education, lower employment rates, poorer integration, and more health concerns among women than men among Pakistani immigrants [28]. Higher participation by women than men in our survey may be a consequence of inclusion criteria, especially regarding interest in prevention and self-care of T2D. Therefore, while we will do our best to recruit informants with balanced gender and age distribution, we prioritize reaching to the aimed sample size. Our study will shed light on challenges with including both genders from the Pakistani immigrant population, which can be useful for future studies.

Lastly, we need to note a potential risk of selection bias, where informants' personal factors may differ from the represented population. Because we do not have our sample ready yet, we refer to a reliability of the sample in the InnvaDiab study [25,60] recruited in the same way to justify our methods. In the InnvaDiab study, the sample was comparable to samples in other studies among Pakistanis in Oslo using other methods [62], and to data from Statistics Norway [28,63], concerning weight, education level, the number of children, and length of stay in Norway. With the mentioned challenges and limitations in mind, we aim to reach a representable sample of the target population and provide an adequate overview of their eHealth use.

Conclusions

For eHealth to be truly a social innovation, it should be readily accessible and useful regardless of users' ethnicity, country of residence, or primary language. This is in line with a claim by World Health Organization [64]. Van Gemert-Pijnen and colleagues [2] propose a holistic framework for a development of eHealth technologies, the Center for eHealth Research and Disease Management roadmap. The roadmap highlights a contextual inquiry as the first activity in a process of gathering information about intended users and the environment where the technology will be implemented. Although such a contextual inquiry presumes who the "intended users" are, a demographic group of "Pakistani immigrants in the Oslo area" is neither sufficient nor appropriate as a definition of the "intended users" to address the issue of digital divide. Results of this study will identify the intended users by highlighting the importance of understanding how people who may not benefit from eHealth could be targeted in the future. The results will then further inform the design of a contextual inquiry study that will be used to design, develop, and disseminate eHealth services for self-care of T2D adapted for the intended users.

The study will also be of importance to research and policy makers that aim to mitigate the social disparity in health among immigrants. In these regards, the study design described in detail in this article will be valuable in providing a basis for designing a survey of eHealth use by immigrants in other contexts.

Acknowledgments

The Department of Computer Science, the Faculty of Technology, Design and Art, Oslo and Akershus University College of Applied Sciences funded this research in December 2014. The authors are grateful for the support given in the phase of writing an internal funding application by professor Else-Lydia Toverud, School of Pharmacy, the Faculty of Mathematics and Natural Sciences, University of Oslo. We also thank Monica Morris and Anica Munir for serving as research assistants, and Tulpesh Patel at the Department of Computer Science, the Faculty of Technology, Design and Art, Oslo and Akershus University College of Applied Sciences for critical comments and proofreading. Last but not least, the authors thank the reviewers for their critical comments.

Authors' Contributions

NT conceived this study. NT drafted the study design and the first version of the manuscript. All the other three authors contributed to further development of the study design and to finalizing the manuscript by giving comments to all versions of the manuscript draft. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Survey questionnaire.

[PDF File (Adobe PDF File), 739KB - resprot_v5i2e79_app1.pdf]

References

1. International Telecommunication Union. Geneva, Switzerland; 2015. The World in 2015: ICT Facts and Figures URL: http://www.itu.int/en/ITU-D/Statistics/Documents/facts/ICTFactsFigures2015.pdf [accessed 2015-12-08] [WebCite Cache ID 6dci9EH55]
2. van Gemert-Pijnen JEWC, Nijland N, van LM, Ossebaard HC, Kelders SM, Eysenbach G, et al. A holistic framework to improve the uptake and impact of eHealth technologies. J Med Internet Res 2011;13:e111 [FREE Full text] [doi: 10.2196/jmir.1672] [Medline: 22155738]
3. Fox S. Pew Research Center's Internet & American Life Project. 2011 May 12. The Social Life of Health Information, 2011 URL: http://www.pewinternet.org/files/old-media//Files/Reports/2011/PIP_Social_Life_of_Health_Info.pdf [accessed 2015-12-09] [WebCite Cache ID 6de8jMlhf]
4. Statistics Canada. 2010. Canadian Internet use survey, Internet use at home, by Internet activity, urban or rural distribution URL: http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/comm29a-eng.htm [accessed 2015-12-09] [WebCite Cache ID 6deA0NW2p]
5. Andreassen HK, Bujnowska-Fedak MM, Chronaki CE, Dumitru RC, Pudule I, Santana S, et al. European citizens' use of E-health services: a study of seven countries. BMC Public Health 2007:53 [FREE Full text] [doi: 10.1186/1471-2458-7-53] [Medline: 17425798]
6. Statistics Norway. 2015. ICT Usage in Households - Table: 06998 Activities Performed Over Internet, the Last Three Months, by Sex and Age (per cent) URL: https://www.ssb.no/statistikkbanken/selectvarval/Define.asp?subjectcode=&ProductId =&MainTable=AktivInternet&nvl=&PLanguage=1&nyTmpVar=true& CMSSubjectArea=teknologi-og-innovasjon&KortNavnWeb=ikthus&StatVariant=&checked=true [accessed 2016-04-15] [WebCite Cache ID 6gmtG5fnt]
7. Kontos E, Blake KD, Chou WS, Prestin A. Predictors of eHealth usage: insights on the digital divide from the Health Information National Trends Survey 2012. J Med Internet Res 2014;16:e172 [FREE Full text] [doi: 10.2196/jmir.3117] [Medline: 25048379]
8. Vaage OF. Statistics Norway. 2015. Norwegian Media Barometer 2014 URL: http://www.ssb.no/forside/_attachment/223839?_ts=14d09e6cbf0 [accessed 2015-12-09] [WebCite Cache ID 6deCW7Mt8]
9. World Health Organization. The Hauge, the Netherlands; 1998. The Role of the Pharmacist in Self-Care and Self-Medication URL: http://apps.who.int/medicinedocs/pdf/whozip32e/whozip32e.pdf [accessed 2015-12-09] [WebCite Cache ID 6deDukuQW]
10. Wangberg SC, Sørensen T, Andreassen HK. Using the internet to support exercise and diet: a Stratified Norwegian Survey. Med 2 0 2015;4(2):e3 [FREE Full text] [doi: 10.2196/med20.4116] [Medline: 26310277]
11. Krebs P, Duncan DT. Health app use among US mobile phone owners: a national survey. JMIR Mhealth Uhealth 2015;3:e101 [FREE Full text] [doi: 10.2196/mhealth.4924] [Medline: 26537656]
12. Bender MS, Choi J, Arai S, Paul SM, Gonzalez P, Fukuoka Y. Digital technology ownership, usage, and factors predicting downloading health apps among caucasian, filipino, korean, and latino americans: the digital link to health survey. JMIR Mhealth Uhealth 2014;2:e43 [FREE Full text] [doi: 10.2196/mhealth.3710] [Medline: 25339246]
13. Fiordelli M, Diviani N, Schulz PJ. Mapping mHealth research: a decade of evolution. J Med Internet Res 2013;15:e95 [FREE Full text] [doi: 10.2196/jmir.2430] [Medline: 23697600]
14. Wildevuur SE, Simonse LWL. Information and communication technology-enabled person-centered care for the "big five" chronic conditions: scoping review. J Med Internet Res 2015;17:e77 [FREE Full text] [doi: 10.2196/jmir.3687] [Medline: 25831199]
15. Martínez-Pérez B, de la Torre-Díez I, López-Coronado M. Mobile health applications for the most prevalent conditions by the World Health Organization: review and analysis. J Med Internet Res 2013;15:e120 [FREE Full text] [doi: 10.2196/jmir.2600] [Medline: 23770578]

16. Arnhold M, Quade M, Kirch W. Mobile applications for diabetics: a systematic review and expert-based usability evaluation considering the special requirements of diabetes patients age 50 years or older. J Med Internet Res 2014;16:e104 [FREE Full text] [doi: 10.2196/jmir.2968] [Medline: 24718852]
17. Statistics Norway. 2015. Immigrants and Norwegian-Born to Immigrant Parents, 1 January 2015 URL: https://www.ssb.no/en/befolkning/statistikker/innvbef/aar/2015-03-04#content [accessed 2016-01-29] [WebCite Cache ID 6gmxrFqQo]
18. Pettersen SV. Statistics Norway. 2009. Innvandrere i norske kommuner. Demografi, levekår og deltakelse i arbeidsstyrken URL: https://www.ssb.no/a/publikasjoner/pdf/rapp_200936/rapp_200936.pdf [accessed 2015-12-18] [WebCite Cache ID 6drY1DDIO]
19. Statistics Norway. 2015. Immigrants 16 Years and Above, by Level of Education, Gender and Age URL: https://www.ssb.no/225177/immigrants-16-years-and-above-by-level-of-education-gender-and-age [accessed 2016-01-29] [WebCite Cache ID 6etrL6Cap]
20. Jenum AK, Diep LM, Holmboe-Ottesen G, Holme IMK, Kumar BN, Birkeland KI. Diabetes susceptibility in ethnic minority groups from Turkey, Vietnam, Sri Lanka and Pakistan compared with Norwegians - the association with adiposity is strongest for ethnic minority women. BMC Public Health 2012;12:150 [FREE Full text] [doi: 10.1186/1471-2458-12-150] [Medline: 22380873]
21. Andersen E, Høstmark AT, Holme I, Anderssen SA. Intervention effects on physical activity and insulin levels in men of Pakistani origin living in Oslo: a randomised controlled trial. J Immigr Minor Health 2013;15:101-110 [FREE Full text] [doi: 10.1007/s10903-012-9686-3] [Medline: 22828963]
22. Kjøllesdal MKR, Telle HV, Bjørge B, Holmboe-Ottesen G, Wandel M. Barriers to healthy eating among Norwegian-Pakistani women participating in a culturally adapted intervention. Scand J Public Health 2010;38(5 suppl):52-59. [doi: 10.1177/1403494810378923] [Medline: 21062839]
23. Fagerli RA, Lien ME, Wandel M. Experience of dietary advice among Pakistani-born persons with type 2 diabetes in Oslo. Appetite 2005;45:295-304. [doi: 10.1016/j.appet.2005.07.003] [Medline: 16129511]
24. Kjøllesdal MKR, Hjellset VT, Bjørge B, Holmboe-Ottesen G, Wandel M. Perceptions of risk factors for diabetes among Norwegian-Pakistani women participating in a culturally adapted intervention. Ethn Health 2011;16:279-297. [doi: 10.1080/13557858.2011.573537] [Medline: 21660786]
25. Helland-Kigen KM, Kjøllesdal MKR, Hjellset VT, Bjørge B, Holmboe-Ottesen G, Wandel M. Maintenance of changes in food intake and motivation for healthy eating among Norwegian-Pakistani women participating in a culturally adapted intervention. Public Health Nutr 2013;16:113-122. [doi: 10.1017/S1368980012002790] [Medline: 22781507]
26. Guthu L, Holm S. VOX (Norwegian Agency for Lifelong Learning). 2010. Innvandrere på nett URL: http://www.vox.no/contentassets/eab2d86f40aa4f118e3b8d6b59565208/innvandrere_pa_nett2.pdf [accessed 2015-12-11] [WebCite Cache ID 6dgtQghtK]
27. Townsend A, Adam P, Li LC, McDonald M, Backman CL. Exploring eHealth Ethics and Multi-Morbidity: Protocol for an Interview and Focus Group Study of Patient and Health Care Provider Views and Experiences of Using Digital Media for Health Purposes. JMIR Res Protoc 2013;2:e38 [FREE Full text] [doi: 10.2196/resprot.2732] [Medline: 24135260]
28. Henriksen K. Statistics Norway. 2010. Levekår og kjønnsforskjeller blant innvandrere fra ti land URL: https://www.ssb.no/a/publikasjoner/pdf/rapp_201006/rapp_201006.pdf [accessed 2016-02-03] [WebCite Cache ID 6f17PKHC0]
29. Or CKL, Karsh BT. A systematic review of patient acceptance of consumer health information technology. J Am Med Inform Assoc 2009;16:550-560 [FREE Full text] [doi: 10.1197/jamia.M2888] [Medline: 19390112]
30. Wilson EV, Lankton NK. Modeling patients' acceptance of provider-delivered e-health. J Am Med Inform Assoc 2004;11:241-248 [FREE Full text] [doi: 10.1197/jamia.M1475] [Medline: 15064290]
31. Kim D, Chang H. Key functional characteristics in designing and operating health information websites for user satisfaction: an application of the extended technology acceptance model. Int J Med Inform 2007;76:790-800. [doi: 10.1016/j.ijmedinf.2006.09.001] [Medline: 17049917]
32. Lanseng EJ, Andreassen TW. Electronic healthcare: a study of people's readiness and attitude toward performing self-diagnosis. Int J of Service Industry Mgmt 2007;18:394-417. [doi: 10.1108/09564230710778155]
33. Svendsen G, Soholt Y, Munch-Ellingsen A, Gammon D, Schurmann A. The Importance of Being Useful and Fun: Factors Influencing Intention to Use a Mobile System Motivating for Physical Activity. USA: IEEE Computer Society; 2009 Presented at: HICSS '09. 42nd Hawaii International Conference on System Sciences; 5-8 Jan. 2009; Big Island, HI p. 1-10 URL: http://doi.ieeecomputersociety.org/10.1109/HICSS.2009.955 [doi: 10.1109/HICSS.2009.955]
34. Or CKL, Karsh BT, Severtson DJ, Burke LJ, Brown RL, Brennan PF. Factors affecting home care patients' acceptance of a web-based interactive self-management technology. J Am Med Inform Assoc 2011;18:51-59 [FREE Full text] [doi: 10.1136/jamia.2010.007336] [Medline: 21131605]
35. Ahadzadeh AS, Pahlevan SS, Ong FS, Khong KW. Integrating health belief model and technology acceptance model: an investigation of health-related internet use. J Med Internet Res 2015;17:e45 [FREE Full text] [doi: 10.2196/jmir.3564] [Medline: 25700481]
36. Mohamed AHHM, Tawfik H, Norton L, Al-Jumeily D. e-HTAM: A Technology Acceptance Model for Electronic Health. 2011 Presented at: Innovations in Information Technology (IIT), 2011 International Conference on; 25-27 April 2011; Abu Dhabi p. 134-138. [doi: 10.1109/INNOVATIONS.2011.5893804]

37. Davis FD. Perceived usefulness, perceived ease of use, and user acceptance of information technology. MIS Quarterly 1989;13:319. [doi: 10.2307/249008]
38. Venkatesh V, Bala H. Technology Acceptance Model 3 and a research agenda on interventions. Decision Sciences 2008;39:273-315. [doi: 10.1111/j.1540-5915.2008.00192.x]
39. Venkatesh V, Morris MG, Davis GB, Davis FD. User acceptance of information technology: toward a unified view. MIS Quarterly 2003;27:425-478.
40. Champion VL, Skinner CS. The health belief model. In: Glanz K, Rimer BK, Viswanath K, editors. Health Behavior and Health Education: Theory, Research, and Practice. San Francisco, CA: Jossey-Bass; 2008:45-65.
41. Prochaska JO, Redding CA, Evers KE. The transtheoretical model and stages of change. In: Glanz K, Rimer BK, Viswanath K, editors. Health Behavior and Health Education: Theory, Research, and Practice. San Francisco, CA: Jossey-Bass; 2008:97-121.
42. Hussain-Gambles M, Leese B, Atkin K, Brown J, Mason S, Tovey P. Involving South Asian patients in clinical trials. Health Technol Assess 2004;8:1-109 [FREE Full text] [Medline: 15488164]
43. Lazar D, Feng D, Hochheiser D, Lazar J, Feng J, Hochheiser H. Research methods in human-computer interaction. West Sussex: John Wiley & Sons; 2010.
44. Merolli M, Sanchez FJM, Gray K. Social Media and Online Survey: Tools for Knowledge Management in Health Research. Darlinghurst, Australia: Australian Computer Society, Inc; 2014 Presented at: the Seventh Australasian Workshop on Health Informatics and Knowledge Management; 20 - 23 January 2014; Auckland, New Zealand p. 21-29.
45. Erkut S, Alarcón O, García CC, Tropp LR, Vázquez García HA. The dual-focus approach to creating bilingual measures. J Cross Cult Psychol 1999;30:206-218 [FREE Full text] [doi: 10.1177/0022022199030002004] [Medline: 21552397]
46. Dawes JG. Do data characteristics change according to the number of scale points used? An experiment using 5 point, 7 point and 10 point scales. International Journal of Market Research 2008;50:61-77.
47. Snell WE, Johnson G. The multidimensional health questionnaire. Am J Health Behav 1997;21:33-42.
48. National Cancer Institute. 2014. Health Information National Trends Survey, Survey Instruments URL: http://hints.cancer.gov/instrument.aspx [accessed 2016-04-15] [WebCite Cache ID 6gn8mYUJa]
49. Deci EL, Koestner R, Ryan RM. A meta-analytic review of experiments examining the effects of extrinsic rewards on intrinsic motivation. Psychol Bull 1999;125:627-68; discussion 692. [Medline: 10589297]
50. National Cancer Institute. 2013. Health Information National Trends Survey (HINTS 4), Cycle 3, Next-Birthday, Full-Contents, English version URL: http://hints.cancer.gov/docs/Instruments/HINTS_4_Cycle_3_English_Annotated_508c_3_21_2014.pdf [accessed 2015-11-30] [WebCite Cache ID 6dQD2Yr0x]
51. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology 2006 Jan;3:77-101. [doi: 10.1191/1478088706qp063oa]
52. Norwegian Social Science Data Services. Participant Observation - Anthropological Research URL: http://www.nsd.uib.no/personvern/en/Research_Topics/Participant_Observation.html [accessed 2016-04-15] [WebCite Cache ID 6gn9KZoHe]
53. Vehawn J, Richards R, West JH, Cougar HP, Crookston BT, Neiger BL. Identifying barriers preventing Latina women from accessing WIC online health information. J Immigr Minor Health 2014;16:699-705. [doi: 10.1007/s10903-013-9801-0] [Medline: 23443981]
54. Wallace L, Lilley L, Lodrigues W, Dreadin-Pulliam J, Xie X, Mathur S, et al. Analysis of internet usage among cancer patients in a county hospital setting: a quality improvement initiative. JMIR Res Protoc 2014;3:e26 [FREE Full text] [doi: 10.2196/resprot.2806] [Medline: 24824330]
55. Zeissig SR, Singer S, Koch L, Zeeb H, Merbach M, Bertram H, et al. Utilisation of psychosocial and informational services in immigrant and non-immigrant German cancer survivors. Psychooncology 2015;24:919-925. [doi: 10.1002/pon.3742] [Medline: 25529132]
56. Wang W, Yu N. Coping with a new health culture: acculturation and online health information seeking among Chinese immigrants in the United States. J Immigr Minor Health 2015;17:1427-1435. [doi: 10.1007/s10903-014-0106-8] [Medline: 25228489]
57. Bonevski B, Randell M, Paul C, Chapman K, Twyman L, Bryant J, et al. Reaching the hard-to-reach: a systematic review of strategies for improving health and medical research with socially disadvantaged groups. BMC Med Res Methodol 2014;14:42 [FREE Full text] [doi: 10.1186/1471-2288-14-42] [Medline: 24669751]
58. Søgaard AJ, Selmer R, Bjertness E, Thelle D. The Oslo Health Study: the impact of self-selection in a large, population-based survey. Int J Equity Health 2004;3:3 [FREE Full text] [doi: 10.1186/1475-9276-3-3] [Medline: 15128460]
59. Kumar BN, Meyer HE, Wandel M, Dalen I, Holmboe-Ottesen G. Ethnic differences in obesity among immigrants from developing countries, in Oslo, Norway. Int J Obes (Lond) 2006;30:684-690. [doi: 10.1038/sj.ijo.0803051] [Medline: 16130029]
60. Hjellset VT, Kjøllesdal MKR, Bjørge B, Holmboe-Ottesen G, Wandel M, Birkeland KI, et al. The InnvaDiab-DE-PLAN study: a randomised controlled trial with a culturally adapted education programme improved the risk profile for type 2 diabetes in Pakistani immigrant women. Br J Nutr 2013;109:529-538. [doi: 10.1017/S000711451200133X] [Medline: 22717286]

61. Merolli M, Gray K, Martin-Sanchez F, Lopez-Campos G. Patient-reported outcomes and therapeutic affordances of social media: findings from a global online survey of people with chronic pain. J Med Internet Res 2015;17:e20 [FREE Full text] [doi: 10.2196/jmir.3915] [Medline: 25616273]
62. Kumar BN, Meyer HE, Wandel M, Dalen I, Holmboe-Ottesen G. Ethnic differences in obesity among immigrants from developing countries, in Oslo, Norway. Int J Obes (Lond) 2006;30:684-690. [doi: 10.1038/sj.ijo.0803051] [Medline: 16130029]
63. Henriksen K. Statistics Norway. 2007. Fakta om 18 innvandrergrupper i Norge URL: https://www.ssb.no/a/publikasjoner/pdf/rapp_200729/rapp_200729.pdf [accessed 2016-02-03] [WebCite Cache ID 6f181F1at]
64. World Health Organization Global Observatory for eHealth. World Health Organization. 2005 May 25. Resolution WHA58.28 eHealth URL: http://apps.who.int/iris/bitstream/10665/20378/1/WHA58_28-en.pdf?ua=1 [accessed 2015-11-30] [WebCite Cache ID 6dQ8Zmdt1]

Abbreviations

BI: behavioral intention
HBM: health belief model
HBTs: health behavior theories
ICT: information and communication technology
NSD: Norwegian Social Science Data Services
TAM: technology acceptance model
T2D: type-2 diabetes
PC: personal computer
PEOU: perceived ease of use
PU: perceived usefulness
SMS: short message service

Edited by G Eysenbach; submitted 21.12.15; peer-reviewed by H Zeeb, C Berterö; comments to author 21.01.16; revised version received 19.02.16; accepted 20.02.16; published 25.04.16.

Please cite as:
Tatara N, Kjøllesdal MKR, Mirkovic J, Andreassen HK
eHealth Use Among First-Generation Immigrants From Pakistan in the Oslo Area, Norway, With Focus on Diabetes: Survey Protocol
JMIR Res Protoc 2016;5(2):e79
URL: http://www.researchprotocols.org/2016/2/e79/
doi:10.2196/resprot.5468
PMID:27113854

Original Paper

An Evaluation of Web- and Print-Based Methods to Attract People to a Physical Activity Intervention

Stephanie Alley[1], BSc (Psych)(Hons); Cally Jennings[2], PhD; Ronald C Plotnikoff[3], PhD; Corneel Vandelanotte[1], PhD

[1]Physical Activity Research Group, School of Human Health and Social Science, Central Queensland University, Rockhampton, Australia

[2]Faculty of Physical Education and Recreation, University of Alberta, Edmonton, AB, Canada

[3]Priority Research Centre for Physical Activity and Nutrition, University of Newcastle, Newcastle, Australia

Corresponding Author:
Stephanie Alley, BSc (Psych)(Hons)
Physical Activity Research Group
School of Human Health and Social Science
Central Queensland University
Building 77
Bruce Highway
Rockhampton, 4700
Australia
Phone: 61 749232263
Fax: 61 749306402
Email: s.alley@cqu.edu.au

Abstract

Background: Cost-effective and efficient methods to attract people to Web-based health behavior interventions need to be identified. Traditional print methods including leaflets, posters, and newspaper advertisements remain popular despite the expanding range of Web-based advertising options that have the potential to reach larger numbers at lower cost.

Objective: This study evaluated the effectiveness of multiple Web-based and print-based methods to attract people to a Web-based physical activity intervention.

Methods: A range of print-based (newspaper advertisements, newspaper articles, letterboxing, leaflets, and posters) and Web-based (Facebook advertisements, Google AdWords, and community calendars) methods were applied to attract participants to a Web-based physical activity intervention in Australia. The time investment, cost, number of first time website visits, the number of completed sign-up questionnaires, and the demographics of participants were recorded for each advertising method.

Results: A total of 278 people signed up to participate in the physical activity program. Of the print-based methods, newspaper advertisements totaled AUD $145, letterboxing AUD $135, leaflets AUD $66, posters AUD $52, and newspaper article AUD $3 per sign-up. Of the Web-based methods, Google AdWords totaled AUD $495, non-targeted Facebook advertisements AUD $68, targeted Facebook advertisements AUD $42, and community calendars AUD $12 per sign-up. Although the newspaper article and community calendars cost the least per sign-up, they resulted in only 17 and 6 sign-ups respectively. The targeted Facebook advertisements were the next most cost-effective method and reached a large number of sign-ups (n=184). The newspaper article and the targeted Facebook advertisements required the lowest time investment per sign-up (5 and 7 minutes respectively). People reached through the targeted Facebook advertisements were on average older (60 years vs 50 years, P<.001) and had a higher body mass index (32 vs 30, P<.05) than people reached through the other methods.

Conclusions: Overall, our results demonstrate that targeted Facebook advertising is the most cost-effective and efficient method at attracting moderate numbers to physical activity interventions in comparison to the other methods tested. Newspaper advertisements, letterboxing, and Google AdWords were not effective. The community calendars and newspaper articles may be effective for small community interventions.

ClinicalTrial: Australian New Zealand Clinical Trials Registry: ACTRN12614000339651; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=363570&isReview=true (Archived by WebCite at http://www.webcitation.org/6hMnFTvBt)

(JMIR Res Protoc 2016;5(2):e94) doi:10.2196/resprot.4826

KEYWORDS

physical activity; web-based intervention; Internet; research subject recruitment; Facebook

Introduction

Recent reviews and meta-analyses have confirmed the short-term effectiveness of Web-based physical activity interventions [1-3]. However the public health impact of these interventions is dependent on how many people they reach when disseminated. It is more difficult and complex to successfully attract people to participate in Web-based health programs than may commonly be perceived. The Internet is a very competitive environment with hundreds of thousands of websites all vying to attract the attention of a potentially vast audience. To date, a range of methods have been used to attract participants to Web-based health interventions including newspaper advertisements [4], leaflets [5], email [6], and social media [7]. However, limited research has measured the cost-effectiveness of these methods [8,9].

Traditional methods including leaflets, posters, and newspaper advertisements are still commonly used by researchers and health professionals to attract people to Web-based heath interventions. This is despite the growing use of Web-based methods, which have the potential to reach larger numbers at lower cost [8]. Email has been successfully used to attract specific groups such as workplace employees to Web-based health interventions when email lists are available [9]. Email is nevertheless inappropriate for a population-wide dissemination as it is becoming increasingly hard to engage people with emails that are not targeted and personally relevant, or not from a trusted source [10]. Internet banners, links on websites, social media, and search engines are popular and effective Web-based marketing methods in the commercial sector [11].

Recent studies have successfully used social media to attract adolescents and adults to nutrition, smoking, and other health interventions [12-14]. Gilligan et al [7] found Facebook advertisements to be 10 times more cost-effective at recruiting mothers of adolescents to complete a survey than traditional media. Furthermore, Morgan et al [15] found Google AdWords to be a cost-effective method for attracting adults to a depression intervention across 6 western countries. Their results also revealed that posts in forums and community notice boards were not effective. A better understanding of how the Internet can be used to attract people to Web-based heath interventions will help researchers and public health workers attract large numbers to Web-based health interventions. Therefore, evaluating the cost-effectiveness of Web- and print-based methods to promote Web-based health interventions requires investigation.

Participants of Web-based physical activity interventions reached through traditional print-based methods have typically been Caucasian, female, and educated [16,17]. Internet use in Australia is currently widespread (83%); however, Internet use decreases with lower education and income [18]. It is unknown whether Web-based advertising is more effective at reaching a representative sample than print-based advertising. Facebook advertising provides the advantage of targeted advertising to assist in reaching desired sample characteristics [12,19]. Therefore, further research is required to determine the characteristics of people reached through different print- and Web-based methods for promoting Web-based health interventions.

This study aims to determine the effectiveness (in terms of cost, time investment, and numbers reached) of multiple Web- and print-based methods to attract Australian adults to a Web-based physical activity intervention. It is hypothesized that the Google AdWords and Facebook advertising will reach a larger number of people at a lower cost and time investment per sign-up than the community calendar and the traditional print-based methods.

Methods

The current study recorded and analyzed methods to attract people to a Web-based physical activity intervention trial in Australia. Data collection began in March 2014. The intervention itself was part of a randomized controlled trial (RCT) comparing the effectiveness (in terms of engagement, retention, and physical activity changes) of computer-tailored advice only and computer-tailored advice with a brief coaching session in an 8-week intervention. A detailed description of the intervention, measures, and study protocol has been published elsewhere [20]. Participants were excluded from the RCT if they were non-English speaking, pregnant, under 18 years of age, currently meeting the Australian physical activity guidelines (assessed by a single item, “do you currently participate in less than 30 minutes of physical activity on average each day?”), or at risk of injury or ill health from increasing their physical activity (assessed by the Physical Activity Readiness Questionnaire [21]). These criteria are stricter than typical population- or community-based physical activity interventions, so all interested participants’ data were included in the current study, regardless of their eligibility to participate in the following RCT. These numbers are more likely to reflect the effectiveness of strategies to attract people to real-world Web-based interventions that aim to sign up as many people as possible. The research has been approved by the Central Queensland University Human Ethics Committee (H13/04-044). Informed consent to participate in the study was obtained from all participants.

Stage 1 Sign-Up

The advertising methods were implemented in the cities of Rockhampton and Mackay, Queensland, Australia. All print-based advertisements including a newspaper advertisement, posters, and leaflets displayed the intervention logo, the CQUniversity logo, the intervention URL and a quick response (QR) code. The QR code directs people to the intervention website when they scan it with a smartphone. Readers were asked “Do you want to get healthy and fit and go in the draw to win some fabulous prizes? You are invited to participate in an online research study where you will gain free access to the ‘My Activity Coach’ program developed by CQUniversity. It will provide you with personalized advice to help you become more active.” The 10x3 cm newspaper advertisements were

printed in a local newspaper (the Morning Bulletin) that has a circulation of 20,000 in the Rockhampton region. The newspaper advertisements contained the same information as the posters and leaflets but in a more concise format, due to space restrictions. A graphic designer assisted with the design of the print advertisements.

The Web-based methods included paid advertisements targeted to Mackay residents on the social media website Facebook and on the Google search engine (Google AdWords). Advertisements were also displayed on Mackay's community websites, including the local newspaper's website (the Daily Mercury) and My Community Connect Mackay at no cost. These advertisements listed the program in the websites' event calendars. Participants could click on the calendar entry to find out more information including a link to the intervention website. The Google advertisements appeared when users searched for terms related to the intervention including fitness, healthy, physical activity, weight loss, and exercise. The Google search engine displays the advertisements that generate the largest number of clicks for each keyword searched. Therefore, each advertisement is competing against similar advertisements linked to the same keyword(s). The advertisement displayed one sentence about the program (see Figure 1) and took people who clicked on the advertisement directly to the intervention website. Multiple advertisements were trialed with different wording. The frequency of the advertisements that generated the largest number of clicks was increased. A daily maximum spend of AUD $10 was applied.

Facebook advertising allows clients to create an advertisement with text and a picture that can be targeted to Facebook user's demographics and interests. The advertisements can be displayed as part of the user's newsfeed, or on the right side of their newsfeed. If the Facebook users click on the feed advertisement, they will be taken to the organization's Facebook page, and if the users click on the side advertisement they will be taken directly to the organization's website. Multiple advertisements can be created within a campaign, with the option to target each advertisement to specific demographics such as age, gender, and location, and/or to people who have shown interest in certain Facebook pages. Only side advertisements were used in the current study to promote direct traffic to the intervention website. Only Facebook users who were over 18 and reside in Mackay were targeted. No additional targeting was implemented to avoid biasing the sample of people reached. Multiple advertisements were trialed with different wording and pictures. Facebook increases the frequency of advertisements that generate the largest number of clicks from the target audience. A limit of AUD $20 per day was applied. The Facebook advertisements displayed a picture and a sentence inviting people to participate in the physical activity intervention (see Figure 2). Both the Facebook advertisements and Google AdWords were checked by an online marketing specialist.

Figure 1. Google advertisement.

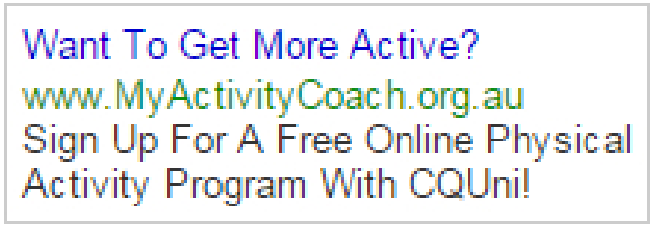


Figure 2. Facebook advertisement.

Stage 2 Sign-up

Stage 2a

At the end of May 2014 after 2 months of promoting the intervention, only 22 people had completed the sign-up survey. To increase the number of sign-ups, the advertising methods were extended to include several other Australian towns: Bundaberg, Townsville, and Brisbane in Queensland; Melbourne (Victoria), Perth (Western Australia), and Sydney (New South Wales). The newspaper advertisements and Google AdWords that had a very high cost per sign-up were discontinued. A new method of delivering leaflets to people's homes was also implemented.

Stage 2b

By August 15, 2014, only 61 people had completed the sign-up survey. Delivering leaflets to people's homes had a very high cost and time investment, so this was discontinued. Furthermore, no additional posters and leaflets were distributed through health care centers. The event listings in the online calendars, however, were continued as they were free and quick to implement. A news article about the program was printed in the Morning Bulletin on September 1, 2014; this was free of cost and took only 1.5 hours to arrange with the newspaper staff. The costly untargeted Facebook advertising was also discontinued. Instead, new highly targeted Facebook advertising was implemented across Australia. From this point forward, this was the main recruitment method (see Table 1). The advertisements were targeted to gender, whereby the advertisements showed a photo of an active person of the same gender. Furthermore, in order to reach individuals most likely to be interested and with the most to gain from the intervention, individuals who had diabetes, depression, cancer, and heart disease were targeted. To do this, people who were members of Facebook pages and support groups on diabetes, depression, cancer, and heart disease were targeted. These advertisements included a statement relating to the condition the user was connected with. Finally some Facebook advertisements were shown only to individuals over 45 years of age. These advertisements displayed a picture of an active older person. Both feed advertisements that are displayed on the user's newsfeed alongside posts from their Facebook friends and groups, and side advertisements displayed on the right border of the Facebook webpage were used. Different combinations of gender, age, disease, and advertisement location were created resulting in 24 different advertisements (eg, feed advertisement targeted to males over 45 years with diabetes; Figure 3). Initially, a daily maximum spend of AUD $5 for each advertisement was selected, but this was regularly updated by increasing the maximum daily spend for the advertisements that had the lowest cost-per click to the intervention website.

Table 1. Timeline of strategies used to attract people to the intervention website.

Strategies	2014										2015		
	Mar	Apr	May	June	July	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar
		Rockhampton and Mackay in QLD				Rockhampton, Mackay, Bundaberg, Townsville and Brisbane in QLD; Melbourne (VIC), Perth (WA), and Sydney (NSW)							
Facebook	√	√	√	√	√								
Google	√	√	√										
Newspaper advertisement	√	√	√										
Calendar[a]	√	√	√	√	√	√	√	√	√	√	√	√	√
Leaflet	√	√	√	√	√	√	√	√	√	√	√	√	√
Poster	√	√	√	√	√	√	√	√	√	√	√	√	√
Letter[b]				√	√								
Newspaper article							√						
Targeted Facebook						√	√	√	√	√	√	√	√

[a]Calendar=online community calendar.

[b]Letter=letterbox drop.

Figure 3. Feed advertisement targeted to males over 45 years with diabetes.

Measures

Participant Numbers

The number of times each advertisement was displayed (impressions) were recorded for the Facebook and Google AdWords advertisements. For the newspaper advertisements, the circulation (estimated number of readers) was used as the measure of impressions. The number of first time website visits from each of the Web-based methods was recorded through Google analytics and the number of website visits for each of the 24 targeted Facebook advertisements was recorded through Facebook. After visiting the homepage, individuals were encouraged to complete a screening survey that asked participants, "how did you hear about this program?" Options included "Google search," "Facebook," "community calendar," "newspaper article," "newspaper advertisement," "leaflet," "letterbox drop," "poster," or "other." This was used as the measure of sign-ups. Generating sign-ups is the main goal of the advertisements and is likely to reflect the number of participants reached though real-world interventions that do not have strict eligibility criteria. Participants who selected "other" were excluded from the current analysis.

Cost

The total cost of each of the methods used to attract people to the intervention was calculated. This included the cost of a research assistant to implement each method based on the Central Queensland University rate of AUD $35/hr. The money spent on each of the 24 targeted Facebook advertisements was also recorded through Facebook. The time spent implementing each method was also calculated. This included the time spent planning, executing, and monitoring each advertisement.

Demographic Characteristics

Participant demographics were assessed only for those people who signed up, were eligible, and who completed the baseline survey (140 out of 278 that signed up). The questionnaire collected participant demographics including gender, marital status, language, income, education, employment, age, body mass index (BMI), and physical activity. Total minutes of physical activity during the previous week was assessed by the validated Active Australia Questionnaire [22].

Data Analysis

Data Screening

All analyses were conducted using SPSS version 20. Significance level was set at $P<.05$. All continuous variables were screened for outliers and normality using Fisher's skewness coefficient. Age, BMI, and total physical activity per week were found to have a significant negative, positive, and positive skewed distribution respectively. A reflect and square root logarithm and square root transformation successfully transformed these variables into normal distributions respectively.

Participant Numbers

The number of impressions, first time visits to the website, and sign-ups for each advertising method were calculated.

Cost

Money spent on the recruitment method plus the hours spent implementing the recruitment method times the hourly cost of employing a research assistant (AUD $35) was calculated and divided first by the number of website visits and second, the number of sign-ups from each recruitment method. Cost per sign-up was the main outcome measure. The time invested in each advertising method per sign-up was calculated as a measure of efficiency.

Demographic Characteristics

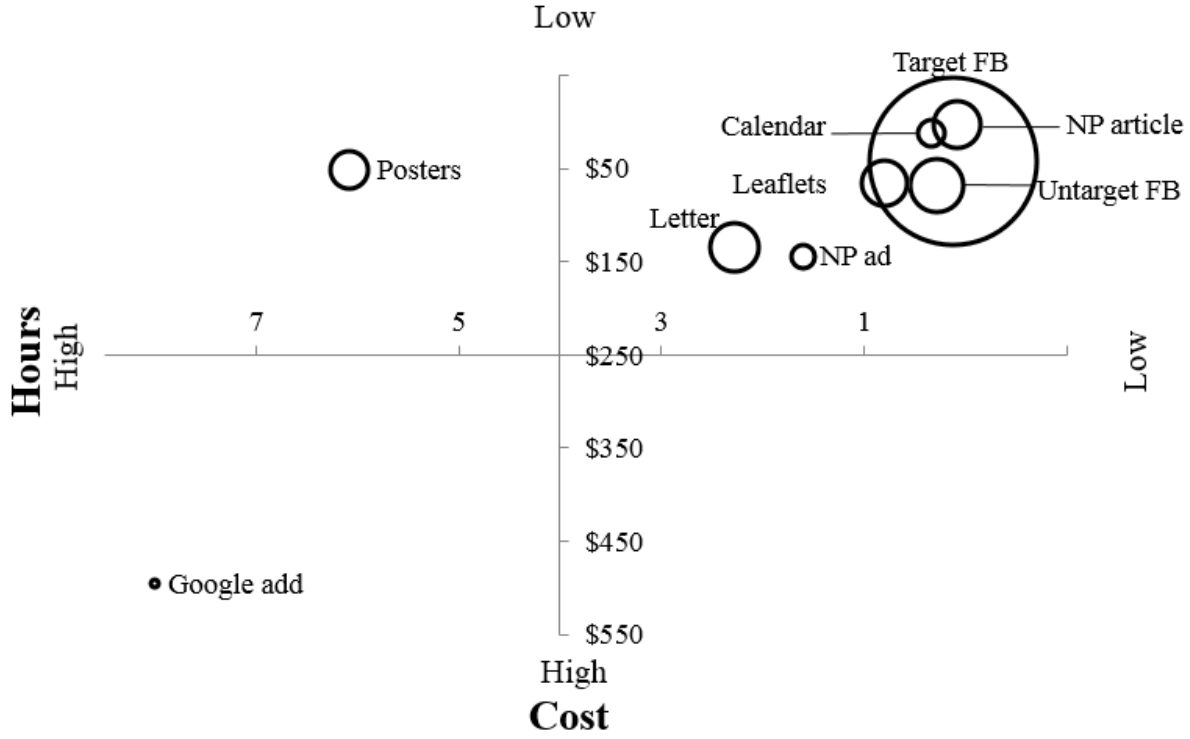
The demographic characteristics of participants reached through the Web-based and print-based recruitment methods were calculated and compared using chi-square analysis for the categorical characteristics (gender, language, marital status, employment, education, and income) and analysis of variance for the continuous characteristics (age, BMI, and physical activity).

Results

Participant Numbers

The strategies implemented in Stage 1 led to 59 sign-ups, and the letterboxing implemented in Stage 2a led to 18 sign-ups. During Stage 2b, the targeted Facebook recruitment led to 184 sign-ups and the newspaper article led to an additional 17 sign-ups (see Table 2 and Figure 4).

Figure 4. Hours per sign-up, cost per sign-up, and number of sign-ups for each advertising method.



Cost

Two newspaper advertisements were printed, which totaled AUD $446. A total of 8 hours was spent organizing the newspaper advertisements costing $280 in research assistant time. In total, 1000 leaflets and 150 posters were displayed in 20 health care centers throughout Rockhampton, and 21 health care centers in Brisbane. The leaflets and posters cost AUD $570.35 and AUD $154 for printing respectively. A total of 24 hours were spent distributing the leaflets and posters, costing AUD $840. Another 3500 and 1500 leaflets were delivered to homes in Rockhampton and Melbourne respectively. The printing for these leaflets cost AUD $990. A total of 41 hours were spent delivering the leaflets, costing $1435.

The calendar entry in the Daily Mercury's website and Mackay's My Community Connect was free of costs. However, the research assistant spent 2 hours organizing this, costing $70. A total of AUD $215 was spent on Google AdWords. The research assistant spent 8 hours developing, implementing, and evaluating the Google advertisements, costing $280. Untargeted side Facebook advertisements totaled $1228. The research assistant spent 6 hours developing, implementing, and monitoring these Facebook advertisements, costing AUD $210. The targeted Facebook advertisements totaled AUD $7021. The research assistant spent 20 hours developing, implementing, and monitoring these Facebook advertisements, contributing AUD $700 to the total cost (see Figure 4).

Table 2. Time investment, costs, impressions, first time visits, and sign-ups of each advertising method.

	Advertising method	Time, hrs	Cost, $	Impressions, n	Visits, n	Sign- ups, n	Time per sign-up, mins	Cost per impression, $	Cost per sign-up, $
Web-based									
	Community calendar	2	70		20	6	20		12
	Untargeted Facebook	6	1438	119,806	877	21	17	0.01	68
	Targeted Facebook	20	7721	547,507	5372	184	7	0.01	42
	Google AdWords	8	495	18,773	34	1	480	0.03	495
Print									
	Posters	12	574	–	–	11	365	–	52
	Health care leaflets	12	990	–	–	15	48	–	66
	Letterbox drop	41	2425	6000	–	18	137	0.4	135
	Newspaper ad	8	726	40,000	–	5	96	0.02	145
	Newspaper article	1.5	53	20,000	–	17	5	0	3
Total		110.5	14,492	752,086	6303	278	1175	0.08	113.11

Demographic Characteristics

A total of 140 participants out of 278 (50.4%) completed the baseline questionnaire. The remaining 49.6% did not meet the inclusion criteria for the RCT (inactive Australian over 18 years with no health conditions that may affect their ability to safely become more active) or failed to complete the baseline questionnaire. This comparison was conducted instead of comparing all print methods to Web-based methods as there was a large variance in effectiveness of the Web-based methods and targeted Facebook advertisements were the most effective method at reaching large numbers at low cost. People reached through the targeted Facebook advertisements were on average older and had a higher BMI than people reached through the other methods. They were also more likely to be divorced or widowed and less likely to have never married, which is likely to be due to the older age group (see Table 3).

Table 3. Descriptive summary of participant characteristics reached using targeted Facebook advertisements and all other methods.

Participant characteristics	Targeted Facebook (n=74)	All other methods (n=66)	Comparison
Gender, n (%)			χ^2=1.24, *P*=.27
Males	19 (26)	12 (18)	
Females	55 (74)	55 (82)	
First language, n (%)			χ^2=0.26, *P*=.61
English	71 (97)	66 (98)	
Other	2 (3)	1 (2)	
Marital status, n (%)			χ^2=6.17, *P*=.01
Never married	0 (0)	5 (7)	
Married	50 (69)	46 (69)	
Divorced or widowed	23 (31)	16 (24)	
Employment, n (%)			χ^2=3.23, *P*=.19
Full time	24 (33)	29 (43)	
Part time/casual	13 (18)	15 (22)	
Unemployed	36 (49)	23 (35)	
Education, n (%)			χ^2=1.55, *P*=.46
Less than secondary	1 (1)	1 (2)	
Secondary	13 (18)	7 (10)	
TAFE or university	59 (81)	59 (88)	
Income, AUD, n (%)			χ^2=1.4, *P*=.50
Over $78,000	24 (49)	28 (50)	
$31,200-77,999	13 (26)	19 (34)	
Under $31,199	12 (25)	9 (16)	
Age in years, mean (SD)	59.72 (.57)	50.21 (1.24)	$F_{1,141}$=57.20, *P*<.001
BMI (kg/m^2), mean (SD)	32.0 (.83)	30.36 (1.04)	$F_{1,139}$=5.081, *P*=.07
Total physical activity (minutes/wk), mean (SD)	161.67 (22.07)	162.84 (24.19)	$F_{1,141}$=0.05, *P*=.83

Targeted Facebook Advertising

The three most cost-effective Facebook advertisements at bringing people to the intervention website were (1) a feed advertisement targeting males over 45 years with diabetes, (2) a side advertisement targeting females over 45 years, and (3) a side advertisement targeting females over 18 years. The female targeted advertisements were more cost-effective per website visit than the male targeted advertisements except for the diabetes, depression, and heart-targeted advertisements. The advertisements targeted to adults over 45 years were more cost-effective per website visit than the advertisements shown to all ages. The advertisements targeted to general health were more cost-effective as a side advertisement, while the targeted health advertisements were more cost-effective as a feed advertisement. Overall, the side advertisements were more cost-effective per website visit than the feed advertisements, except for the diabetes-targeted feed advertisement (see Table 4). The advertisements targeting females were more cost-effective than the advertisements targeting males. The advertisements targeting general health were more cost-effective than the advertisements targeting specific diseases, and the advertisements targeting adults over 45 years were more cost-effective than the advertisements targeting adults over 18 years (see Figure 5).

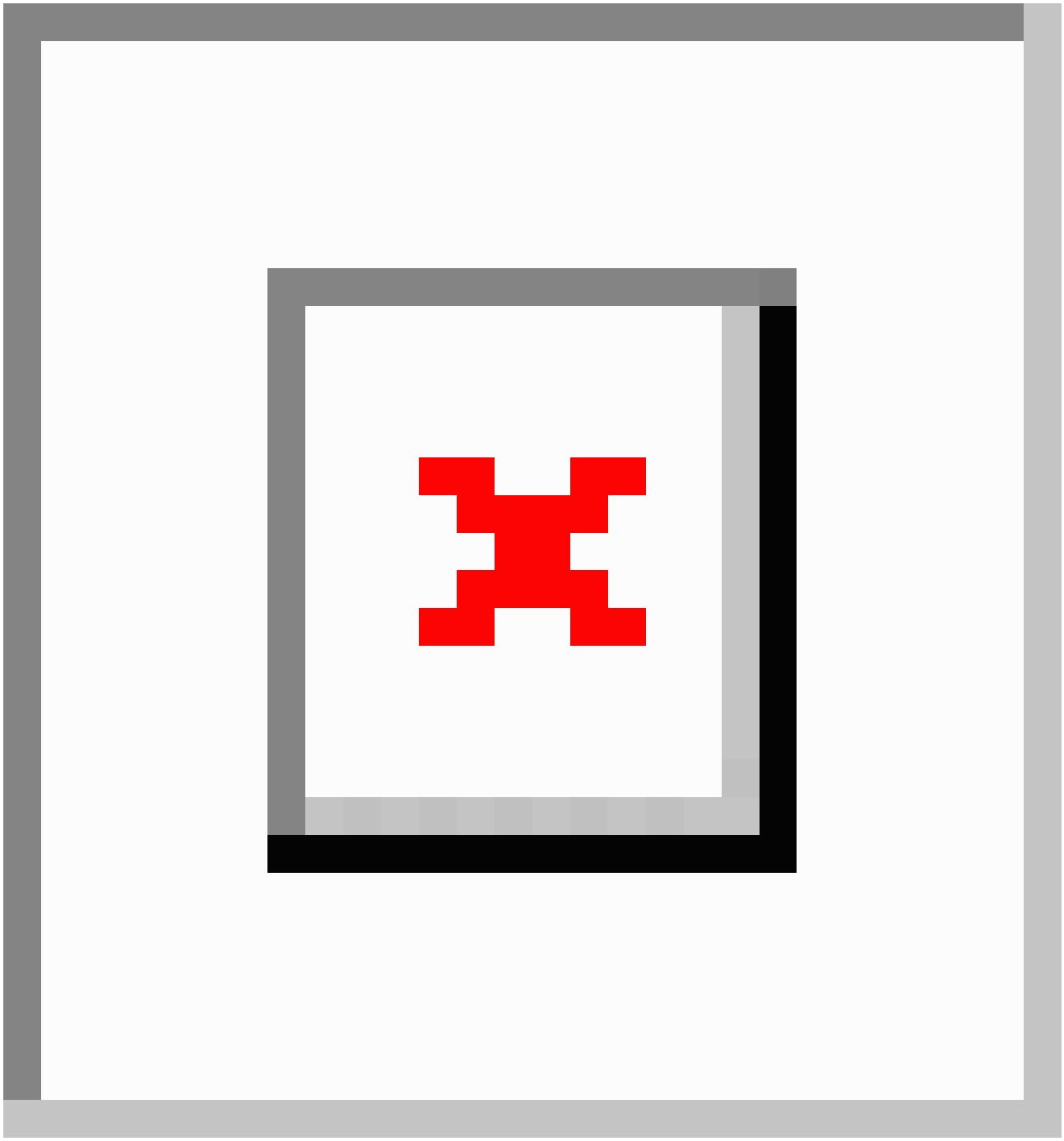
Table 4. Cost, impressions, website visits, and sign-ups for each Facebook advertisement ordered by cost per visit.

Facebook advertisement	Real cost, $	Outcomes			Cost per outcome	
		Impressions	Visits	Sign-ups	Cost per impression, $	Cost per visit, $
Feed[a], diabetes, male	85.49	3805	127	2	0.02	0.67
Side, health[b], female	2500.92	259,992	3237	53	0.01	0.77
Side, health, female, all ages	646.91	175,051	762	0	0.00	0.85
Side, health, male, all ages	123.72	65,069	144	0	0.00	0.86
Side, health, male	566.64	113,949	648	9	0.00	0.87
Side, cancer, female	144.44	19,456	165	1	0.01	0.88
Feed, diabetes, female	315.09	11,828	354	9	0.03	0.89
Side, diabetes, male	241.46	3111	268	2	0.08	0.90
Side, depression, male	38.06	3901	39	0	0.01	0.98
Side, diabetes, female	564.05	8051	547	2	0.07	1.03
Side, heart, male	215.47	6141	210	1	0.04	1.03
Side, heart, female	590.06	13148	569	7	0.04	1.04
Side, depression, female	87.72	7310	84	0	0.01	1.04
Side, cancer, male	29.49	5043	24	0	0.01	1.23
Feed, cancer, female	103.17	5123	72	0	0.02	1.43
Feed, heart, female	111.42	4663	65	0	0.02	1.71
Feed, depression, female	116.73	5054	67	0	0.02	1.74
Feed, health, female	93.03	6400	48	15	0.01	1.94
Feed, health, female, all ages	80.34	9584	41	0	0.01	1.96
Feed, health, male	32.67	3709	16	1	0.01	2.04
Feed, heart, male	14.18	1019	6	1	0.01	2.36
Feed, health, male, all ages	45.36	6,037	19	0	0.01	2.39
Feed, cancer, male	22.61	1382	8	0	0.02	2.83
Feed, depression, male	8.98	735	3	0	0.01	2.99
Can’t remember	–	–	–	37	–	–
Total	6778.01	739,561	7523	140	0.01	0.90

[a]Feed advertisements are displayed on the user’s newsfeed alongside posts from their Facebook friends and groups, and side advertisements are displayed on the right border of the Facebook webpage.

[b]Health refers to advertisements that were not targeted to a physical activity related chronic disease.

Figure 5. Average number of visits per $100 spent on each Facebook advertisement target.



Discussion

Principal Findings

The effectiveness of the Web-based strategies hypothesized to be the most effective (Facebook and Google AdWords) was highly varied. The results demonstrate the low cost-effectiveness of the Google AdWords (AUD $495), while the targeted Facebook advertisements were the most cost-effective (AUD $42 per sign-up) method at reaching a large number of sign-ups (n=184). This is line with previous research demonstrating Facebook to be a cost-effective method for recruiting adolescent and young adults to nutrition and smoking interventions in Australia and North America [12-14]. The effectiveness of Facebook advertisements per sign-up may be due to the low cost per impression and the ability to tailor advertisements to individuals who are more likely to be interested in a Web-based physical activity intervention (eg, females over 45 years). The Facebook advertisements were not as effective when the targeting was not used, confirming that the effectiveness of the Facebook advertisements is partially due to tailoring. Health professionals implementing Facebook advertising in future interventions should target the advertisements to reduce costs; however, they need to be aware that this can bias the sample reached. Researchers and public health professionals must balance cost-effectiveness with how representative the sample reached through Facebook advertising will be. On the other hand, targeted Facebook advertisements can be used to reach underrepresented demographics (eg, people with a mental health

condition) or those most in need of a physical activity intervention (eg, males, people over 45 years), but this may result in a higher cost per click. Although the Facebook advertising was the most cost-effective method at reaching moderate numbers, AUD $42 is still too costly for population-wide dissemination of interventions. Facebook advertising may need to be used in conjunction with mass media and viral marketing strategies to be cost-effective for large-scale disseminations [23]. Overall, the findings from the current study provide evidence to support the use of targeted Facebook advertising to attract people to a Web-based physical activity intervention.

Facebook advertisements displayed on the right side panel that target females over 45 years and general health were generally more cost-effective at attracting people to the physical activity intervention website. It is not surprising that the advertisements targeted to older females are the most cost-effective as this is the demographic that is typically more interested in physical activity interventions [16,17]. In many physical activity interventions, women outnumber men 60% to 40% [1]. Furthermore, it is not surprising that the smaller side advertisements were more cost-effective than the feed advertisements. The feed advertisements resulted in more clicks per dollar spent. However, the feed advertisements take users to another Facebook page (about the physical activity intervention) and then users need to click again to go to the intervention website itself. It is therefore likely that many people were lost at this additional step. It is surprising, however, that the advertisements targeted to people who had liked Facebook pages about diabetes, heart disease, depression, or cancer were not as effective as the advertisements targeted to general health. This could be due to the people who had liked these pages not having the disease themselves. Alternatively it could be due to a small number of users fitting the target criteria, resulting in a high number of impressions made to the same people (ie, repeated displays of the same advertisement to the same uninterested users).

Participants were asked in the sign-up survey which Facebook advertisement allowed them to find out about the program. Due to 37 out of 140 participants' "not remembering" (26.4%), we did not include the analysis of cost per sign-up for each Facebook advertisement. The result of this analysis suggests that the feed advertisements targeted to specific diseases were the most cost-effective at recruiting participants. This means that more people clicked on the side advertisements per dollar spent, but many decided they were not interested after visiting the intervention website and did not sign up. On the other hand, fewer people clicked on the feed advertisements per dollar spent, but a higher percentage of these people signed up to the intervention making it the more cost-effective for achieving sign-ups. Although we cannot draw any conclusions from this data, it highlights the importance of future interventions to monitor website visits as well as sign-ups to evaluate the performance of each Facebook advertisement. Facebook now allows customers to do this by choosing a "conversion" behavior (eg, clicking on the sign-up button) to automatically track how many people from each advertisement begin the sign-up questionnaire on the website.

The high cost and low effectiveness of Google AdWords was not expected as Google AdWords is an effective marketing strategy in the commercial sector, and the advertisements were shown to people who were searching for information related to the intervention. This means that the advertisements were viewed by people more likely to be interested in physical activity and health, compared to Facebook or print-based advertisements, which are shown to people who are not searching for information on physical activity and health. Further, these findings are inconsistent with Morgan et al [15] who found Google AdWords to be a cost-effective method for attracting adults to a depression intervention across 6 western countries ($12 per participant). The high cost of the Google AdWords for the current physical activity program could be due to a high level of competition for the AdWords used including exercise and weight loss. Google increases the frequency of the advertisements that generate the most clicks. Our Google advertisements were therefore competing against commercial weight loss and exercise-related companies in the multibillion dollar fitness industry, which are more likely to gain clicks and therefore be shown more frequently.

The newspaper article and calendar cost the least per sign-up (AUD $3 and AUD $12 respectively); however, they reached only a small number of sign-ups (n=6 and 17 respectively). This is in line with the findings from Morgan et al [15], that community forums and notice boards resulted in few participants. Furthermore, it may not be possible for state- or national-wide interventions to use community forums and calendars as many accept only local events. The only forums that accepted the advertisement for the current project were in Mackay, as Mackay has a Central Queensland University campus through which the program was run. The newspaper article was easy to arrange in Rockhampton where the main campus of the university is located; however, newspapers in other towns were not interested. Although Web-based community forums and newspaper articles did not reach many people, small community interventions may benefit from these methods as they can reach a few additional people for a minimal time and monetary investment.

It is not surprising that the newspaper article and Facebook advertisements required the least amount of time investment per sign-up. The newspaper article was organized by newspaper staff at their expense, so the only time investment was contacting them about the program and answering some interview questions over the phone. The tailored Facebook advertisements can be set up online without any face-to-face meetings or need to manually distribute. Only a small time investment was required to choose appropriate figures and wording for the advertisements and to monitor and adjust them when they were running. The other advertisements needed to be distributed to health clinics (posters and leaflets), delivered to people homes (leaflets), and arranged with face-to-face meetings (newspaper advertisement). This further supports the use of targeted Facebook advertising to attract large numbers to Web-based physical interventions with a wide reach.

There are currently 12 million Facebook users in Australia [24], and the demographics of Facebook users has broadened in recent years [25]. Due to the wide reach of Facebook, Facebook

advertising has reached a representative sample of the target population in many Australian studies [7,26]. It was therefore surprising that people reached through the targeted Facebook advertisements in our study were significantly older than those reached through the other methods. This may have been influenced by the Facebook advertisements that were targeted to people over 45 years. These advertisements were displayed more frequently as they resulted in a lower cost per click. The high prevalence of chronic conditions related to physical inactivity in older adults (eg, osteoarthritis, cardiovascular disease, diabetes, and falls), and the aging population means there is a specific need for physical activity interventions that can reach older adults [27]. The finding that participants reached through targeted Facebook advertising had a significantly higher BMI than participants reached through the other methods may be due to the advertisements targeting individuals with cardiovascular disease and diabetes. It is encouraging that the findings of this study demonstrate the capability of Web-based methods at reaching people most in need of a physical activity intervention.

Limitations

This study presents data to help researchers and public health professionals understand the cost, effectiveness, and issues surrounding different methods to attract people to a Web-based health intervention. However, the findings have limitations, including that the demographic data were collected only for participants eligible to participate in the RCT and who completed the baseline assessment. Thus, it did not include people who signed up but were not eligible. Further, to ensure enough people participated in the RCT, the amount of funds allocated to the advertisements was continuously evaluated and directed to the more successful advertisements over the recruitment period (hence Stages 1, 2a, and 2b during the recruitment phase). Therefore, the most successful advertisement method (eg, Facebook ads) was used for longer than the non-successful advertisements (eg, Google AdWords and newspaper ads). The differences in time of year and total amount spent on different advertisement methods may have affected their success.

Conclusion

Our findings reveal that targeted Facebook advertising is the most cost-effective method to attract moderate numbers to a Web-based health intervention while Google AdWords, despite being a popular marketing method in the commercial sector, was the least cost-effective method. However, the cost of Facebook advertisements are unsustainable for large population-based interventions that seek widespread implementation. Such interventions may need to use mass media in addition to Facebook advertising to reach larger numbers at a lower cost. Community calendars and newspaper articles were the cheapest methods; however, they reached a limited number of sign-ups. These interventions may therefore be beneficial for local community-based interventions. In summary, our findings suggest that Facebook advertising is the most cost-effective method at attracting moderate numbers to physical activity interventions in comparison to the other methods tested. However, it is still too costly for population-based interventions. Further research is needed to determine alternative recruitment procedures more effective at reaching large numbers of participants at low cost.

Acknowledgments

SA conducted the data collection, carried out the data analysis, and drafted the manuscript. CJ, RP, and CV played a significant role in establishing the study design and drafting the manuscript. Project and personal support for SA was provided by the National Health and Medical Research Council of Australia (ID 1055804). RCP is supported by a Salary Award from the National Health and Medical Research Council of Australia. CV (ID 100427) is supported by a Future Leader Fellowship from the National Heart Foundation of Australia.

Conflicts of Interest

None declared.

References

1. Davies CA, Spence JC, Vandelanotte C, Caperchione CM, Mummery WK. Meta-analysis of internet-delivered interventions to increase physical activity levels. Int J Behav Nutr Phys Act 2012;9:52 [FREE Full text] [doi: 10.1186/1479-5868-9-52] [Medline: 22546283]
2. Joseph RP. Internet-Based Physical Activity Interventions. Am J Lifestyle Med 2013;8(1):42-67. [doi: 10.1177/1559827613498059]
3. Foster C, Richards J, Thorogood M, Hillsdon M. Remote and web 2.0 interventions for promoting physical activity. Cochrane Database Syst Rev 2013 Sep 30;9:CD010395 [FREE Full text] [doi: 10.1002/14651858.CD010395.pub2] [Medline: 24085594]
4. Steele R, Mummery WK, Dwyer T. Using the Internet to promote physical activity: a randomized trial of intervention delivery modes. J Phys Act Health 2007 Jul;4(3):245-260. [Medline: 17846455]
5. Ferney SL, Marshall AL, Eakin EG, Owen N. Randomized trial of a neighborhood environment-focused physical activity website intervention. Prev Med 2009 Feb;48(2):144-150. [doi: 10.1016/j.ypmed.2008.10.022] [Medline: 19028519]

6. Herman CW, Musich S, Lu C, Sill S, Young JM, Edington DW. Effectiveness of an incentive-based online physical activity intervention on employee health status. J Occup Environ Med 2006 Sep;48(9):889-895. [doi: 10.1097/01.jom.0000232526.27103.71] [Medline: 16966955]
7. Gilligan C, Kypri K, Bourke J. Social networking versus facebook advertising to recruit survey respondents: a quasi-experimental study. JMIR Res Protoc 2014;3(3):e48 [FREE Full text] [doi: 10.2196/resprot.3317] [Medline: 25230740]
8. Foster CE, Brennan G, Matthews A, McAdam C, Fitzsimons C, Mutrie N. Recruiting participants to walking intervention studies: a systematic review. Int J Behav Nutr Phys Act 2011;8:137 [FREE Full text] [doi: 10.1186/1479-5868-8-137] [Medline: 22171531]
9. Healy GN, Eakin EG, Lamontagne AD, Owen N, Winkler EAH, Wiesner G, et al. Reducing sitting time in office workers: short-term efficacy of a multicomponent intervention. Prev Med 2013 Jul;57(1):43-48. [doi: 10.1016/j.ypmed.2013.04.004] [Medline: 23597658]
10. Gopal RD, Walter ZD, Tripathi AK. Admediation: New horizons in effective email advertising. Commun. ACM 2001 Dec 01;44(12):91-96. [doi: 10.1145/501317.501318]
11. Wakolbinger LM, Denk M, Oberecker K. The Effectiveness of Combining Online and Print Advertisements. J Advertising Res 2009 Sep 01;49(3):360-372. [doi: 10.2501/s0021849909090436]
12. Lohse B. Facebook is an effective strategy to recruit low-income women to online nutrition education. J Nutr Educ Behav 2013;45(1):69-76. [doi: 10.1016/j.jneb.2012.06.006] [Medline: 23305805]
13. Lohse B, Wamboldt P. Purposive facebook recruitment endows cost-effective nutrition education program evaluation. JMIR Res Protoc 2013;2(2):e27 [FREE Full text] [doi: 10.2196/resprot.2713] [Medline: 23948573]
14. Ramo DE, Rodriguez TMS, Chavez K, Sommer MJ, Prochaska JJ. Facebook Recruitment of Young Adult Smokers for a Cessation Trial: Methods, Metrics, and Lessons Learned. Internet Interv 2014 Apr;1(2):58-64. [doi: 10.1016/j.invent.2014.05.001] [Medline: 25045624]
15. Morgan AJ, Jorm AF, Mackinnon AJ. Internet-based recruitment to a depression prevention intervention: lessons from the Mood Memos study. J Med Internet Res 2013;15(2):e31 [FREE Full text] [doi: 10.2196/jmir.2262] [Medline: 23403043]
16. McCoy MR, Couch D, Duncan ND, Lynch GS. Evaluating an internet weight loss program for diabetes prevention. Health Promot Int 2005 Sep;20(3):221-228 [FREE Full text] [doi: 10.1093/heapro/dai006] [Medline: 15797900]
17. Lewis B, Williams D, Dunsiger S, Sciamanna C, Whiteley J, Napolitano M, et al. User attitudes towards physical activity websites in a randomized controlled trial. Prev Med 2008 Nov;47(5):508-513 [FREE Full text] [doi: 10.1016/j.ypmed.2008.07.020] [Medline: 18773915]
18. Australian Bureau of Statistics. Household Use of Information Technology. Canberra, Australia; 2012. URL: http://www.abs.gov.au/AUSSTATS/abs@.nsf/allprimarymainfeatures/ACC2D18CC958BC7BCA2568A9001393AE?opendocument [accessed 2015-06-13] [WebCite Cache ID 6ZFQNqwWx]
19. Baltar F, Brunet I. Social research 2.0: virtual snowball sampling method using Facebook. Internet Research 2012 Jan 27;22(1):57-74. [doi: 10.1108/10662241211199960]
20. Alley S, Jennings C, Plotnikoff RC, Vandelanotte C. My Activity Coach - using video-coaching to assist a web-based computer-tailored physical activity intervention: a randomised controlled trial protocol. BMC Public Health 2014;14:738 [FREE Full text] [doi: 10.1186/1471-2458-14-738] [Medline: 25047900]
21. Thomas S, Reading J, Shephard RJ. Revision of the Physical Activity Readiness Questionnaire (PAR-Q). Can J Sport Sci 1992 Dec;17(4):338-345. [Medline: 1330274]
22. Australian Institute of Health and Welfare. The Active Australia Survey. A guide for manual implimentation, analysis and reporting. Canberra, Australia; 2003. URL: http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=6442454895 [accessed 2015-06-15] [WebCite Cache ID 6ZI8WuPCY]
23. Wakefield MA, Loken B, Hornik RC. Use of mass media campaigns to change health behaviour. Lancet 2010 Oct 9;376(9748):1261-1271 [FREE Full text] [doi: 10.1016/S0140-6736(10)60809-4] [Medline: 20933263]
24. Hopewell L. Gizmodo. Australia; 2014. How many Australians are on Facebook? URL: http://www.gizmodo.com.au/2014/02/how-many-australians-are-on-facebook/ [accessed 2015-02-03] [WebCite Cache ID 6ZFPa3Bko]
25. Saul DJ. ISL. DC, USA; 2014. 3 Million Teens Leave Facebook In 3 Years: The Facebook Demographic Report URL: http://istrategylabs.com/2014/01/3-million-teens-leave-facebook-in-3-years-the-2014-facebook-demographic-report/ [WebCite Cache ID 6ZFPgBoaT]
26. Fenner Y, Garland SM, Moore EE, Jayasinghe Y, Fletcher A, Tabrizi SN, et al. Web-based recruiting for health research using a social networking site: an exploratory study. J Med Internet Res 2012;14(1):e20 [FREE Full text] [doi: 10.2196/jmir.1978] [Medline: 22297093]
27. Nelson ME, Rejeski WJ, Blair SN, Duncan PW, Judge JO, King AC, American College of Sports Medicine, et al. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. Circulation 2007 Aug 28;116(9):1094-1105 [FREE Full text] [doi: 10.1161/CIRCULATIONAHA.107.185650] [Medline: 17671236]

Abbreviations

BMI: body mass index
QR: quick response
RCT: randomized controlled trial

Edited by P Bamidis; submitted 15.06.15; peer-reviewed by L Militello, C Forbes, V Dedov; comments to author 13.07.15; revised version received 03.08.15; accepted 15.03.16; published 27.05.16.

Please cite as:
Alley S, Jennings C, Plotnikoff RC, Vandelanotte C
An Evaluation of Web- and Print-Based Methods to Attract People to a Physical Activity Intervention
JMIR Res Protoc 2016;5(2):e94
URL: http://www.researchprotocols.org/2016/2/e94/
doi:10.2196/resprot.4826
PMID:27235075

Protocol

A Decision Aid for Women Considering Neoadjuvant Systemic Therapy for Operable Invasive Breast Cancer: Development and Protocol of a Phase II Evaluation Study (ANZ1301 DOMINO)

Nicholas Zdenkowski[1,2,3], B Med, FRACP; Phyllis Butow[4], PhD; Elizabeth Hutchings[5], BNursing; Charles Douglas[3], B Med, PhD; Joseph R Coll[4], PhD; Frances M Boyle[1,5,6], MBBS, PhD

[1]Northern Clinical School, Faculty of Medicine, University of Sydney, North Sydney, Australia

[2]Department of Medical Oncology, Calvary Mater Newcastle, Waratah, Australia

[3]School of Medicine and Public Health, Faculty of Medicine, Unversity of Newcastle, Callaghan, Australia

[4]School of Psychology, University of Sydney, Sydney, Australia

[5]Australia and New Zealand Breast Cancer Trials Group, Waratah, Australia

[6]Patricia Ritchie Centre for Cancer Care and Research, North Sydney, Australia

Corresponding Author:
Nicholas Zdenkowski, B Med, FRACP
Northern Clinical School
Faculty of Medicine
University of Sydney
Patricia Ritchie Centre for Cancer Care and Research
25 Rocklands Rd
North Sydney, 2060
Australia
Phone: 61 249850134
Fax: 61 249850135
Email: nick.zdenkowski@newcastle.edu.au

Abstract

Background: Neoadjuvant systemic therapy is offered to selected women with large and/or highly proliferative operable breast cancers. This option adds further complexity to an already complex breast cancer treatment decision tree. Patient decision aids are an established method of increasing patient involvement and knowledge while decreasing decisional conflict. There is currently no decision aid available for women considering neoadjuvant systemic therapy.

Objective: We aimed to develop a decision aid for women diagnosed with operable breast cancer and considered suitable for neoadjuvant systemic therapy, and the protocol for a multicenter pre-post study evaluating the acceptability and feasibility of the decision aid.

Methods: The decision aid was developed through literature review, expert advisory panel, adherence to the International Patient Decision Aid Standards, and iterative review. The protocol for evaluation of the decision aid consists of the following: eligible women will undertake a series of questionnaires prior to and after using the decision aid. The primary endpoint is decision aid acceptability to patients and investigators and the feasibility of use. Secondary endpoints include change in decisional conflict, participant knowledge, and information involvement preference. Feasibility is defined as the proportion of eligible participants who use the decision aid to help inform their treatment decision.

Results: This study has recruited 29 out of a planned 50 participants at four Australian sites. A 12-month recruitment period is expected with a further 12-months follow-up.

Conclusions: The decision aid has the potential to allow patients with operable breast cancer, who have been offered neoadjuvant systemic therapy, decreased decisional conflict, and greater involvement in the decision. If this study finds that an online decision aid is feasible and acceptable, it will be made widely available for routine clinical practice.

Trial Registration: Australian and New Zealand Clinical Trials Registry ACTRN12614001267640; http://www.anzctr.org.au/TrialSearch.aspx?searchTxt=ACTRN12614001267640&isBasic=True (Archived by WebCite at http://www.webcitation.org/6gh7BPZdG)

(JMIR Res Protoc 2016;5(2):e88) doi:10.2196/resprot.5641

KEYWORDS

breast neoplasm; decision aid; neoadjuvant; chemotherapy; protocol

Introduction

Neoadjuvant systemic therapy (NAST) has become a routine treatment option for selected women with operable breast cancer, endorsed by international guidelines [1, 2], patients [3], doctors [4], and breast cancer advocates [5]. We estimate that at least 20% of patients with breast cancer might benefit from NAST; however, this rate varies among clinicians [6]. It has the advantages of down-staging some larger tumors from mastectomy to lumpectomy [7], providing prognostic information depending on the degree of tumor response [8], and facilitating translational research for early biomarkers of response [9]. In tumors with higher rates of proliferation such as triple negative and HER2 (human epidermal growth factor receptor 2)-positive, pathological complete response is considered a surrogate outcome for the approval of novel therapies [10]. Additional potential benefits include additional time for surgical decision making, genetic testing, and downstaging of the axilla [11]. Overall survival and disease-free survival are equivalent following either neoadjuvant or adjuvant systemic therapy with appropriate local therapy [12]. Despite these advantages, NAST is not frequently used for women with operable disease, with one Australian study reporting an estimated rate of 2.75% [4], and in the United States 3.8% [13]. Possible reasons for this low rate of NAST use include the need for changes in workflow practices, patient expectation for upfront surgery, patient lack of awareness of NAST, and lack of available clinical trials [6]. Potential disadvantages to NAST include the loss of detailed pathology to guide multidisciplinary management; the (low) potential to delay surgery in patients who do not respond to NAST; and reduced time between surgery and radiotherapy, which may impact on breast reconstruction outcomes [4].

In a series of semistructured interviews conducted by our group, women with breast cancer expressed interest in NAST, for down-staging, prognostication, and to allow additional time to plan surgery [3]. However, they were not able to be as involved as they would like in the decision to receive NAST rather than adjuvant systemic therapy. They reported a lack of information, meaning that they did not feel adequately informed about the options available. They felt that clinicians tended to direct them toward one option, rather than their preference of shared control. This skewed distribution of decisional control was echoed in a survey of 207 Australian and New Zealand breast cancer specialists, where the majority of clinicians directed the decision about whether NAST would be given for operable breast cancer. This study, using an adaptation of the Control Preferences Scale [14], found that no clinicians reported that their patients made the final decision about NAST [15]. This indicates a mismatch between patient wishes and the experience of shared decision making [16], and suggests that strategies are required to better involve patients in the decision about NAST.

Women with early stage breast cancer typically desire involvement [17] and decisional control over their treatment [18]. Those who are at least as involved as they wanted experience better decision-related outcomes including consultation satisfaction, satisfaction with decision making, perception of clinician-shared decision-making skills, and decreased decisional conflict [18]. Being involved in decision making about breast cancer is associated with improved quality of life up to 10 years postdiagnosis [19]. However, it may be particularly difficult to engage women in decisions about NAST due to the complexity of the decision, distress from breast cancer diagnosis, perceived urgency, and an expectation that surgery will be the first treatment offered [3]. Patients may also want to proceed with up-front curative surgery in the hope that chemotherapy, which is seen as toxic and intrusive [20], may be avoided entirely.

Patient decision aids (DA) are an established method to improve the quality of shared decision making. Patient decision aids for treatment decisions have been shown to decrease decisional conflict, increase knowledge about options, improve risk perception, and improve patient-practitioner communication [21]. Decision aids are particularly suited to decisions where the various risks and benefits of the alternative treatment options may be valued differently by different individuals [22]. The choice between NAST and conventional sequencing (surgery followed by chemotherapy) is such a decision. In a systematic review of decision aids for patients with early stage breast cancer, we could not find any reports of a decision aid for NAST [23]. In our Australian survey, 86% of breast cancer specialists expressed interest in using a decision aid for women with operable breast cancer who are offered NAST. Women who were interviewed endorsed the development of a NAST DA and expressed a preference for a tool in print form that was accessible from a trusted source. In this paper, we describe the development of such a DA and the protocol for a study that will evaluate that DA.

Methods

Decision Aid Development

A DA (see Multimedia Appendix 1) was developed based on a literature review and then refined in an iterative process by an expert advisory panel comprising medical oncologists, breast surgeons, a psycho-oncologist, consumers, a breast care nurse, and a breast cancer advocacy organization representative according to the systematic process described by Coulter et al [24]. A skilled consumer advocate with personal experience of breast cancer reviewed the decision aid on multiple occasions and provided constructive advice. The structure of the DA was based on the International Patient Decision Aid Standards Collaboration statement, to include a balanced description of adjuvant and neoadjuvant therapy, including advantages and disadvantages, outcome probabilities for each option, graphics, and a values clarification exercise. The DA was then circulated

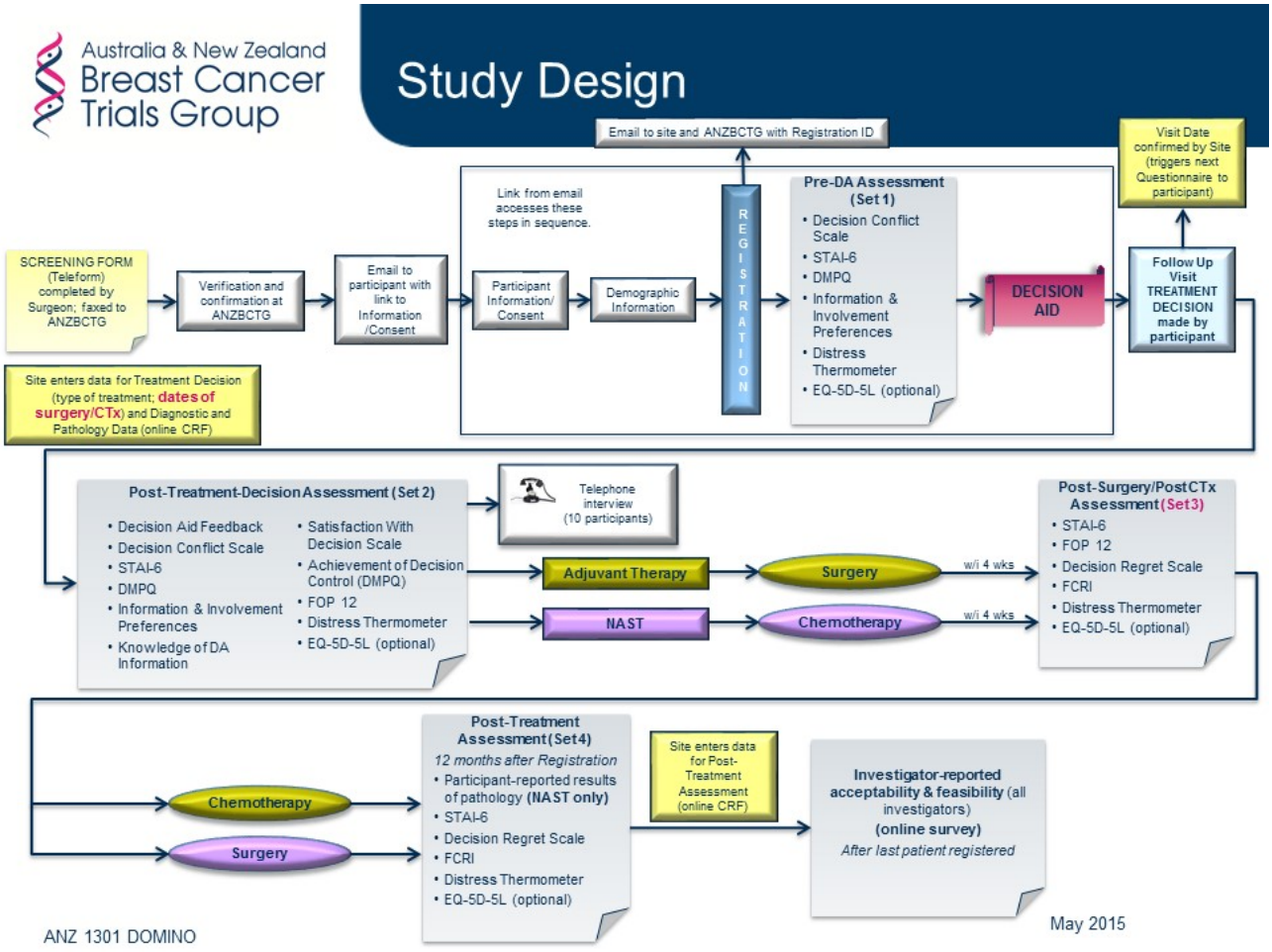
to an additional stakeholder group with similar composition to the first, who had not seen the DA, for further refinement. It was then professionally formatted in portable document format (.pdf) to be downloadable and printable in either color or black and white.

The final DA includes an introduction, brief general information about breast cancer and the treatments used, explanation of the options for the timing of chemotherapy and surgery, the advantages and disadvantages of neoadjuvant and adjuvant therapy, a values clarification exercise, a page for notes, a glossary, and information about where to find additional resources. Using the readability statistics package embedded in Microsoft Word, the decision aid has a grade 10 Flesch-Kincaid readability level. The introduction is necessary for newly diagnosed breast cancer patients to understand basic concepts about treatment modalities because they may not have received other written general information at the time that NAST is being discussed. A diagram represents the options of either chemotherapy followed by surgery or surgery followed by chemotherapy. Radiotherapy (if indicated), HER2-directed therapy (if HER2 positive), and endocrine therapy (if estrogen [ER] and/or progesterone receptor [PR] positive) follow in the flow diagram in Multimedia Appendix 1. The diagram is designed to demonstrate that treatment duration is expected to be similar with either option.

Key components of risk are presented using visual, numeric, and narrative formats with appropriate labeling, tailored to individual tumor characteristics [25]. The likelihood of a pathological complete response is presented according to breast cancer subtype: ER/PR (hormone receptor [HR]) positive, HER2 negative; HR positive, HER2 positive; HR negative, HER2 positive; and HR negative and HER2 negative (triple negative [TNBC]). The probability of remaining alive and free of breast cancer at 5 years is presented, based on whether a pathological complete response was achieved, or not. These estimates are based on a meta-analysis of neoadjuvant clinical trial results reported by von Minckwitz et al [26] and Cortazar et al [8]. A 1000-dot diagram, with each dot representing one patient, illustrates the likelihood of tumor progression (3%) or becoming inoperable (0.3%) on neoadjuvant chemotherapy, based on a case series by Caudle et al [27].

The values clarification exercise in this DA is a diagram with statements about advantages and disadvantages of either option [28]. Patients can nominate how important each factor is to them and then make a mark on a linear analogue scale to show which option they prefer and how strong their view is. Patients are encouraged to discuss their options with friends, family, and other health professionals if they wish. The final decision is made at a follow-up visit with their surgeon or medical oncologist.

Figure 1. Study schema.



Evaluation of Decision Aid

ANZ1301 is a multicenter study using a pre-post design to evaluate the acceptability and feasibility of the decision aid (Figure 1) described above. The project is being led by the Australia and New Zealand Breast Cancer Trials Group (ANZBCTG) in collaboration with the Psycho-oncology Co-operative Research Group. It is funded by an HCF Research Foundation grant with central trial coordination by the ANZBCTG. All four sites have received ethics approval from the Hunter New England Local Health District Human Research Ethics Committee, under the Australian National Mutual Acceptance multicenter ethics scheme.

Study Participants

Clinicians

In total, 26 clinicians from four ANZBCTG sites have been recruited to identify women eligible for the DOMINO (DecisiOn MakIng about NeOadjuvant) study. Participating sites are Calvary Mater Newcastle, Waratah, NSW; The Breast and Endocrine Center, Gateshead, NSW; The Mater Hospital, North Sydney, NSW; and Royal Melbourne Hospital, Parkville, VIC. Patients are screened at those four sites and in the private practices of associated clinicians. All participating clinicians and site study personnel receive training on the online system developed for this study.

Patients

Patients are eligible to participate in the DOMINO study if they are female and aged over 18 years; have a histological diagnosis of invasive breast cancer; have an operable invasive breast tumour; are considered appropriate for neoadjuvant systemic therapy (NAST) with curative intent using chemo- and/ or endocrine therapy; are able and agree to access study information via the Internet; are able to comply with the study procedures for the duration of the study; and give voluntary, informed consent.

Patients are ineligible if they are expected to receive fewer than 3 months of NAST; have a hearing or other impairment that would preclude a phone interview; are unable to access the Internet using a laptop or desktop computer, or do not have an active email address with which to participate in the study; have insufficient English language skills for participation in online surveys and oral interviews; have inflammatory, metastatic, or inoperable breast cancer; or have a medical or psychiatric condition that precludes informed consent or prevents adherence to study procedures.

Study Design

Screening

Potentially eligible patients are identified during the planning of their initial treatment strategy at participating Australian sites during multidisciplinary meetings and at surgical and medical oncology appointments. Patients are approached by their clinician during their appointment to consider receiving additional information about the DOMINO study via a Web link that is sent to the patient via an auto-generated email. At the time of the initial offer of study participation, patients are asked to indicate written consent on a screening form for their personal information (name, email address, and telephone number) to be provided to the ANZBCTG. A Web link to the study consent page and questionnaires is then sent to them by email. Patients who consent to share personal information are provided with a copy of their signed screening consent form along with study-specific written information about their breast cancer. This information is intended to aid understanding of their diagnosis when using the decision aid. Clinicians are required at this time to record details regarding the primary reason for NAST, as well as an opinion of the patient's current distress levels and information preferences. The completed screening consent form is sent via Teleform (Hewlett Packard) fax to the ANZBCTG to be verified, and email contact with the patient is established.

If the patient does not consent to share personal information, the clinician records information on the screening consent form so a log can be kept of each patient who is ineligible and screened out, eligible but not offered participation, and offered participation but declines. The number of patients who consent to screening but do not participate in the study will also be recorded. Screening data will be used to describe feasibility of DA use.

Registration

Patients are registered to the study through the following process. The screening form is received at the ANZBCTG for validation and confirmation of eligibility criteria. Patients who consent to release their details on the screening form receive an automatically generated email. These patients are now considered eligible for the DOMINO study. Patients who access, read the online DOMINO Information Statement and Consent page, and agree to participate in the study are redirected to a series of demographic questions. On submission of responses to demographics and consent, patients are considered registered to the study. Patients at this stage are also given the opportunity to opt in to a telephone interview. Eligible patients have a 6-week window in which to view and agree to participate in the DOMINO study before being considered a screen failure. We aim to register 50 patients to the DOMINO study.

Electronic Communication Processes

At the point of registration, patients are requested to enter a password to access the DOMINO website. Thereafter, an individual's username is defined by their email address.

Site trial coordinators input dates of patient appointments and projected treatment completion dates, which are then used to calculate and trigger all communication with the patient and reminders to site coordinators. Pre-designed patient and site coordinator emails are sent automatically at specific timepoints, as guided by information entered by sites as to the treatment decision (either NAST or surgery), to patients. A reminder email is sent to the patient if the survey remains unsubmitted 3 calendar days after the initial email. If after an additional 2 calendar days a patient has not submitted a questionnaire, an automatically generated email is sent to the ANZBCTG study coordinator prompting a telephone call to the patient. Site study coordination staff are sent automatically generated emails

prompting completion of data via the online system or informing them of their patient's submission of a questionnaire.

Outcome Measures

Primary Outcomes

DA acceptability is the first outcome. It is defined as at least half of patients considering the DA useful for their decision and at least half of clinicians indicating that they would use the DA in their routine clinical practice. Acceptability will be assessed using a single question from the DA feedback questionnaire developed by Juraskova et al [29] about whether the patient considered the DA useful for their decision. This questionnaire also measures general satisfaction with the DA.

Feasibility of DA use will also be assessed as an outcome. We define it as at least half of patients who were offered participation in the study accessing the DA, and at least half of those who access the DA stating that they read it.

Secondary Hypotheses and Outcome Measures

We hypothesize that with use of the DA the Decisional Conflict Scale score will decrease [30]; knowledge about NAST, using a custom-designed questionnaire, will increase; information and involvement preference will increase [31]; agreement between preferred and achieved decision control will be high, based on an adaptation of the Control Preferences Scale to include achieved control [14]; and the Control Preferences Scale score will increase [14]. Further, there will be no change in cost of health care delivery or in the 6-item State-Trait Anxiety Inventory score [32]. Fear of cancer progression will be unchanged while receiving neoadjuvant therapy [33]; the Decisional Regret score after chemotherapy and after surgery will be low [34]; fear of cancer recurrence score will be low [35]; distress thermometer score will decrease [36, 37]; satisfaction with decision score will be high [38]; and there will be no change in outcomes between those who decided to receive neoadjuvant chemotherapy with those who decided not to have neoadjuvant therapy.

Exploratory Hypotheses

Correlation will be good between baseline investigator assessment of participant information and involvement preference and participant report of DA acceptability. Correlation will be good between high baseline participant information and involvement preference and high acceptability of DA to participants. Correlation will be good between baseline investigator assessment of distress and participant report of distress. Participants will be willing to complete the EuroQol 5-Dimensions (EQ-5D-5L) questionnaire, a health utility measure.

Knowledge Questionnaire

A custom-designed 7-item knowledge questionnaire has been developed based on the content of the DA to test recall and comprehension (see Multimedia Appendix 2). Questions were taken from information throughout the DA. The number of correct responses will be transformed to a score out of 100.

Demographic, Tumor, and Treatment Information

The following demographics will be recorded: age, marital status, level of education, health insurance, occupation, and native language. Tumor characteristics consist of tumor size, nodal status, estrogen/progesterone receptor, HER2 amplification, and grade. Investigations and treatment received include duration of chemotherapy, radiotherapy, surgical procedure(s) performed, biopsies, and imaging performed.

Telephone Interview

Participants will be asked to participate in a semistructured interview using a pre-planned interview guide, to gain a deeper understanding of their attitude toward the utility and acceptability of the DA. Participants are asked at the time of consent to tick a box indicating their willingness to be contacted for an interview. Interviews will undergo immediate initial analysis and will be conducted until thematic saturation is reached, defined as no new major themes in three consecutive interviews. Further rounds of analysis will be conducted in an iterative fashion after all interviews are complete. Interviews will be recorded, transcribed verbatim, and analyzed using qualitative methodology. Qualitative descriptive methodology will be used, as is appropriate when lived experience, views, and preferences are the target of investigation, and there are little existing data available. This method can be used to gain a rich description of an experience, founded in existing knowledge and interpreted in the context of the clinical experience of the research group [39].

Clinician Questionnaire

After 50 patients have completed their post-DA questionnaire, all clinicians will receive an electronic questionnaire. The questions include specialty (surgeon or medical oncologist), intent to use the DA in routine clinical practice, patient selection for DA use, effect on consultation duration and number, apparent effect on decision making, and comments on content. The DA will be considered acceptable to clinicians if more than 50% report that they would use the DA in routine clinical practice.

Questionnaire Administration

A series of validated questionnaires where available, and custom designed where a questionnaire is not available, are presented to patients at four timepoints before and after access to the decision aid (see Table 1). Prior to access to the decision aid, patients are asked to report demographics and to complete 6 questionnaires that address decisional conflict, decision-making preference, information and involvement preferences, anxiety, distress, and an optional health economic instrument.

At the completion and submission of the first set of questionnaires, patients are able to access an electronic copy of the decision aid. This document can be printed, saved, and accessed by a patient at any stage of the study by logging in to the DOMINO website. Patients are asked to complete and read the decision aid prior to attending their next appointment with their clinician, at which time a decision regarding treatment may be made. At this visit, the clinician refers to the decision aid and asks whether the patient has any questions about it. After the attendance at an appointment where a decision was made regarding treatment and specific data have been entered

by the site, the patient receives an autogenerated email informing them that a second set of questionnaires is available for completion. Questionnaires at this timepoint ask the patient to reflect on the information provided in the DA and its role in their treatment decision. Patients who do not submit both questionnaire sets 1 and 2 will be replaced to ensure that pre-post outcomes are recorded for 50 patients.

Based on treatment details supplied by the site trial coordinator about treatment option chosen and date of completion, an email link to questionnaire set 3 is sent to the patient. This questionnaire is to be completed after the initial treatment strategy of either chemotherapy or surgery. It is expected that most participants will then proceed with surgery or systemic therapy respectively as their subsequent treatment strategy. This assessment aims to determine the effect of the first treatment strategy on decision-related outcomes, without the influence of the alternative strategy.

Questionnaire set 4 is answered 12 months after registration, to investigate longer-term outcomes including anxiety, distress, regret, and recollection of pathology results. This is the last questionnaire, and participants complete their study involvement at this time.

Table 1. Questionnaire content according to assessment timepoint.

	Pre-DA assessment	Posttreatment decision assessment	Postchemo assessment (NAST)[a]	Postsurgery (non-NAST)[b]	Posttreatment assessment[c]
Decision conflict scale	X	X			
State-Trait Anxiety Inventory 6 Anxiety	X	X	X	X	X
Decision-making preference questionnaire					
Preferred	X	X			
Actual		X			
Distress thermometer	X	X	X	X	X
Information and involvement preferences	X	X			
EQ-5D-5L (optional)	X	X	X	X	X
Knowledge of decision aid information		X			
Decision aid feedback		X			
Satisfaction with decision scale		X			
Fear of progression (FOP 12)		X	X	X	
Decision regret scale			X	X	X
Fear of Cancer Recurrence Inventory			X	X	X
Participant-reported pathology results (NAST only)					X

[a]Postchemotherapy, before surgery.

[b]Postsurgery, before adjuvant chemotherapy.

[c]12 months (+/- 1 month) after registration.

Statistical Analysis

A sample size of 50 participants is planned. The primary analysis will include all registered patients and clinicians as two separate cohorts. The proportion of patients and investigators who consider the DA acceptable will be reported with 95% exact confidence limits. The primary outcome will be considered positive if more than half of patients and clinicians consider the DA acceptable, and feasible if more than half of eligible patients who are offered participation register and subsequently use the DA. Assuming a sample size of 50 participants, the primary outcome of percentage of participants finding the DA acceptable can be estimated to within ±15% based on 95% exact confidence limits. To ensure that the lower 95% one-tailed exact confidence limit is greater than 50%, at least 32 of the 50 participants will need to indicate DA acceptability. Although the study is not powered to test the secondary hypotheses, there is 80% power to detect a change of at least 0.40 standard deviations from the pre- to post-DA assessments using a two-tailed *t*-test with alpha=.05 and a sample size of 50 participants.

Changes in secondary outcome measures from the pre-DA assessment, including decisional conflict, information preference, anxiety, distress, and fear of progression, will be evaluated using repeated measures analysis of covariance (ANCOVA). All outcomes will be described using mean and standard deviation for continuous measures and frequency for categorical outcomes. If data are skewed, median and interquartile range will be reported and the appropriate linearizing transformation will be used. Analyses will be

performed unadjusted and adjusted for age, level of education, information preferences, and tumor characteristics (size, grade, node involvement, ER/PR/HER2). Agreement in decisional control before and after using the DA, and between preferred and actual control, will be assessed using a weighted kappa statistic with McNemar test. Knowledge will be reported as mean proportion of items correct with standard deviation. Cost will be recorded using Australian Medical Benefits Scheme item numbers and Pharmaceutical Benefits Scheme prices, and a comparison made between those who receive surgery first and those who receive systemic therapy first.

Missing Data

Patients are encouraged to complete all questions but are not compelled to enter responses to any of the individual questions within each set of questionnaires and can submit responses with blank fields. Prior to questionnaire submission, patients will receive a prompt informing them that not all questions have been answered and to amend if they wish. During the study, levels of missing data are being monitored. If data completion rates drop below 70%, remedial action will be taken. An analysis of missing data will be completed at the end of the study.

Results

The study is currently recruiting at four Australian centers. As of February 2016, 29 of the planned 50 participants have been registered to the study. Recruitment is expected to be complete in mid-2016, with early results available late 2016.

Discussion

Principal Considerations

This study intends to evaluate the acceptability and feasibility of a DA for women with operable breast cancer who have been offered NAST. It is designed as a single arm pre-post study to allow all participants access to the intervention. The population of Australian women who currently receives NAST is relatively small, limiting the feasibility of a larger, randomized controlled trial with comparative outcomes. However, the proportion of patients receiving NAST in Australia and New Zealand is expected to increase as a result of increased awareness, availability of neoadjuvant clinical trials, and from the results of ongoing neoadjuvant and post-neoadjuvant trials.

The study primary endpoints are pragmatic. We expect that some participants will not find the DA beneficial, based on their decision-making style and information-seeking behavior. However, we hypothesize that the number who find it helpful in their decision-making process will be greater than the number who do not find it useful. Because DAs have variable use across centers and individual clinicians [40], feasibility was included as an endpoint. A screening log is designed to quantify the number of patients who are seen at recruiting sites who are candidates for NAST for operable breast cancer; are eligible for the study; are offered study participation; accept study participation; and go on to access the DA. This will identify the proportion of eligible patients who are not offered participation (clinician feasibility) and the proportion of eligible patients who do not access the DA after being offered it (patient feasibility). Acceptability will be assessed using direct questions to patients and clinicians.

Outcome measures were selected based on the availability of valid, reliable questionnaires that assess outcomes relevant to decision making in the context of a decision aid. In a systematic review of the quality of measures to test the effectiveness of decision support strategies, the Decisional Conflict Scale and the Control Preferences Scale satisfied the largest number of quality criteria [41]. These are commonly used measures of DA effectiveness [21, 42]. Knowledge assessment necessitates a custom-designed questionnaire. The Fear of Progression questionnaire is suited to the neoadjuvant setting where the primary cancer is present and has the potential to impact on psychological and physical domains [33]. The Information and Involvement Preferences questionnaire was included to determine the information needs of patients and to correlate the result with patient and clinician acceptability. The EQ-5D-5L is a health economic utility measure [43] and was included as an optional measure to determine patients' willingness to complete this additional questionnaire. If patients are willing to complete it, then it will be considered for future comparative studies as a health economic measure. Satisfaction with decision is of interest as an acute measure to be assessed after the decision has been made, but prior to experiencing the consequences of the decision [34]. Decision regret is a longer-term outcome measure, to be assessed after the consequences of the decision have been experienced [38].

Increased anxiety is associated with both more effective decision strategies and stressful health interventions, so is not a good measure of the benefit of DA use [44]. Anxiety therefore is not expected to decrease as a result of a DA, but nor should it increase and therefore anxiety has been included as a safety measure [21].

Decision aids are most beneficial if endorsed by a clinician at the time they are offered to the patient and referred to after the decision has been made [45]. This decision aid is introduced at a time when patients have recently been diagnosed with breast cancer and are faced with a number of complex decisions that are influenced by a variety of sources including clinicians, family, and the media [46, 47]. Patients are identified as suitable for the decision aid by their doctor (usually a surgeon) and are generally referred to a medical oncologist to discuss systemic therapy. The decision aid is suited to this situation as there is often a period of several days (or more) before an available appointment with a medical oncologist. If the decision aid is effective, the patient will be more prepared to be involved in the decision when they come to the medical oncologist. Balancing the provision of complex information with adequate readability proved difficult, as demonstrated by a higher Flesch-Kincaid grade than would be ideal.

Decision aids have been shown to have a variable effect on treatment choices [21]. For selected treatment decisions, some patients change their preferred treatment after a DA, but for others decision aids have been shown to have a neutral effect. We anticipate that study patients will not change their decisions after accessing the DA, as decisions such as this tend to be made based on a number of information sources [48].

If shown to be feasible and acceptable, the DOMINO decision aid has the potential to be offered to patients as part of routine clinical practice. There is good evidence for the efficacy of decision aids that are designed according to international standards [22,24]. Thus, a randomized controlled trial is not considered a prerequisite for dissemination. Clinicians who enroll participants in this study will be asked whether they would continue to use the decision aid as part of routine practice, as an indicator of perceived implementability.

Conclusion

Use of the DOMINO decision aid has the potential to decrease decisional conflict, increase knowledge, and increase patient involvement in women who have been offered NAST. Increased involvement in decisions by women with breast cancer is associated with improved decision-related outcomes [18] and long-term quality of life [19]. Neoadjuvant clinical trials are an established drug development pathway, and the decision aid may allow better understanding of the rationale behind neoadjuvant therapy. The patient may then be able to be better informed about the trial. It may also assist clinicians who are introducing neoadjuvant systemic therapy into their practice but have not yet become confident addressing the concept with their patients.

Acknowledgments

We thank the Australia and New Zealand Breast Cancer Trials Group Supportive Care Subcommittee and Scientific Advisory Committee for scientific input and the Trials Coordination Department for protocol development. Newton Green Technologies developed the database, online questionnaires, and electronic case report forms. The ANZ1301 DOMINO study is funded by an HCF Research Foundation grant and by the Breast Cancer Institute of Australia.

NZ is supported by Sydney Catalyst and the Hunter New England Local Health District. FB is supported by the Friends of the Mater Foundation.

Authors' Contributions

NZ, PB, JC, CD, and FB conceived the study and refined the design. All authors developed the protocol. NZ and FB will contribute patients and data. EH will coordinate the study centrally. NZ and EH drafted the manuscript. All authors have reviewed and approved the manuscript prior to submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Decision aid for neoadjuvant systemic therapy.

[PDF File (Adobe PDF File), 711KB - resprot_v5i2e88_app1.pdf]

Multimedia Appendix 2

Custom designed knowledge questionnaire.

[PDF File (Adobe PDF File), 31KB - resprot_v5i2e88_app2.pdf]

References

1. Kaufmann M, von MG, Mamounas EP, Cameron D, Carey LA, Cristofanilli M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012 May;19(5):1508-1516. [doi: 10.1245/s10434-011-2108-2] [Medline: 22193884]
2. Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, et al. Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol 2015 Aug;26(8):1533-1546 [FREE Full text] [doi: 10.1093/annonc/mdv221] [Medline: 25939896]
3. Zdenkowski N, Butow P, Fewster S, Beckmore C, Wells K, Forbes JF, et al. Exploring Decision-Making about Neo-adjuvant Chemotherapy for Breast Cancer. Breast J 2016 Jan;22(1):133-134. [doi: 10.1111/tbj.12537] [Medline: 26530428]
4. Read RL, Flitcroft K, Snook KL, Boyle FM, Spillane AJ. Utility of neoadjuvant chemotherapy in the treatment of operable breast cancer. ANZ J Surg 2015 May;85(5):315-320. [doi: 10.1111/ans.12975] [Medline: 25612239]
5. Perlmutter J, Axler S, Baas C, Beckwith BJ, Bonoff A, Brain S, et al. Advocates' perspective: neoadjuvant chemotherapy for breast cancer. J Clin Oncol 2012 Dec 20;30(36):4586-4588 [FREE Full text] [doi: 10.1200/JCO.2012.44.1824] [Medline: 23169512]

6. Zdenkowski N, Butow P, Mann G, Fewster S, Beckmore C, Isaacs R. Neoadjuvant systemic therapy for breast cancer: A survey of Australian and New Zealand (ANZ) specialists. In: Breast. 2015 Mar 01 Presented at: St Gallen International Breast Cancer Conference; March 1, 2015; Vienna, Austria.
7. Mieog JSD, van der Hage JA, van de Velde CJH. Preoperative chemotherapy for women with operable breast cancer. Cochrane Database Syst Rev 2007(2):CD005002. [doi: 10.1002/14651858.CD005002.pub2] [Medline: 17443564]
8. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014 Jul 12;384(9938):164-172. [doi: 10.1016/S0140-6736(13)62422-8] [Medline: 24529560]
9. DeMichele A, Yee D, Berry DA, Albain KS, Benz CC, Boughey J, et al. The Neoadjuvant Model Is Still the Future for Drug Development in Breast Cancer. Clin Cancer Res 2015 Jul 1;21(13):2911-2915. [doi: 10.1158/1078-0432.CCR-14-1760] [Medline: 25712686]
10. Prowell TM, Pazdur R. Pathological complete response and accelerated drug approval in early breast cancer. N Engl J Med 2012 Jun 28;366(26):2438-2441. [doi: 10.1056/NEJMp1205737] [Medline: 22646508]
11. Beatty JD, Precht LM, Lowe K, Atwood M. Axillary-conserving surgery is facilitated by neoadjuvant chemotherapy of breast cancer. Am J Surg 2009 May;197(5):637-641; discussion 641. [doi: 10.1016/j.amjsurg.2008.12.009] [Medline: 19321159]
12. Mauri D, Pavlidis N, Ioannidis JPA. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. J Natl Cancer Inst 2005 Feb 2;97(3):188-194 [FREE Full text] [doi: 10.1093/jnci/dji021] [Medline: 15687361]
13. Onitilo AA, Onesti JK, Single RM, Engel JM, James TA, Aiello Bowles EJ, et al. Utilization of neoadjuvant chemotherapy varies in the treatment of women with invasive breast cancer. PLoS One 2013;8(12):e84535 [FREE Full text] [doi: 10.1371/journal.pone.0084535] [Medline: 24376822]
14. Degner LF, Sloan JA, Venkatesh P. The Control Preferences Scale. Can J Nurs Res 1997;29(3):21-43. [Medline: 9505581]
15. Zdenkowski N, Butow P, Mann B, Fewster S, Douglas C, Boyle FM. Decisions about neoadjuvant systemic therapy for breast cancer: a survey of Australian and New Zealand specialists. ANZ J Surg 2015 Nov;85(11):797-798. [doi: 10.1111/ans.13266] [Medline: 26798858]
16. Elwyn G, Frosch D, Thomson R, Joseph-Williams N, Lloyd A, Kinnersley P, et al. Shared decision making: a model for clinical practice. J Gen Intern Med 2012 Oct;27(10):1361-1367 [FREE Full text] [doi: 10.1007/s11606-012-2077-6] [Medline: 22618581]
17. Oskay-Ozcelik G, Lehmacher W, Könsgen D, Christ H, Kaufmann M, Lichtenegger W, et al. Breast cancer patients' expectations in respect of the physician-patient relationship and treatment management results of a survey of 617 patients. Ann Oncol 2007 Mar;18(3):479-484 [FREE Full text] [doi: 10.1093/annonc/mdl456] [Medline: 17272832]
18. Brown R, Butow P, Wilson-Genderson M, Bernhard J, Ribi K, Juraskova I. Meeting the decision-making preferences of patients with breast cancer in oncology consultations: impact on decision-related outcomes. J Clin Oncol 2012 Mar 10;30(8):857-862 [FREE Full text] [doi: 10.1200/JCO.2011.37.7952] [Medline: 22312102]
19. Andersen MR, Bowen DJ, Morea J, Stein KD, Baker F. Involvement in decision-making and breast cancer survivor quality of life. Health Psychol 2009 Jan;28(1):29-37. [doi: 10.1037/0278-6133.28.1.29] [Medline: 19210015]
20. Passik SD, Kirsh KL, Rosenfeld B, McDonald MV, Theobald DE. The changeable nature of patients' fears regarding chemotherapy: implications for palliative care. J Pain Symptom Manage 2001 Feb;21(2):113-120. [Medline: 11226762]
21. Stacey D, Légaré F, Col NF, Bennett CL, Barry MJ, Eden KB, Wu Julie H C. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev 2014;1:CD001431. [doi: 10.1002/14651858.CD001431.pub4] [Medline: 24470076]
22. Volk RJ, Llewellyn-Thomas H, Stacey D, Elwyn G. Ten years of the International Patient Decision Aid Standards Collaboration: evolution of the core dimensions for assessing the quality of patient decision aids. BMC Med Inform Decis Mak 2013;13 Suppl 2:S1 [FREE Full text] [doi: 10.1186/1472-6947-13-S2-S1] [Medline: 24624947]
23. Zdenkowski N, Butow P, Tesson S, Boyle F. A systematic review of decision aids for patients making a decision about treatment for early breast cancer. Breast 2016 Apr;26:31-45. [doi: 10.1016/j.breast.2015.12.007] [Medline: 27017240]
24. Coulter A, Stilwell D, Kryworuchko J, Mullen PD, Ng CJ, van der Weijden T. A systematic development process for patient decision aids. BMC Med Inform Decis Mak 2013;13 Suppl 2:S2 [FREE Full text] [doi: 10.1186/1472-6947-13-S2-S2] [Medline: 24625093]
25. Trevena LJ, Zikmund-Fisher BJ, Edwards A, Gaissmaier W, Galesic M, Han PKJ, et al. Presenting quantitative information about decision outcomes: a risk communication primer for patient decision aid developers. BMC Med Inform Decis Mak 2013;13 Suppl 2:S7 [FREE Full text] [doi: 10.1186/1472-6947-13-S2-S7] [Medline: 24625237]
26. von Minckwitz G, Untch M, Blohmer J, Costa SD, Eidtmann H, Fasching PA, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012 May 20;30(15):1796-1804 [FREE Full text] [doi: 10.1200/JCO.2011.38.8595] [Medline: 22508812]
27. Caudle AS, Gonzalez-Angulo AM, Hunt KK, Liu P, Pusztai L, Symmans WF, et al. Predictors of tumor progression during neoadjuvant chemotherapy in breast cancer. J Clin Oncol 2010 Apr 10;28(11):1821-1828 [FREE Full text] [doi: 10.1200/JCO.2009.25.3286] [Medline: 20231683]

28. Fagerlin A, Pignone M, Abhyankar P, Col N, Feldman-Stewart D, Gavaruzzi T, et al. Clarifying values: an updated review. BMC Med Inform Decis Mak 2013;13 Suppl 2:S8 [FREE Full text] [doi: 10.1186/1472-6947-13-S2-S8] [Medline: 24625261]
29. Juraskova I, Butow P, Bonner C, Bell ML, Smith AB, Seccombe M, et al. Improving decision making about clinical trial participation - a randomised controlled trial of a decision aid for women considering participation in the IBIS-II breast cancer prevention trial. Br J Cancer 2014 Jul 8;111(1):1-7 [FREE Full text] [doi: 10.1038/bjc.2014.144] [Medline: 24892447]
30. O'Connor AM. Validation of a decisional conflict scale. Med Decis Making 1995;15(1):25-30. [Medline: 7898294]
31. Cassileth BR, Zupkis RV, Sutton-Smith K, March V. Information and participation preferences among cancer patients. Ann Intern Med 1980 Jun;92(6):832-836. [Medline: 7387025]
32. Marteau T, Bekker H. The development of a six-item short-form of the state scale of the Spielberger State—Trait Anxiety Inventory (STAI). Br J Clin Psychol 1992;31(3):301-306. [doi: 10.1111/j.2044-8260.1992.tb00997.x] [Medline: 1393159]
33. Mehnert A, Berg P, Henrich G, Herschbach P. Fear of cancer progression and cancer-related intrusive cognitions in breast cancer survivors. Psychooncology 2009 Dec;18(12):1273-1280. [doi: 10.1002/pon.1481] [Medline: 19267364]
34. Brehaut JC, O'Connor AM, Wood TJ, Hack TF, Siminoff L, Gordon E, et al. Validation of a decision regret scale. Med Decis Making 2003;23(4):281-292. [Medline: 12926578]
35. Simard S, Savard J. Fear of Cancer Recurrence Inventory: development and initial validation of a multidimensional measure of fear of cancer recurrence. Support Care Cancer 2009 Mar;17(3):241-251. [doi: 10.1007/s00520-008-0444-y] [Medline: 18414902]
36. Hegel MT, Collins ED, Kearing S, Gillock KL, Moore CP, Ahles TA. Sensitivity and specificity of the Distress Thermometer for depression in newly diagnosed breast cancer patients. Psychooncology 2008 Jun;17(6):556-560 [FREE Full text] [doi: 10.1002/pon.1289] [Medline: 17957755]
37. Mitchell AJ. Pooled results from 38 analyses of the accuracy of distress thermometer and other ultra-short methods of detecting cancer-related mood disorders. J Clin Oncol 2007 Oct 10;25(29):4670-4681 [FREE Full text] [doi: 10.1200/JCO.2006.10.0438] [Medline: 17846453]
38. Holmes-Rovner M, Kroll J, Schmitt N, Rovner DR, Breer ML, Rothert ML, et al. Patient satisfaction with health care decisions: the satisfaction with decision scale. Med Decis Making 1996;16(1):58-64. [Medline: 8717600]
39. Neergaard MA, Olesen F, Andersen RS, Sondergaard J. Qualitative description - the poor cousin of health research? BMC Med Res Methodol 2009;9:52 [FREE Full text] [doi: 10.1186/1471-2288-9-52] [Medline: 19607668]
40. Molenaar S, Sprangers MA, Postma-Schuit FC, Rutgers EJ, Noorlander J, Hendriks J, de Haes H C. Feasibility and effects of decision aids. Med Decis Making 2000;20(1):112-127. [Medline: 10638544]
41. Kryworuchko J, Stacey D, Bennett C, Graham ID. Appraisal of primary outcome measures used in trials of patient decision support. Patient Educ Couns 2008 Dec;73(3):497-503. [doi: 10.1016/j.pec.2008.07.011] [Medline: 18701235]
42. Sepucha KR, Borkhoff CM, Lally J, Levin CA, Matlock DD, Ng CJ, et al. Establishing the effectiveness of patient decision aids: key constructs and measurement instruments. BMC Med Inform Decis Mak 2013;13 Suppl 2:S12 [FREE Full text] [doi: 10.1186/1472-6947-13-S2-S12] [Medline: 24625035]
43. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011 Dec;20(10):1727-1736 [FREE Full text] [doi: 10.1007/s11136-011-9903-x] [Medline: 21479777]
44. Bekker HL, Legare F, Stacey D, O'Connor A, Lemyre L. Is anxiety a suitable measure of decision aid effectiveness: a systematic review? Patient Educ Couns 2003 Jul;50(3):255-262. [Medline: 12900095]
45. Silvia KA, Sepucha KR. Decision aids in routine practice: lessons from the breast cancer initiative. Health Expect 2006 Sep;9(3):255-264. [doi: 10.1111/j.1369-7625.2006.00393.x] [Medline: 16911140]
46. Passalacqua R, Caminiti C, Salvagni S, Barni S, Beretta GD, Carlini P, et al. Effects of media information on cancer patients' opinions, feelings, decision-making process and physician-patient communication. Cancer 2004 Mar 1;100(5):1077-1084 [FREE Full text] [doi: 10.1002/cncr.20050] [Medline: 14983505]
47. O'Brien MA, Charles C, Whelan TJ, Ellis PM, Gafni A, Lovrics P. Women's perceptions of their involvement in treatment decision making for early stage breast cancer. Support Care Cancer 2013 Jun;21(6):1717-1723. [doi: 10.1007/s00520-013-1718-6] [Medline: 23344655]
48. Entwistle VA, Carter SM, Cribb A, McCaffery K. Supporting patient autonomy: the importance of clinician-patient relationships. J Gen Intern Med 2010 Jul;25(7):741-745 [FREE Full text] [doi: 10.1007/s11606-010-1292-2] [Medline: 20213206]

Abbreviations

DA: decision aid
ER: estrogen receptor
EQ-5D-5L: EuroQol 5-dimension, 5-level health status measure
HER2: human epidermal growth receptor 2
NAST: neoadjuvant systemic therapy
PR: progesterone receptor

Edited by G Eysenbach; submitted 16.02.16; peer-reviewed by L Lowenstein; comments to author 28.03.16; revised version received 30.03.16; accepted 30.03.16; published 20.05.16.

Please cite as:
Zdenkowski N, Butow P, Hutchings E, Douglas C, Coll JR, Boyle FM
A Decision Aid for Women Considering Neoadjuvant Systemic Therapy for Operable Invasive Breast Cancer: Development and Protocol of a Phase II Evaluation Study (ANZ1301 DOMINO)
JMIR Res Protoc 2016;5(2):e88
URL: http://www.researchprotocols.org/2016/2/e88/
doi:10.2196/resprot.5641
PMID:27207563

Protocol

The Sandwich Generation Diner: Development of a Web-Based Health Intervention for Intergenerational Caregivers

Ann M Steffen[1*], PhD; Joel Epstein[2*], PhD; Nika George[3], PhD; Megan MacDougall[1], MA

[1]Department of Psychological Sciences, University of Missouri-St. Louis, St. Louis, MO, United States

[2]Missouri Institute of Mental Health, University of Missouri-St. Louis, St. Louis, MO, United States

[3]St. Louis VA Medical Center, St. Louis, MO, United States

[*]these authors contributed equally

Corresponding Author:
Ann M Steffen, PhD
Department of Psychological Sciences
University of Missouri-St. Louis
325 Stadler Hall
One University Blvd
St. Louis, MO, 63121
United States
Phone: 1 314 516 5382
Fax: 1 314 516 5392
Email: ann_steffen@umsl.edu

Abstract

Background: Women are disproportionately likely to assist aging family members; approximately 53 million in the United States are involved with the health care of aging parents, in-laws, or other relatives. The busy schedules of "sandwich generation" women who care for older relatives require accessible and flexible health education, including Web-based approaches.

Objective: This paper describes the development and implementation of a Web-based health education intervention, The Sandwich Generation Diner, as a tool for intergenerational caregivers of older adults with physical and cognitive impairments.

Methods: We used Bartholomew's Intervention Mapping (IM) process to develop our theory-based health education program. Bandura's (1997) self-efficacy theory provided the overarching theoretical model.

Results: The Sandwich Generation Diner website features four modules that address specific health care concerns. Our research involves randomly assigning caregiver participants to one of two experimental conditions that are identical in the type of information provided, but vary significantly in the presentation. In addition to structured Web-based assessments, specific website usage data are recorded.

Conclusions: The Sandwich Generation Diner was developed to address some of the informational and self-efficacy needs of intergenerational female caregivers. The next step is to demonstrate that this intervention is: (1) attractive and effective with families assisting older adults, and (2) feasible to embed within routine home health services for older adults.

(JMIR Res Protoc 2016;5(2):e91) doi:10.2196/resprot.5488

KEYWORDS

intergenerational relations; health education; caregivers; intervention studies; Internet

Introduction

Background

Researchers are faced with minimal operational guidance when attempting to develop complex interventions to reduce the gap between clinical evidence and behavioral practice [1]. There is, however, a growing recognition that behavioral-health interventions should be grounded upon a solid theoretical framework [2]. Not only are theory-based interventions more likely to be effective, they can also provide an understanding of causal pathways for change [2]. Unfortunately, although there are numerous behavioral-health theories to draw upon, it is challenging to translate these theories into practical interventions [2,3].

In an effort to address these issues, Bartholomew [4] developed an Intervention Mapping (IM) protocol that provides a process

for developing theory-based health education programs. In IM, researchers use these six iterative and reciprocal tasks to create their interventions: (1) assessing the problem, (2) specifying program objectives, (3) identifying theory- and evidence-based behavior change methods, (4) creating the intervention, (5) planning the implementation, and (6) planning the evaluation [5]. In this article, we describe the development of our *Sandwich Generation Diner* intervention for intergenerational caregivers within the context of the IM framework.

Intervention Mapping Step 1: Assessing the Problem

Prevalence and Correlates of Medication Nonadherence in Older Adults

Older adults have more chronic medical conditions and a corresponding higher rate of medication use, spending three times the national average for prescription drugs [6]. Although some do an excellent job of managing their medications, a significant number have difficulty with this task. Medication mismanagement and errors may have dire consequences for seniors, including a higher risk for falls, delirium, excess disability, hospitalizations, and death [7].

The Role of Family Involvement in Medication-Related Behaviors

Many older adults have close reciprocal relationships with younger members of their family, and due to physical or cognitive limitations, receive assistance with health care visits and medication management. There are an estimated 3.3 million older adults in the United States who receive assistance with both physician visits and prescribed medications, and these are a high-need group [8]. More than 75% of this population require aid with mobility, self-care, or household activities, and approximately 60% have possible or probable dementia. Involvement by a family care partner typically persists over time, and is more likely to be a younger female family member rather than a spouse [8]. Women make approximately 80% of health care decisions for their families and are more likely than men to be the caregiver when an older family member is ill [9]. Although caring for an older relative may have negative impacts on women's mental and physical health, caregivers often view their role as deeply meaningful [10].

Health Education for Intergenerational Caregivers

Few community-based health education programs offer support explicitly targeting intergenerational caregivers [10-12]. Those that are available have significant limitations. Community-based programs are often inaccessible or burdensome due to the care recipient's need for ongoing supervision. In-home programs can affect a number of care outcomes, but also include challenges such as the cost of individualized services and staff travel. Psychoeducational groups may be helpful, but they require participants to travel to the program. Consequently, the "sandwich generation" women who care for older relatives require more accessible and flexible health education approaches than is generally available.

Intervention Mapping Step 2: Specifying Program Objectives

Web-Based Health Education

Technological advances have created new opportunities for reaching consumers through Web-based and other distance-based health education and support [13-15]. The Internet has become an important source of health information. Eighty percent of internet users, and 59% of the US population, look on the Internet for health information [16]. The proportion of adults aged 65 and older who use the Internet to search for information has grown to 53%; of these, 70% report using the Internet daily [17]. As providers continue to adopt eHealth technologies, the range of activities for consumers to participate in their health care continues to expand and includes everything from engaging in condition-specific discussions to entering information in personal health records [18]. Not only does participating in Web-based health care programs provide clear benefits in terms of wellness, it can also result in increased motivation and self-efficacy for managing care [19].

Receipt of Grant Award

Our team has had a long history of developing eHealth interventions including an interactive public education exhibit, continuing education courseware, and smartphone apps [20,21]. These efforts, along with our experience developing video-based interventions for dementia caregivers [14,15,22] led to an award from the authors' university.

The primary aims for our project were to: (1) increase caregivers' knowledge and use of effective medication management strategies, (2) decrease medication-related hassles perceived by women caring for an older relative, and (3) decrease rates of adverse medication-related events for older care recipients. We assembled a diverse work group from units on campus (ie, Psychological Sciences, Gerontology, and the Missouri Institute of Mental Health) as well as a community advisory board and an interdisciplinary panel of consultants to assist with study content and dissemination.

Methods

Intervention Mapping Step 3: Identifying Theory- and Evidence-Based Behavior Change Methods

In their meta-analysis of the features of effective Web-based health promotion interventions, Lustria et al [13] describe the importance of grounding programs in empirically supported theories of change. Davis and colleagues [2] argue that many of these theories provide little guidance regarding how to translate underlying concepts into practical interventions. Bandura's Social Cognitive Theory (SCT) [23] is a notable exception. Bandura states that learning occurs in a social context and is shaped by reciprocal relationships between the person, environment, and behavior. SCT involves a heavily agentic perspective, in which individuals are seen as goal-directed and exert intentional influence over their functioning; these intentional actions then impact the course of events. A number of principles are incorporated within this theory, including reciprocal determinism (interaction of person, environment, and

behavior), behavioral capacity (actual ability to perform a behavior through knowledge and skills), observational learning, reinforcements, outcome expectations, and self-efficacy [23]. The construct of self-efficacy is an important facet of SCT, and refers to beliefs in one's ability to execute courses of actions to manage situations important within a specific life domain. In Bandura's theory, self-efficacy beliefs influence whether coping efforts will be initiated, how much effort will be invested, how long effort is sustained in the face of aversive experiences and obstacles, and affect vulnerability to emotional distress. Self-efficacy beliefs can be shaped by various means including mastery experiences, social observation, and social persuasion [24].

In the area of aging, the model has been applied to understanding dementia family caregiving [25] and medication adherence [26]. When individuals face health-related caregiving challenges, those with low self-efficacy focus on negative aspects of the situation (eg, personal deficiencies, task difficulties). In essence, they "lose heart." This focus on negative cognitions reduces motivation to initiate an activity, impacts task persistence, and leads to negative affective states, which then perpetuates the cycle [27].

Because Bandura argues that self-efficacy can be improved via social observation, many interventions attempt to promote behavior change by increasing self-efficacy through observational learning of similar others. These interventions often use dramatic enactments of scenarios that the target audience may face in their daily lives. By identifying with and watching others successfully master challenges, viewers gain an improved sense of their own mastery. Using this model, researchers have successfully used serial radio dramas to improve human immunodeficiency virus outcomes [28,29]. Our own work has demonstrated the benefits of video-based stories for improving knowledge of substance abuse [30].

Based on this prior validation, we chose to ground our current intervention on Bandura's SCT, with a particular focus on influencing the caregiving self-efficacy beliefs of intergenerational caregivers. We incorporated a number of elements of SCT, while aiming to: (1) acknowledge the importance of social context by distinguishing among skills needed in different caregiving situations, (2) influence behavioral capacity through instruction in specific health care management and interpersonal communication skills, (3) foster observational learning through serial video narratives of caregivers, and (4) enhance self-efficacy beliefs by developing story lines that show characters mastering progressively more challenging situations. We hypothesized that individuals who viewed true-to-life vignettes of individuals successfully overcoming difficulties providing care for their elderly family members would demonstrate improved outcomes as compared with individuals who received information presented in a more didactic format.

Intervention Mapping Step 4: Creating the Intervention

Content Outlines

We began our development efforts by creating detailed content outlines of the information we wanted to convey to our target audience. We had a team of expert consultants including pharmacists and nurse practitioners, as well as social work, psychology, and public health professionals consult with us about the most common difficulties associated with health care and medication management in older adults. We cross-referenced these content areas with existing behavioral health literature regarding best practice guidelines. We then included the overlapping recommendations as final content to be included in the intervention script, making sure to couch them within the context of social cognitive theory (eg, selecting situations identified as common challenges, developing the vignettes to show an increase in challenge/difficulty over the narrative, linking the behaviors of the characters to specific skills, having the characters demonstrate mastery at the end). This process resulted in the creation of four subject areas: (1) medication management, (2) recognizing and responding to alterations in cognition (delirium and dementia), (3) managing health care appointments and communication with providers, and (4) communication and planning strategies for family members.

Development of Creative Approach

With the content clearly articulated, we were ready to develop the overarching creative approach for our intervention. In past work, we discovered that developing an underlying story or metaphor to convey our content helped to increase participant engagement. For example, in one of our early educational programs designed to teach students about the biology of addiction, we embedded our learning objectives within a narrative story about aliens coming to Earth to learn how to play basketball [31].

For the current intervention, we needed to develop a creative approach that would not only engage our target audience (middle-aged women caring for elderly family members), but would also reflect a diverse set of demographic characteristics. During a series of brainstorming sessions, we finally settled upon the idea of our intervention taking place in a diner with a wise and seasoned waitress serving as the primary character. Through interactions with her various customers, viewers would be able to see various health care challenges being overcome.

Script Writing

It was only after the content and creative approach were finalized that we were able to begin writing the intervention's scripts. For each of the four content modules, we structured the story to evolve over the course of five separate vignettes. Each story began with the waitress character introducing the primary dilemma the characters were facing. Then, in each subsequent vignette, the characters demonstrated a growing sense of efficacy in their ability to solve the problems they were having while caring for their family members. In order to increase the likelihood of participants watching the vignettes, each is less than 4-minutes long.

Review of Intervention Plans

When the scripts for each module were completed, we engaged in a second round of expert consultation. Once again, we used our interdisciplinary approach to discuss the relevance, use, and goals of this portion of our intervention. After completing suggested modifications to the script, we presented it to a small group of selected "beta testers." These individuals were lay persons unaffiliated with the intervention who we asked to review the scripts for readability and clarity of the dialogue. We incorporated this group's suggestions into the final script.

Content Acquisition

After completing the scripts, we then created detailed storyboards for our Web-based intervention. Following these specifications, we produced custom graphics for the program's logo and interface. In this way, we were able to "brand" our intervention with an engaging appearance and name – "Sandwich Generation Diner." We used these graphics for all materials associated with the intervention (eg, marketing pieces, downloadable files, etc).

The scripts themselves called for a number of characters across a broad set of demographic characteristics. Through advertisements on local actor's message boards, word of mouth, and notes to previous actors we had worked with in the past, we assembled a pool of candidates to appear in our production. We then used a series of phone and live auditions to settle upon the final cast.

In order to improve the authenticity of our production, we placed a special emphasis on finding the perfect location at which to shoot our videos. We eventually arranged with the management of a local diner and were able to use their space for eight, after-hours sessions during the course of a single month. In addition to providing us authentic props, the management also cooked us the food that was specified in the script.

We asked the actors to memorize their lines; prior to shooting each scene, we had them run their lines in place. This procedure reduced rehearsal time and facilitated the production process. For each scene, we recorded both wide and close-up shots. Although this process required the actors to deliver their lines multiple times, it also provided us with multiple options for editing the final footage.

Coding

Because we wanted to roll out our intervention to participants across the course of a month, we needed to develop a solution that allowed for flexibility in the way our content would be displayed and delivered. In the end we chose to create a WordPress site and assigned all participants a unique login. By using the s2Member plug-in, we were able to code the site in such a way that it would modify its display according to the credentials we assigned each user. This procedure allowed us to set user's access levels in terms of being part of the control or experimental condition and how far along they were in the intervention protocol. Each week, we increased the participants' access level so that they would automatically see subsequent portions of the intervention.

Results

Program Description

Regardless of experimental condition to which they were assigned, all participants log onto our site and are automatically presented with the appropriate content based on their user credentials. By manipulating user's access levels in the website's control panel, we have been able to sequentially roll out the intervention across 4 weeks (Phase I) and test impact of accessing all intervention materials at once (Phase II). To encourage viewing of our materials, we send weekly reminder emails to the participants.

The overall appearance of our site is largely the same for participants in both the Narrative Vignette and Comparison Didactic conditions. See Multimedia Appendix 1 for a screen shot of our site's main menu. After clicking on one of the primary content areas, participants are presented one of the submenus illustrated in Multimedia Appendix 2. Although participants in both groups have access to the didactic portable document format (PDF) informational sheets (see Multimedia Appendix 3) and talking head expert videos (see Multimedia Appendix 4) presented in the left column, only participants in the Narrative condition have access to the scripted vignettes (described above and illustrated in Multimedia Appendix 5). Although all links are visible throughout the entire intervention period, we sequentially enable them throughout the course of an individual participant's 4-week trial. Participants are free to choose to view the information in any order and spend as much or little time on the site as they would like.

Health Education Content

In keeping with the self-efficacy literature, we developed storylines consistent with common situations and needs of intergenerational female caregivers. Actors were selected who represented our target demographics for this study.

Managing Medications

This content area includes a discussion of adverse events linked to medications (eg, falls, delirium, nursing home placement, negative health outcomes), and provides information about the most effective ways to manage scheduling of doses and refills. This module also includes psychoeducation about the role a pharmacist can play in medication management problem solving, as well as a list of basic and advanced questions that can be used to help improve medication management and organizational skills. The module also provides further information about the benefits of assessing interaction effects of over-the-counter medications with prescriptions that the care recipient already takes. The module highly encourages consultation with pharmacy staff.

Signs of Confusion

Given that caregivers of older adults with undiagnosed cognitive impairment may not know how thinking abilities relate to medication management, this content area provides participants with information about the signs and symptoms of delirium and dementia, as well as ways to distinguish the two. Caregivers are given information about the high rates of undiagnosed

delirium and dementia in community-dwelling older adults and the benefits of medical evaluation and diagnosis. The module also presents information about the process for obtaining a diagnosis for a progressively dementing neurocognitive illness, including material about brief cognitive screens and neuropsychological testing.

Health Care Visits

This content area provides caregivers with information about how to prepare for health care visits that they attend with their loved one. Caregivers are given a list of example questions they can ask medical providers about current medications, newly prescribed medications, over the counter medications, and side-effects. This module also addresses legal and Health Insurance Portability and Accountability Act (HIPAA) barriers to full communication between family members and health care professionals. The content area explains the need for signed releases on file in the patient's chart to allow these conversations and provides an example of a nationally available form for durable power of attorney for health care, named "Five Wishes."

Talking Together

This content area focuses on developing communication skills between the caregiver and care recipient. Caregivers are given instruction on how to use basic communication strategies such as eye contact, tone, and "I" language. This module also provides examples of medication-related conflict between the caregiver and care recipient, and offers suggestions for effective communication strategies when negotiating these disagreements. In addition, caregivers are encouraged to use these communication skills when discussing potentially conflictual topics such as housing, financial planning, driving, and health care plans. This module also addresses legal and HIPAA requirements for full communication between family members and health care professionals.

Intervention Mapping Step 5: Planning the Implementation

Our goal is to demonstrate that this intervention is (1) attractive and effective with families assisting older adults enrolled in home health care (a medically vulnerable population), and is (2) feasible to embed within routine home health services for older adults. We aim to evaluate the intervention's impact on family–clinician communication and reported caregiving self-efficacy and role overload. The original funding source (an internal grant from the investigators' university) supported the development of the Web-based intervention and collection of pilot data.

Intervention Mapping Step 6: Planning the Evaluation

We first developed a preliminary evaluation with a community sample. Initial pilot data supporting the intervention will be valuable in developing collaborative relationships with health care agencies and systems serving older adults.

Participants

Adult women providing informal care to an older adult are recruited through print advertisements placed in health care and community locations throughout a large Midwestern city, and through study announcements posted on social media. Interested individuals are directed to a brief Web-based screening survey.

Intervention Procedure

We email eligible participants who consent to the study a longer preintervention survey. Upon completion of the preintervention survey, we randomly assign participants to either the Narrative Vignette or Comparison Didactic condition. We use block randomization to balance dementia caregivers and nondementia caregivers across study conditions. After randomization, we email participants with their unique login and password along with instructions for using the website. We also instruct them not to allow anyone else to log in to the website using their credentials.

During the 4-week intervention period, we send participants weekly emails. At the end of their trial, we send participants a postintervention assessment survey, and a 1-month follow-up survey. We then conduct a brief phone interview to collect qualitative data. For participants who had been in the Comparison Didactic condition, we then allow them to have access to the narrative vignettes. Finally, 6 months after completing the intervention, we invite participants to complete another brief follow-up Web-based assessment.

Participants complete Web-based assessments at preintervention, postintervention, 1-month follow-up, and 6-month follow-up. We collect descriptive information about the participant's caregiving situation and demographic information about the caregiver and care recipient. Measures include medication risk [32], falls, and the Centers for Disease Control Healthy Days for the care recipient [33], caregiving medication administration hassles [34], role overload [35], self-efficacy beliefs [25], and family–health care provider communication [36]. We gather qualitative data about project feedback via a brief phone interview 1 month after completing the intervention. Participants receive US$25 gift cards after completing each of the assessments. Participant's website usage is automatically tracked including information about the dates and times of website use and any downloads of Web-based material over the study period.

We are presently in the data collection phase of this process, and initial participant characteristics and satisfaction ratings are promising. Caregiver participants (N=137) are ethnically diverse at 31% (43/137) non-White compared with 26% of US residents being non-White. Participants predominantly care for a frail parent, with 85% (117/137) being a daughter or daughter-in-law of the older adult. Caregivers engaged in significant medical management tasks for older adults with a number of chronic and comorbid health conditions. Participants reported satisfaction with the intervention (mean=5.65, standard deviation= .97) on a 7-point scale with a score of 7 being most satisfied.

Discussion

Summary

We developed and are currently evaluating an eHealth intervention (in a randomized trial format) for female intergenerational family caregivers actively involved with the health care of an older relative. Both conditions are designed

to improve medication management and related health care behaviors in informal caregivers of older persons with physical and/or cognitive impairments. The didactic comparison condition contains a series of downloadable PDF "Handouts" with information about managing medications, attending a health care visit, causes of confusion in older adults, and communication with the older family member. Each section includes one video of an expert providing information in traditional didactic voice. The narrative vignette condition includes the same content as above, with additional serial Web episode storylines that show caregivers interacting with their loved one, and problem solving concerns in each of the aforementioned domains.

Program Strengths

Strengths of our program include a solid conceptual grounding of the intervention within self-efficacy theory [27], and creation of a flexible Web-based format that allows caregivers to explore health education content areas of most interest to them. We also believe that targeting intergenerational caregivers involved in medication management for older adults is novel and justified, given the literature describing differences between spousal caregivers and adult children in levels of frustration with these types of tasks [37]. Many studies show that caregivers have increased time constraints when compared with similar noncaregiving individuals [10]; the Web-based availability of our intervention materials may decrease the time investment necessary for caregivers to obtain aid [12].

Limitations and Lessons Learned

Because this study occurs over a relatively brief period (1 month), future research may benefit by extending the amount of follow-up contact and assessment points. This study has not implemented specific strategies to improve access for caregivers who are lower income or who demonstrate lower educational attainment. Such individuals generally have limited access to technological resources or may show lower general engagement with health care and health-related interventions. Future studies may explore the current barriers to technological access and eliminate these by providing other avenues to Internet resources (ie, library cards or rented tablets).

Conclusions

The *Sandwich Generation Diner* has been developed to address some of the informational and self-efficacy needs of intergenerational women caregivers. Within the IM framework, development of the *Sandwich Generation Diner* intervention involved: (1) assessing the problem, (2) specifying program objectives, (3) selecting an overarching theoretical model, (4) creating the intervention, (5) implementing the intervention, and (6) evaluating the intervention. Bandura's self-efficacy theory [27] provided the overarching theoretical model. The integration of serial narrative vignettes with multimedia resources is intended to result in a rich and meaningful intervention. We look forward to completion of the ongoing efficacy trial to evaluate the extent that we have accomplished these aims.

Acknowledgments

This work is supported by an award to the first two authors: "Medication Assistance by Intergenerational Caregivers of Older Adults: Online Health Education Approaches." University of Missouri-St. Louis Express Scripts Social Science Research Program, $249,871.

Conflicts of Interest

None declared.

Multimedia Appendix 1

[PNG File, 905KB - resprot_v5i2e91_app1.png]

Multimedia Appendix 2

[PNG File, 838KB - resprot_v5i2e91_app2.png]

Multimedia Appendix 3

[PDF File (Adobe PDF File), 93KB - resprot_v5i2e91_app3.pdf]

Multimedia Appendix 4

[MP4 File (MP4 Video), 20MB - resprot_v5i2e91_app4.mp4]

Multimedia Appendix 5

[MP4 File (MP4 Video), 15MB - resprot_v5i2e91_app5.mp4]

References

1. French SD, Green SE, O'Connor DA, McKenzie JE, Francis JJ, Michie S, et al. Developing theory-informed behaviour change interventions to implement evidence into practice: a systematic approach using the Theoretical Domains Framework. Implement Sci 2012;7:38 [FREE Full text] [doi: 10.1186/1748-5908-7-38] [Medline: 22531013]
2. Davis R, Campbell R, Hildon Z, Hobbs L, Michie S. Theories of behaviour and behaviour change across the social and behavioural sciences: a scoping review. Health Psychol Rev 2015;9:323-344 [FREE Full text] [doi: 10.1080/17437199.2014.941722] [Medline: 25104107]
3. Kok G, Schaalma H, Ruiter RAC, van Empelen P, Brug J. Intervention mapping: protocol for applying health psychology theory to prevention programmes. J Health Psychol 2004;9:85-98. [doi: 10.1177/1359105304038379] [Medline: 14683571]
4. Bartholomew LK, Parcel GS, Kok G. Intervention mapping: a process for developing theory- and evidence-based health education programs. Health Educ Behav 1998;25:545-563. [Medline: 9768376]
5. Kok G, Bartholomew LK, Parcel GS, Gottlieb NH, Fernández ME. Finding theory- and evidence-based alternatives to fear appeals: Intervention Mapping. Int J Psychol 2014;49:98-107 [FREE Full text] [doi: 10.1002/ijop.12001] [Medline: 24811880]
6. Murray MD, Callahan CM. Improving medication use for older adults: an integrated research agenda. Ann Intern Med 2003;139(Pt 2):425-429. [Medline: 12965970]
7. Bates DW. Preventing medication errors: a summary. Am J Health Syst Pharm 2007;64(Suppl 9):S3-S9; quiz S24. [doi: 10.2146/ajhp070190] [Medline: 17617512]
8. Wolff JL, Spillman B. Older adults receiving assistance with physician visits and prescribed medications and their family caregivers: prevalence, characteristics, and hours of care. J Gerontol B Psychol Sci Soc Sci 2014;Suppl 1:S65-S72 [FREE Full text] [doi: 10.1093/geronb/gbu119] [Medline: 25342825]
9. Wang H. 65+ in the United States: 2005. Washington, DC: US Census Bureau; 2005.
10. Schulz R, Martire LM. Family caregiving of persons with dementia: prevalence, health effects, and support strategies. Am J Geriatr Psychiatry 2004;12:240-249 [FREE Full text] [Medline: 15126224]
11. Gallagher-Thompson D, Coon DW. Evidence-based psychological treatments for distress in family caregivers of older adults. Psychol Aging 2007;22:37-51. [doi: 10.1037/0882-7974.22.1.37] [Medline: 17385981]
12. Steffen A, Gant J, Gallagher-Thompson D. Reducing psychosocial distress in family caregivers. Handbook of behavioral and cognitive therapies with older adults e-book. New York: Springer Science + Business Media; 2008:102-117.
13. Lustria MLA, Noar SM, Cortese J, Van Stee SK, Van Stee SK, Glueckauf RL, et al. A meta-analysis of web-delivered tailored health behavior change interventions. J Health Commun 2013;18:1039-1069. [doi: 10.1080/10810730.2013.768727] [Medline: 23750972]
14. Steffen AM. Anger management for dementia caregivers: a preliminary study using video and telephone interventions. Behavior Therapy 2000;31:281-299. [doi: 10.1016/S0005-7894(00)80016-7]
15. Steffen AM, Gant JR. A telehealth behavioral coaching intervention for neurocognitive disorder family carers. Int J Geriatr Psychiatry 2015 [FREE Full text] [doi: 10.1002/gps.4312] [Medline: 26077904]
16. Fox S. Who doesn't gather health information online? Pew Research Center 2011 [FREE Full text]
17. Smith A. Older adults and internet usage. Pew Research Center 2012 [FREE Full text]
18. Chan CV, Kaufman DR. A framework for characterizing eHealth literacy demands and barriers. J Med Internet Res 2011;13:e94 [FREE Full text] [doi: 10.2196/jmir.1750] [Medline: 22094891]
19. Solomon M, Wagner SL, Goes J. Effects of a Web-based intervention for adults with chronic conditions on patient activation: online randomized controlled trial. J Med Internet Res 2012;14:e32 [FREE Full text] [doi: 10.2196/jmir.1924] [Medline: 22353433]
20. Epstein J, Sage L, Wedding D. A multimedia program to educate the public about mental and addictive disorders. Behavior Research Methods, Instruments, & Computers 1995;27:289-292. [doi: 10.3758/BF03204748]
21. Epstein J. Bacon Brains: video games for teaching the science of addiction. Journal of Child and Adolescent Substance Abuse 2017 (forthcoming).
22. Gant JR, Steffen AM, Lauderdale SA. Comparative outcomes of two distance-based interventions for male caregivers of family members with dementia. Am J Alzheimers Dis Other Demen 2007;22:120-128. [doi: 10.1177/1533317506298880] [Medline: 17545139]
23. Bandura A. Social cognitive theory: an agentic perspective. Annu Rev Psychol 2001;52:1-26. [doi: 10.1146/annurev.psych.52.1.1] [Medline: 11148297]
24. Bandura A. Health promotion by social cognitive means. Health Educ Behav 2004;31:143-164. [doi: 10.1177/1090198104263660] [Medline: 15090118]
25. Steffen AM, McKibbin C, Zeiss AM, Gallagher-Thompson D, Bandura A. The revised scale for caregiving self-efficacy: reliability and validity studies. J Gerontol B Psychol Sci Soc Sci 2002;57:P74-P86 [FREE Full text] [Medline: 11773226]
26. Risser J, Jacobson TA, Kripalani S. Development and psychometric evaluation of the Self-efficacy for Appropriate Medication Use Scale (SEAMS) in low-literacy patients with chronic disease. J Nurs Meas 2007;15:203-219. [Medline: 18232619]
27. Bandura A. Self-Efficacy: The Exercise Of Control. New York: W H Freeman/Times Books/ Henry Holt & Co; 1997.

28. Nambiar D, Ramakrishnan V, Kumar P, Varma R, Balaji N, Rajendran J, et al. Knowledge, stigma, and behavioral outcomes among antiretroviral therapy patients exposed to Nalamdana's radio and theater program in Tamil Nadu, India. AIDS Educ Prev 2011;23:351-366. [doi: 10.1521/aeap.2011.23.4.351] [Medline: 21861609]
29. Smith RA, Downs E, Witte K. Drama theory and entertainment education: exploring the effects of a radio drama on behavioral intentions to limit HIV transmission in Ethiopia. Communication Monographs 2007;74:133-153. [doi: 10.1080/03637750701393048]
30. Epstein J, Collins KK, Thomson NR, Pancella T, Pauley D. The doubles: evaluation of a substance abuse education curriculum for elementary school students. Journal of Child & Adolescent Substance Abuse 2007;16:1-22. [doi: 10.1300/J029v16n04_01]
31. Epstein J, Thomson NR, Collins KK, Pancella T. A longitudinal comparison of two versions of an interactive multimedia substance abuse education program. Journal of Child & Adolescent Substance Abuse 2009;18:302-321. [doi: 10.1080/10678280902973286]
32. Levy HB, Steffen AM. Validating the Medication Risk Questionnaire with family caregivers of older adults. The Consultant Pharmacist 2016;31:321-329 (forthcoming).
33. Centers for Disease Control and Prevention: Measuring Healthy Days: Population Assessment of Health Related Quality of Life. 2000. URL: http://www.cdc.gov/hrqol/pdfs/mhd.pdf [accessed 2016-04-28] [WebCite Cache ID 6h7CxfYSw]
34. Travis SS, Bernard MA, McAuley WJ, Thornton M, Kole T. Development of the family caregiver medication administration hassles scale. Gerontologist 2003;43:360-368. [Medline: 12810899]
35. Aneshensel C, Pearlin L, Mullan J, Zarit S, Whitlatch C. Profiles In Caregiving: The Unexpected Career. San Diego: Academic Press; 1995.
36. Lorig K, Stewart A, Ritter P, González V, Laurent D, Lynch J. Construction of Measures of Behaviors, Self-Efficacy and Outcomes. In: Outcome Measures for Health Education and other Health Care Interventions. Thousand Oaks, CA: Sage Publications; 1996:10-33.
37. Steffen AM, Berger S. Relationship differences in anger intensity during caregiving-related situations. Clinical Gerontologist 2000;21:3-19 [FREE Full text] [doi: 10.1300/J018v21n02_02]

Abbreviations

HIPPA: Health Insurance Portability and Accountability Act
IM: intervention mapping
PDF: portable document format
SCT: social cognitive theory

Edited by G Eysenbach; submitted 31.12.15; peer-reviewed by G Kok, D Kaufman, M Solomon; comments to author 31.01.16; revised version received 19.02.16; accepted 20.02.16; published 06.06.16.

Please cite as:
Steffen AM, Epstein J, George N, MacDougall M
The Sandwich Generation Diner: Development of a Web-Based Health Intervention for Intergenerational Caregivers
JMIR Res Protoc 2016;5(2):e91
URL: http://www.researchprotocols.org/2016/2/e91/
doi:10.2196/resprot.5488
PMID:27269632

Protocol

Attitudes to and Understanding of Risk of Acquisition of HIV Over Time: Design and Methods for an Internet-based Prospective Cohort Study Among UK Men Who Have Sex With Men (the AURAH2 Study)

Janey Sewell[1], BNurs; Andrew Speakman[1], PhD; Andrew N Phillips[1], PhD; Valentina Cambiano[1], PhD; Fiona C Lampe[1], PhD; Richard Gilson[1], MBBS; David Asboe[2], MBBS; Nneka Nwokolo[2], MBBS; Amanda Clarke[3], MBBS; Ali Ogilvy[2], BNurs; Simon Collins[4]; Alison J Rodger[1], MBBS

[1]Department of Infection and Population Health, UCL, London, United Kingdom
[2]Chelsea and Westminster Hospital NHS Foundation Trust, London, United Kingdom
[3]Brighton and Sussex University Hospitals NHS Trust, Brighton, United Kingdom
[4]HIV i-Base, London, United Kingdom

Corresponding Author:
Janey Sewell, BNurs
Department of Infection and Population Health
UCL
Royal Free Campus
London, NW3 2PF
United Kingdom
Phone: 44 07792096376
Fax: 44 20 3758 2000
Email: j.sewell@ucl.ac.uk

Abstract

Background: The annual number of new human immunodeficiency virus (HIV) infections among men who have sex with men (MSM) has risen in the United Kingdom and, of those who are HIV positive, the proportion undiagnosed is high.

Objective: The prospective AURAH2 study aims to assess factors associated with HIV acquisition among MSM in the United Kingdom and to investigate changes over time within individuals in sexual behavior and HIV-testing practices.

Methods: AURAH2 is a prospective study among MSM without diagnosed HIV, aiming to recruit up to 1000 sexually active MSM attending sexual health clinics in London and Brighton in the United Kingdom. Participants complete an initial paper-based questionnaire, followed by online follow-up questionnaires every 4 months collecting sociodemographic, health and behavioral data, including sexual behavior, recreational and other drug use, HIV testing practices, and pre-exposure prophylaxis use, over a planned 3-year period.

Results: The study is ongoing.

Conclusions: The results from AURAH2 study will provide important insight into established and emerging risk behaviors that may be associated with acquisition of HIV in MSM in the United Kingdom, changes over time within individuals in sexual behavior, and information on HIV testing practices. These data will be crucial to inform future HIV prevention strategies.

(JMIR Res Protoc 2016;5(2):e128) doi:10.2196/resprot.5582

KEYWORDS

HIV infection; HIV negative; HIV transmission; HIV testing; men who have sex with men; sexual risk behaviour; pre-exposure prophylaxis; recreational drug use; chemsex; HIV self-testing; health and well-being; study design

Introduction

Background

In 2014, the number of men who have sex with men (MSM) that were newly diagnosed with human immunodeficiency virus (HIV) continued to rise with 3360 new diagnoses in the United Kingdom [1]. Currently, there are an estimated 43,500 MSM living with HIV, of whom around 16% are undiagnosed [2]. It is thought that MSM unaware of their HIV infection disproportionately contribute to onward transmission (60-82% of new transmissions come from people not diagnosed [3,4]) and that delay in diagnosis and treatment is associated with increased risk to health [5]. HIV prevention approaches have historically focused on condom use, which, if correctly and consistently used, is a reliable and established method to reduce transmission [6]; however, consistent condom use is difficult to achieve [7,8]. There is a clear need for improved HIV prevention and testing strategies targeted at HIV negative MSM to reduce the number of new HIV infections and increase HIV testing rates.

The AURAH study was a cross-sectional questionnaire study that collected data from 2013-2014 in a large sample of HIV-negative patients attending Genito-Urinary Medicine (GUM) clinics in the United Kingdom with a focus on two populations: black Africans and MSM [9]. It used a self-completed questionnaire to assess knowledge of and attitudes to HIV transmission risks and the role of antiretroviral therapy (ART), and to assess the prevalence of medical and psychological symptoms (eg, depression and anxiety), quality of life, lifestyle factors (eg, drug and alcohol use), and possible links to sexual risk behaviors. The AURAH2 study will build on the work of the AURAH study and is the first large prospective observational study of MSM in the United Kingdom. It will provide longitudinal data on HIV transmission risk in a group of HIV negative (at enrollment) MSM using online questionnaires for data collection over a 3-year period. It will collect baseline socioeconomic, health and lifestyle information (including recreational drug use and chemsex) with longitudinal information on sexual activity, HIV testing, sexual behavior, and occurrence of new HIV infections among UK MSM.

Understanding attitudes of HIV negative or undiagnosed MSM towards condomless sex with individuals of unknown HIV status, and examining risk behavior in the context of psychological or general health status, history of sexually transmitted infection (STI), alcohol and drug use, could elucidate reasons for the observed ongoing HIV transmission among the UK MSM population. Studies have consistently found associations between increased sexual risk behavior, such as condomless anal sex and group sex [10-13], with recreational drug use, and longitudinal data has highlighted the bi-directional relationship between sexual pleasure and drug use [14]. Longitudinal data from Australia has demonstrated an association between drug use and increased risk of HIV infection, in particular the use of oral erectile dysfunction medication in combination with methamphetamines to enhance sexual pleasure [12], and similar evidence was recently reported from a US study that showed a clear link between increased sexual risk behavior and starting methamphetamine use [15]. Although not a new concept in the United States [16-18], a recent UK report on “chemsex” [19], which is defined as the use of certain sexually disinhibiting recreational drugs for facilitating or enhancing sex, has highlighted a need for more research into behaviors that put MSM at high risk of HIV and STI acquisition as a public health priority. Longitudinal data on recreational drug use, chemsex and associations with high risk sexual behaviors, such as group sex, in HIV negative or undiagnosed MSM would provide valuable insight into potential causes for the observed increases in HIV and STI acquisition among MSM in the United Kingdom.

Reducing the large proportion of MSM with undiagnosed HIV that potentially contribute to onward transmission of HIV is a public health priority [20], and data from HIV-negative or undiagnosed MSM in the United Kingdom are currently needed to inform and develop better provision of HIV testing options. Despite high coverage (86%) of HIV testing among MSM attending sexual health clinics [21], generally the frequency of HIV testing among UK MSM remains low (estimated 30% never tested, 75% not in past year) [4], and alternative ways to test for HIV, other than through sexual health clinics, are urgently required [1]. HIV self-testing (HIVST) was made legal in the United Kingdom in April 2015 [22] and is defined by the test being collected, performed, and interpreted in private by the individual who wants to know their HIV status [23]. HIVST has the potential to alleviate some of the perceived barriers to other forms of HIV testing, such as stigma, discrimination, and inaccessibility of health services [24], due to the environment the test is performed in, which may encourage more people to test. Increased HIV testing and resulting diagnoses could have prevention benefits if newly diagnosed men are more likely to use condoms and have fewer sexual partners after diagnosis [25,26]. However, it is not known whether the availability of HIVST will increase the diagnosis rates of HIV in the United Kingdom. The AURAH2 study will seek to collect information on the acceptability and uptake of HIVST as it becomes more widely available.

The expansion of HIV testing options is also of particular relevance since it was demonstrated that HIV transmission is preventable through ART in 2011 [27]. Evidence that ART greatly reduces onward sexual transmission of HIV in MSM [28], as well as heterosexuals [27,29], was demonstrated through the interim results of the PARTNER study [28]. Furthermore, the concept of treatment as prevention (TasP) has been widely explored as an HIV prevention strategy and is recommended in the British HIV Association’s treatment guidelines to prevent onward transmission [30]. However, access to and uptake of ART is dependent on a person knowing their HIV status and, in the United Kingdom, research has shown that although widespread ART coverage among MSM at a population level may reduce HIV infectivity, it is unlikely to reduce the number of HIV transmissions in the absence of increased coverage and frequency of HIV testing [31]. There is some evidence that sexual risk behavior declines after an HIV diagnosis, as it has been demonstrated that behavior is modified to prevent onward transmission [25,26]. However, this has not been explored in the context of TasP, and little is known regarding changes in

sexual behavior during primary HIV infection (a period characterized by very high infectiousness) and on the variability in sexual risk behavior over time at an individual level (eg, the duration of periods of very high risk). There are cohort studies of MSM that provide some information on these issues from Europe, the United States, and Australia [32-35]; however, there have been no follow-up studies among individuals at risk of HIV infection in the United Kingdom, which the AURAH2 study will seek to address. The role of TasP is also critical in HIV-negative MSM's sexual decision making and risk reduction behaviors and, as yet, is largely unexplored among UK HIV-negative MSM. Further investigation is needed, particularly in light of TasP, into the risk reduction strategies that HIV negative or undiagnosed MSM utilize at a community level [36], such as sero-sorting (choosing a partner of believed sero-concordant status), negotiated safety (condomless sex with a sero-concordant main partner), strategic positioning (choosing a different sexual position or practice depending on the sero-status of a partner), and withdrawal (in which the negative partner is receptive during intercourse but without ejaculation by his partner) [37]. To investigate the role of TasP in sexual decision making and risk reduction strategies, the AURAH2 study will collect data to inform on these themes, including information on knowledge of an HIV-positive partner's viral load. Collection of longitudinal data will help describe the sexual behaviors and risk reduction strategies among HIV negative MSM and assess the extent to which patterns of sexual behavior and condomless sex change over time within individuals. This information will play a key role when developing effective, targeted HIV prevention strategies.

A further significant development for HIV prevention strategies that the AURAH2 study will provide information on is pre-exposure prophylaxis (PrEP), which has been used as an HIV prevention tool for HIV-negative men in the United States since 2012 [38]. Although PrEP is not currently available on the UK National Health Service (NHS), generic formulations have been increasingly available via websites. In 2015, the results from the UK PROUD study [39] and the French IPERGAY study [40] demonstrated that daily [39] and "on demand" [40] dosing of Truvada, the antiretroviral tablet used for PrEP, reduced the risk of HIV acquisition in HIV-negative men by 86%. There has been increasing community [41] and clinical [42] pressure to make PrEP available through the NHS. New PrEP websites that have been developed by activists [43,44] acknowledge the potential to access PrEP in a number of different ways that include ordering it online, which may challenge how the access and uptake of PrEP is monitored and may lead people to obtain PrEP without the appropriate counselling and follow-up [42]. Self-reported changes in attitudes, access to, and use of PrEP and factors associated with PrEP use by HIV negative men in the United Kingdom will be vital to inform policy and inform on acceptability and uptake of PrEP in sexually active HIV-negative gay men.

The landscape of HIV prevention is changing as concepts such as TasP and PrEP are introduced, and advances in HIV testing technologies potentially make testing for HIV more accessible. In conjunction with evolving HIV prevention strategies, emerging patterns in lifestyle choices that affect sexual behavior are important to consider if current and effective HIV prevention interventions are to be designed and implemented. The information provided by the AURAH2 study will contribute to the understanding of the social, psychological, and health-related factors that are linked to high-risk sexual behaviors that potentiate transmission of HIV. The study will provide data highly relevant to HIV prevention efforts among MSM and will help inform national policies aimed at reducing HIV incidence and increasing HIV testing in the United Kingdom.

Study Aims and Objectives

The aim of the AURAH2 study is to evaluate the incidence and predictors of new infections among HIV-negative MSM at risk of acquiring HIV and to assess changes over time in risk behavior and testing practices within individuals.

The detailed study objectives are to assess:

1. In MSM without diagnosed HIV:

(i) the prevalence and correlates of specific sexual behaviors, including numbers of condomless sex partners, condomless sex with casual partners and partners of unknown HIV status, insertive/receptive condomless sex, and other specific higher-risk sexual activities such as group sex and chemsex

(ii) the number of condomless sex partners before, during, and after the estimated period of primary HIV-infection and time of HIV diagnosis in men who become infected during the study, as well as correlates of within-person changes in sexual behavior

(iii) the frequency and type of HIV testing accessed over time (sexual health clinic, self-testing, general practitioner, surgery, hospital, other)

2. The extent to which baseline demographic, socioeconomic, and health and lifestyle factors (including recreational drug use and chemsex) are predictive of subsequent levels of condomless sex, incident HIV infection, and HIV-testing behaviors

3. The association of attitudes to HIV transmission, disclosure, treatment, and prognosis, with high-risk sexual behaviors, HIV-testing behaviors, and subsequent HIV acquisition

4. The associations of participant characteristics, sexual behavior, and attitudes with reported use of, and willingness to consider use of, post exposure prophylaxis (PEP) and PrEP

Methods and Design

Study Design

AURAH2 is a prospective cohort study of UK MSM not diagnosed with HIV. Baseline information is collected on each participant through the AURAH study paper questionnaire [9], which is completed during a sexual health clinic attendance. Follow-up questionnaires are made available online every 4 months through the study website and consist of two brief and one extensive questionnaire per year. Online follow-up will continue for up to 3 years from the time a participant joined the study during the recruitment period in 2015.

Population and Setting

HIV negative or undiagnosed MSM adults attending sexual health clinics at three sites in the United Kingdom for STI screening or HIV testing are eligible to take part in the study. The three clinical sites are as follows: The Mortimer Market Centre, London; 56 Dean Street Clinic, London; and the Claude Nicol Centre, Brighton.

These three clinical sites were chosen based on their ability to provide access to large numbers of MSM attending sexual health services and previous successful collaboration with the researchers for the AURAH study [9]. During the AURAH study recruitment process, the three sites demonstrated their ability to provide a broad sample of homosexually active men, including gay, bisexual, and non-gay identified MSM.

The eligibility criteria to join the study is (1) self-reported HIV-negative, (2) self-defining as MSM, (3) being aged 18 years or over, (4) attending or having previously attended for routine STI or HIV testing in the study clinics, and (5) willing to be contacted for longitudinal follow-up for up to a 3-year period.

Sample Size

The sample size calculation was based on our objective to assess within-person changes in sexual behavior after receiving an HIV diagnosis. This outcome is more constrained by power than others because it relies on comparisons of participants within the group who are infected with HIV during follow-up. For sexual behavior classified as whether or not a man reports >3 condomless sex partners in the past 3 months, 85 new HIV diagnoses would be needed to detect, with 80% power and 5% significance level, the following changes: 17 (20%) men newly diagnosed switching from >3 to ≤3 condomless sex partners pre to post diagnosis, and 4 (5%) men newly diagnosed switching from ≤3 to >3 condomless sex partners pre to post diagnosis. With 1000 HIV-negative men initially enrolled in the study sample, assuming an annual HIV incidence of 4% (for high-risk MSM) and a dropout rate of 15% per year, 96 new HIV infections would be expected to accrue over a 3-year period. This sample size of 1000 should provide adequate power for the other objectives.

Recruitment

Participants are recruited to the AURAH2 study through two separate recruitment routes. The recruitment route 1 group consists of HIV negative or undiagnosed MSM who were (1) enrolled in the AURAH cross-sectional study [9] from the three clinics detailed above during targeted recruitment of MSM (until March 2015) and (2) who had indicated interest in future follow-up on the AURAH study consent form. An email invitation to participate in the AURAH2 study was sent to this group from the AURAH2 study website in March 2015. Participants who joined the AURAH2 study from AURAH were assigned the same study number in their online follow-up as their original AURAH study number so that online follow-up could be linked to responses in the original cross-sectional study.

The recruitment route 2 group consists of HIV-negative or undiagnosed MSM who are prospectively recruited in person through the three clinic sites from March 2015 until December 2016. This group is directly consented into the AURAH2 study in their sexual health clinic and completes the baseline AURAH paper questionnaire during their clinic attendance. Online registration with the study website using a personal smartphone or iPad is explained during the consent procedure, or participants are contacted within 2 weeks with an email invitation to register.

Consent

Consent for the study is gained through two mechanisms, according to the recruitment route. Participants from recruitment route 1 (contacted in March 2015) were required to complete an online consent form for the AURAH2 study. This was presented to them on the study website after they had read the online patient information sheet and prior to registration.

Consent for participants via recruitment route 2 is obtained at study enrollment in the clinic setting via a paper-based information sheet and consent form. Participants recruited through recruitment route 2 do not need to complete an additional online consent form as information on the AURAH2 study is provided in the Patient Information Sheet. In both consent processes, participants are (1) made aware of the study aims, (2) made aware that participation means they are expected to complete brief online questionnaires about sexual behavior and HIV testing on a regular basis over a 3-year period, (3) asked to provide their email address and mobile phone number and consent to receive reminders to complete the online questionnaires via email and/or text message, but are also told that there will be a maximum of two reminders by email followed by one text message if they do not respond, (4) asked to provide their full name and date of birth and made aware that this information will be used to link with matching data in UK national clinical databases including the national HIV/AIDS Reporting System (HARS) database (see clinical data), (5) made aware that results of any HIV test results from the day they joined the study, or that they self-report during the study period (up to 3 years), will be recorded and stored securely and separately from the study questionnaire, (6) made aware that they can withdraw from the study at any point and ask for their personal data to be deleted and that this will not affect their care at their GUM clinic, and (7) advised that should they wish to withdraw from the study they should send an email to a specified contact address to make this request.

Online Registration Procedure

Participants are sent a maximum of three “invitation to register” messages via the study website (see below). The first contact is an email containing an individualized link, which, when selected, allows the recipient to register an account with the study website. A second similar reminder email is sent a week later to participants who have not registered, and finally a text message is sent a week after the second email (if a mobile phone number was provided during the consent procedure). In each email, participants are provided with information on how to opt out of the study and any further contact. Participants who do not register within 1 week after the two reminder emails and a text message have been sent are removed from the study lists and not contacted further.

Website Design and Features

The AURAH2 website was designed to provide full information on the study to the general public and the study participants. The home page provides a login box that allows only registered participants to gain access to the study questionnaires by entering a username and password. Once a participant has registered and completed the first online questionnaire, automated reminder emails are sent every 4 months when follow-up questionnaires are due. Each reminder email informs the participant that a questionnaire is due for completion and contains a link to the study website homepage to login and access a questionnaire. The message also contains information on how to receive a username and password change prompt if login details have been forgotten. If a participant does not log in and complete a questionnaire, a second automated reminder email is sent 1 week after the initial email, and a final reminder is sent by text message a week later. If a participant does not log in and complete a questionnaire after the third reminder, no further contact is made until the next questionnaire is due, 4 months later.

The secure website provides facilities for content management including the ability to change information pages and add new items and details of study publications. The administration pages are accessible only to user accounts controlled by the study coordinator and data manager. From the administration pages of the website, the "invitation to register" and follow-up messages are managed and the status reports and questionnaire results data can be securely downloaded on a regular basis.

Study Questionnaires

Baseline Data

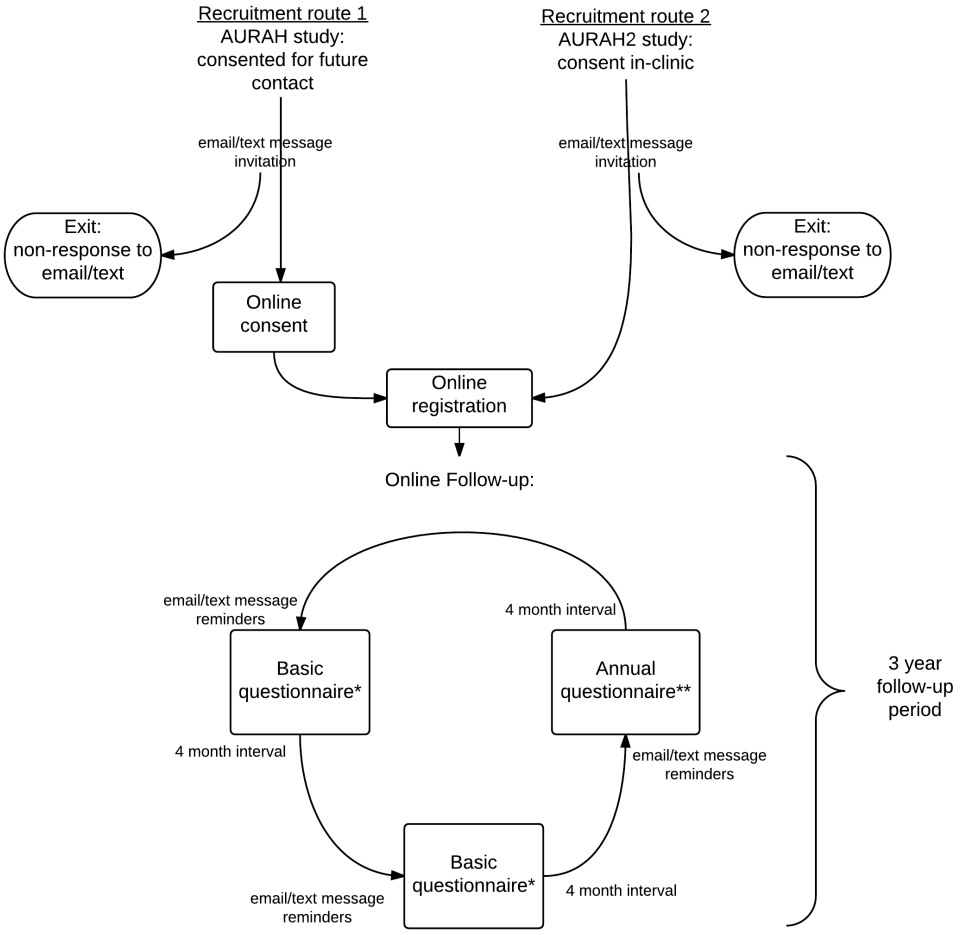
Extensive baseline data are collected through the pen-and-paper AURAH baseline questionnaire, details of which have been published elsewhere [9]. The questionnaire gathers detailed information on demographics, socioeconomic factors, physical and psychological health and well-being, knowledge and understanding of HIV and antiretroviral treatment, lifestyle factors (smoking, alcohol, and recreational drug use), HIV testing, knowledge and use of PEP, and sexual behavior. Both recruitment routes use the baseline AURAH questionnaire for initial data collection, which takes approximately 20-25 minutes to complete.

Online Questionnaires

Online data collection every 4 months will be ongoing until 2018. It consists of a brief online questionnaire that assesses sexual risk behavior, HIV testing history, self-reported STIs, and use and frequency of chemsex drugs from the preceding 3 months. The basic 4-monthly online questionnaire takes approximately 5 minutes to complete. A more detailed questionnaire is undertaken on an annual basis that includes the information collected in the 4-month questionnaire and additional information on use of HIV testing preferences, PEP and PrEP, physical and psychological symptoms, and attitudes to HIV transmission. The annual online questionnaire takes approximately 20 minutes to complete.

Each online questionnaire commences with a question on the most recent date and result of a participant's previous HIV test. If a participant consistently reports negative HIV test results or "not tested," then the questionnaires remain specific to an HIV negative or unknown status. However, if a participant reports a positive HIV test result, the questionnaire is programmed to collect information on the number of partners, sexual behavior, and recreational drug use pre and post diagnosis. At each subsequent login, an HIV-positive participant will complete questionnaires that are similar to the HIV-negative participants, but tailored to reflect the HIV-positive sero-status of the participant. A flowchart to demonstrate recruitment from clinic to the online questionnaire sequence is shown in Figure 1.

Figure 1. Flowchart of AURAH2 recruitment and questionnaire sequence.



* Basic questionnaire (recall period 3 months): last HIV test/result, sexual history, STI diagnoses, chemsex drug use

* *Annual questionnaire (recall period 3 and 12 months): last HIV test/result, sexual history, STI diagnoses, chemsex drug use, recreational drug use, alcohol intake, PEP and PrEP use, physical and psychological symptoms

Clinical Data

The result of any HIV test taken in clinic at the same time as the baseline questionnaire completion is stored as part of the study records. At each online follow-up questionnaire, participants are asked to self-report the result of their most recent HIV test and any diagnosed STIs. At the end of the study period, in collaboration with Public Health England, data will be checked against corresponding records and data in national clinical databases such as HARS, the Genitourinary medicine clinical activity dataset (GUMCAD), and the Office for National Statistics. The linkage of the AURAH2 data to these databases will provide confirmation on the self-reported HIV status of participants as well as identify any new HIV diagnoses that have not been self-reported through the questionnaires.

Data Processing and Security

Baseline paper questionnaires completed in clinic are collected by the study nurses and transferred regularly to the study management center via registered post or collected in person from the clinic sites by the study researchers. At the study management center, the original paper questionnaires are stored securely in locked cabinets. Baseline questionnaires are identifiable only by an assigned study number to maintain confidentiality, and participant details linked with the study number are collected in a separate study log. The study log is maintained securely and updated daily at each clinical site. The study log contains study numbers, clinic identifiers, and details of consent status for all patients invited to participate in the study, whether or not HIV and other STI tests had been done, and the result of any HIV test. Contact details of participants are also entered in the log. A copy of the study log (with contact details removed for non-consenting participants) is transferred on a regular basis to the study management center using the NHS mail system, which is approved by the Department of Health for the purpose of sharing personal identifiable information and sensitive information.

Baseline questionnaires are digitized at the management center using the REDCap data capture system for secure double data entry. The study website is hosted in a secure data center and

network environment, and the online questionnaire response datasets are directly downloaded to encrypted data drives at the study management center on a monthly basis. Linkage to Public Health England's datasets will be done at the end of the study using limited participant identifiers: surname Soundex, sex, and date of birth.

The final resulting study datasets, including scanned images of the questionnaires, are stored on the University College London Data Safe Haven, which is a secure technical solution for storing, handling, and analyzing identifiable data. This has been certified to the ISO27001 information security standard and conforms to the NHS Information Governance Toolkit.

The contact details of any participants who did not join the AURAH2 study after the email invitations from recruitment route 1 were removed from the study records 1 month after their final email reminder or the text message had been sent (if provided). All AURAH2 participants contact details will be erased from the study database 6 months after the completion of the study.

Ethics Approval

The research protocol and all versions of the study documents (information sheet, consent form, questionnaires, and versions of the online questionnaires) were approved by the designated research ethics committee (NRES committee London-Hampstead, ref: 14/LO/1881 in November 2014). Based on these documents, the study subsequently received permission for clinical research at the three participating National Health Service sites: Chelsea and Westminster NHS Foundation Trust, Central and North West London NHS Foundation Trust, and the Brighton and Sussex University Hospitals NHS Trust.

Results

Data collection commenced in March 2015 and is ongoing until March 2018. Initial results from analysis of the baseline questionnaires are expected in 2016, and results from longitudinal data are expected in 2018.

Discussion

Principal Considerations

The AURAH2 study will provide important longitudinal data on sexual risk behavior, HIV testing habits, and risk factors for ongoing transmission of HIV in UK MSM who were HIV negative at entry to the study but who are at risk of HIV infection. It uses a novel approach to data collection by combining paper-based questionnaires collected in the clinic setting and online follow-up questionnaires that participants access at their convenience. We applied a short recall period of 3 months in the questionnaire responses to maximize self-report accuracy and diminish recall bias [45] and to better capture within-person changes over time in sexual behavior. The request to complete questionnaires was sent on a 4-monthly basis to decrease the study burden for the participant and reduce attrition during the long follow-up period. The online recall period is reflective of the timeframes that are used in the paper-based questionnaires and is closely aligned to the frequency of survey completion in an attempt to capture ongoing and new behavioral information. The Internet has been increasingly used as a tool with which to collect survey data as it offers a low-cost, flexible, and fast way to collect data while reducing participant burden [46], and Internet surveys have been shown to be an acceptable method in researching MSM at risk of acquisition of HIV [47].

A similar study to AURAH2 is currently being conducted in the United States, using online follow-up over a 3-year period in a sample of 1000 gay and bisexual men who will complete self-administered HIV/STI tests and online surveys [48], which may offer comparisons of survey response rates and attrition over the 3 years. Despite some design differences, notably in recruitment routes (ie, the *One Thousand Strong* study recruited in partnership with a marketing firm via email invitation as opposed to face to face in sexual health clinics) and methods (ie, AURAH2 does not use biological methodologies for HIV/STI tests [48]), both studies will demonstrate the feasibility of using the Internet to engage MSM in online data collection and contribute substantial insight into sexual risk behavior and HIV testing. Longitudinal online follow-up in the HIV negative or undiagnosed population has not been widely explored among MSM in the United Kingdom but will be key to understanding how individual sexual behaviors change over time. The annual Gay Men's Sex survey "Vital Statistics" has been successfully conducted among participants since 1993, although the survey is a one-off online survey [49], as opposed to the follow-up and retention of the same group of individuals over time. The AURAH2 study will provide valuable insight into the feasibility of recruiting and retaining MSM in a study that requires regular ongoing follow-up over a period of 3 years using the Internet as a tool for data collection.

Limitations

A recognized limitation of the study is the restricted recruitment of MSM from attendance at GUM clinics, which may not be reflective of the wider MSM population, and in particular from the two clinics (56 Dean Street and the Mortimer Market Clinic) that provide services for patients seeking support for drug use. However, recruitment is from the general clinic attendees, not from specific drug use services. Although the majority of MSM in London do appear to be engaged with GUM sexual health services [50], there is less information on engagement with these services in the rest of the United Kingdom, so recruiting from a site outside London will allow some comparison. Recruitment through GUM clinics was essential for this study so that the self-reported HIV test results of participants could be confirmed with UK national clinical HIV databases (in collaboration with Public Health England) and so that the study sampling frame was clearly based on MSM who had attended a sexual health clinic. Recruitment online or through other settings could have potentially provided larger numbers of anonymous participants but would have been limited by the inability to confirm HIV status during or at the end of the study period due to participant anonymity.

We identify a further limitation of the study in the lack of recruitment from clinical sites outside two major cities that have large gay communities. It is recognized that this will limit the study's generalizability given the potential differences in

lifestyle, HIV testing opportunities, and access to sexual health services between urban and rural settings. Future studies might address this issue using the Internet or other digital platforms to enroll participants so that a broader sample of MSM from across the United Kingdom could be included.

Conclusion

Evidence that HIV incidence is increasing among MSM in the United Kingdom [1] indicates a clear need for ongoing research in this group. The AURAH2 study will provide detailed longitudinal data on the incidence and predictors of new infections among HIV-negative MSM at particular risk of HIV infection and will further provide some of the first data on emerging behaviors such as chemsex that have raised concern for sexual health and well-being among MSM, as well as interest and uptake of PrEP and expanded HIV testing options for this group. The study completed recruitment of participants in March 2016, and it is hoped that the wide range of topics explored by the AURAH2 study renders results that will help improve a variety of targeted health promotion strategies that are specific to the men that need them. The study will be highly relevant to HIV prevention efforts among MSM, and it is planned for the data to feed into a mathematical model that simulates different scenarios to inform prevention strategies [4,51,52]. The results of the study will also inform national policies aimed at reducing HIV incidence and increase HIV testing in the United Kingdom in this population.

Acknowledgments

This paper summarizes independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (Grant Reference Number RP-PG-1212-20006). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

We would like to thank all the study participants for their time and effort. We gratefully acknowledge the three participating sites and the contributions and efforts of the following at each site:

1. The Mortimer Market Centre, London: Ana Milinkovic, Fabienne Styles, Rosanna Laverick, Marzena Orzol, Emmi Suonpera

2. 56 Dean Street Clinic, London: Ali Ogilvy

3. The Claude Nicol Centre, Brighton: Celia Richardson, Elaney Youssef, Sarah Kirk, Marion Campbell, Lisa Barbour

Conflicts of Interest

None declared.

References

1. Skingsley A, Kirwan P, Yin Z, Nardone A, Gill ON, Hughes G, and contributors. HIV New Diagnoses, Treatment and Care in the UK 2015 report. London: Public Health England; 2015. URL: https://www.gov.uk/government/statistics/hiv-in-the-united-kingdom [accessed 2016-01-05] [WebCite Cache ID 6etbylDl1]
2. Skingsley A, Kirwan P, Croxford S, Chau C, Conti S, Presanis A, et al. HIV in the UK – Situation Report 2015: data to end 2014. London: Public Health England; 2015. URL: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/477702/HIV_in_the_UK_2015_report.pdf [accessed 2016-01-04] [WebCite Cache ID 6etcNSivE]
3. Marks G, Crepaz N, Janssen RS. Estimating sexual transmission of HIV from persons aware and unaware that they are infected with the virus in the USA. AIDS 2006 Jun 26;20(10):1447-1450. [doi: 10.1097/01.aids.0000233579.79714.8d] [Medline: 16791020]
4. Phillips AN, Cambiano V, Nakagawa F, Brown AE, Lampe F, Rodger A, et al. Increased HIV incidence in men who have sex with men despite high levels of ART-induced viral suppression: analysis of an extensively documented epidemic. PLoS One 2013;8(2):e55312 [FREE Full text] [doi: 10.1371/journal.pone.0055312] [Medline: 23457467]
5. INSIGHT START Study Group, Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med 2015 Aug 27;373(9):795-807 [FREE Full text] [doi: 10.1056/NEJMoa1506816] [Medline: 26192873]
6. Weller S, Davis K. Condom effectiveness in reducing heterosexual HIV transmission. Cochrane Database Syst Rev 2002(1):CD003255. [doi: 10.1002/14651858.CD003255] [Medline: 11869658]
7. Silverman BG, Gross TP. Use and effectiveness of condoms during anal intercourse. A review. Sex Transm Dis 1997 Jan;24(1):11-17. [Medline: 9018778]
8. Stone E, Heagerty P, Vittinghoff E, Douglas JM, Koblin BA, Mayer KH, et al. Correlates of condom failure in a sexually active cohort of men who have sex with men. J Acquir Immune Defic Syndr Hum Retrovirol 1999 Apr 15;20(5):495-501. [Medline: 10225233]
9. Sewell J, Speakman A, Phillips AN, Lampe FC, Miltz A, Gilson R, et al. A Cross-Sectional Study on Attitudes to and Understanding of Risk of Acquisition of HIV: Design, Methods and Participant Characteristics. JMIR Res Protoc 2016 Apr 18;5(2):e58. [doi: 10.2196/resprot.4873] [Medline: 26537832]

10. Prestage G, Grierson J, Bradley J, Hurley M, Hudson J. The role of drugs during group sex among gay men in Australia. Sex Health 2009 Dec;6(4):310-317. [doi: 10.1071/SH09014] [Medline: 19917200]
11. Heiligenberg M, Wermeling PR, van Rooijen MS, Urbanus AT, Speksnijder AGCL, Heijman T, et al. Recreational drug use during sex and sexually transmitted infections among clients of a city sexually transmitted infections clinic in Amsterdam, the Netherlands. Sex Transm Dis 2012 Jul;39(7):518-527. [doi: 10.1097/OLQ.0b013e3182515601] [Medline: 22706213]
12. Prestage G, Jin F, Kippax S, Zablotska I, Imrie J, Grulich A. Use of illicit drugs and erectile dysfunction medications and subsequent HIV infection among gay men in Sydney, Australia. J Sex Med 2009 Aug;6(8):2311-2320. [doi: 10.1111/j.1743-6109.2009.01323.x] [Medline: 19493293]
13. Pappas MK, Halkitis PN. Sexual risk taking and club drug use across three age cohorts of HIV-positive gay and bisexual men in New York City. AIDS Care 2011 Nov;23(11):1410-1416 [FREE Full text] [doi: 10.1080/09540121.2011.565027] [Medline: 22022849]
14. Prestage G, Degenhardt L, Jin F, Grulich A, Imrie J, Kaldor J, et al. Predictors of frequent use of amphetamine type stimulants among HIV-negative gay men in Sydney, Australia. Drug Alcohol Depend 2007 Dec 1;91(2-3):260-268. [doi: 10.1016/j.drugalcdep.2007.06.009] [Medline: 17640831]
15. Hoenigl M, Chaillon A, Moore D, Morris SR, Smith DM, Little SJ. Clear Links Between Starting Methamphetamine and Increasing Sexual Risk Behavior: A Cohort Study Among Men Who Have Sex With Men. J Acquir Immune Defic Syndr 2016 Apr 15;71(5):551-557. [doi: 10.1097/QAI.0000000000000888] [Medline: 26536321]
16. Mustanski BS, Newcomb ME, Du Bois SN, Garcia SC, Grov C. HIV in young men who have sex with men: a review of epidemiology, risk and protective factors, and interventions. J Sex Res 2011 Mar;48(2-3):218-253 [FREE Full text] [doi: 10.1080/00224499.2011.558645] [Medline: 21409715]
17. Colfax G, Vittinghoff E, Husnik MJ, McKirnan D, Buchbinder S, Koblin B, et al. Substance use and sexual risk: a participant- and episode-level analysis among a cohort of men who have sex with men. Am J Epidemiol 2004 May 15;159(10):1002-1012 [FREE Full text] [Medline: 15128613]
18. Halkitis PN, Green KA, Mourgues P. Longitudinal investigation of methamphetamine use among gay and bisexual men in New York City: findings from Project BUMPS. J Urban Health 2005 Mar;82(1 Suppl 1):i18-i25 [FREE Full text] [doi: 10.1093/jurban/jti020] [Medline: 15738324]
19. McCall H, Adams N, Mason D, Willis J. What is chemsex and why does it matter? BMJ 2015:351. [doi: 10.1136/bmj.h5790]
20. Public Health England. Promoting the health and wellbeing of gay, bisexual and other men who have sex with men. 2015 Oct. PHE publications gateway number: 2014685 URL: https://www.researchgate.net/publication/277555569_PHE_action_plan_2015-16_Promoting_the_health_and_wellbeing_of_gay_bisexual_and_other_men_who_have_sex_with_men [accessed 2016-06-08] [WebCite Cache ID 6i77RwYyJ]
21. Public Health England. HIV in the United Kingdom: 2014 Report. 2014. URL: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/401662/2014_PHE_HIV_annual_report_draft_Final_07-01-2015.pdf [accessed 2016-06-08] [WebCite Cache ID 6i77ay4ea]
22. The Guardian. 2015. HIV self-testing kit goes on sale in UK URL: http://www.theguardian.com/society/2015/apr/27/hiv-self-testing-kit-on-sale-uk-biosure [accessed 2016-06-08] [WebCite Cache ID 6i77nNzaH]
23. World Health Organization. The legal, ethical, gender, human rights and public health implications of HIV self-testing scale-up. Geneva, Switzerland; 2013. Report on the First International Symposium on self-testing for HIV URL: http://apps.who.int/iris/bitstream/10665/85267/1/9789241505628_eng.pdf [accessed 2016-06-08] [WebCite Cache ID 6i780XHry]
24. Pant PN, Sharma J, Shivkumar S, Pillay S, Vadnais C, Joseph L, et al. Supervised and unsupervised self-testing for HIV in high- and low-risk populations: a systematic review. PLoS Med 2013;10(4):e1001414 [FREE Full text] [doi: 10.1371/journal.pmed.1001414] [Medline: 23565066]
25. Fox J, White PJ, Macdonald N, Weber J, McClure M, Fidler S, et al. Reductions in HIV transmission risk behaviour following diagnosis of primary HIV infection: a cohort of high-risk men who have sex with men. HIV Med 2009 Aug;10(7):432-438 [FREE Full text] [doi: 10.1111/j.1468-1293.2009.00708.x] [Medline: 19459996]
26. Marks G, Crepaz N, Senterfitt JW, Janssen RS. Meta-analysis of high-risk sexual behavior in persons aware and unaware they are infected with HIV in the United States: implications for HIV prevention programs. J Acquir Immune Defic Syndr 2005 Aug 1;39(4):446-453. [Medline: 16010168]
27. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, HPTN 052 Study Team. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 2011 Aug 11;365(6):493-505 [FREE Full text] [doi: 10.1056/NEJMoa1105243] [Medline: 21767103]
28. Rodger AJ, Bruun T, Cambiano V, Vernazza P, Estrada V, Van Lunzen J, et al. HIV transmission risk through condomless sex if HIV+ partner on suppressive ART: PARTNER Study. 2014 Presented at: 21st Conference on Retroviruses and Opportunistic Infections; Mar. 3-6, 2014; Boston, MA. [doi: 10.1056/NEJMoa1105243]
29. Vernazza P, Hirschel B, Bernasconi E, Flepp M. Les personnes séropositives ne souffrant d'aucune autre MST et suivant un traitement antirétroviral efficace ne transmettent pas le VIH par voie sexuelle. 2015. URL: http://www.unige.ch/sciences-societe/socio/files/4814/0533/6055/Vernazza_2008.pdf [accessed 2016-06-08] [WebCite Cache ID 6i79TNEgj]

30. British HIV Association. Guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015. 2015. URL: http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf [accessed 2016-06-08] [WebCite Cache ID 6i79eHynJ]
31. Brown AE, Gill ON, Delpech VC. HIV treatment as prevention among men who have sex with men in the UK: is transmission controlled by universal access to HIV treatment and care? HIV Med 2013 Oct;14(9):563-570 [FREE Full text] [doi: 10.1111/hiv.12066] [Medline: 23890150]
32. Ostrow DG, Silverberg MJ, Cook RL, Chmiel JS, Johnson L, Li X, Multicenter AIDS Cohort Study. Prospective study of attitudinal and relationship predictors of sexual risk in the multicenter AIDS cohort study. AIDS Behav 2008 Jan;12(1):127-138. [doi: 10.1007/s10461-007-9223-x] [Medline: 17410419]
33. Jin F, Jansson J, Law M, Prestage GP, Zablotska I, Imrie JCG, et al. Per-contact probability of HIV transmission in homosexual men in Sydney in the era of HAART. AIDS 2010 Mar 27;24(6):907-913 [FREE Full text] [doi: 10.1097/QAD.0b013e3283372d90] [Medline: 20139750]
34. Samji H, Cescon A, Hogg RS, Modur SP, Althoff KN, Buchacz K, North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of IeDEA. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. PLoS One 2013;8(12):e81355 [FREE Full text] [doi: 10.1371/journal.pone.0081355] [Medline: 24367482]
35. Heijman T, Geskus RB, Davidovich U, Coutinho RA, Prins M, Stolte IG. Less decrease in risk behaviour from pre-HIV to post-HIV seroconversion among MSM in the combination antiretroviral therapy era compared with the pre-combination antiretroviral therapy era. AIDS 2012 Feb 20;26(4):489-495. [doi: 10.1097/QAD.0b013e32834f9d7c] [Medline: 22156971]
36. Elford J. Changing patterns of sexual behaviour in the era of highly active antiretroviral therapy. Curr Opin Infect Dis 2006 Feb;19(1):26-32. [Medline: 16374214]
37. Jin F, Crawford J, Prestage GP, Zablotska I, Imrie J, Kippax SC, et al. Unprotected anal intercourse, risk reduction behaviours, and subsequent HIV infection in a cohort of homosexual men. AIDS 2009 Jan 14;23(2):243-252 [FREE Full text] [doi: 10.1097/QAD.0b013e32831fb51a] [Medline: 19098494]
38. US Public Health Service. Preexposure Prophylaxis for the Prevention of HIV Infection in the United States–2014. A Clinical Practice Guideline.: CDC; 2014. URL: http://www.cdc.gov/hiv/pdf/prepguidelines2014.pdf [accessed 2016-06-08] [WebCite Cache ID 6i7Apae3v]
39. McCormack S, Dunn D, Desai M, Dolling DI, Gafos M, Gilson R, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. The Lancet 2016 Jan;387(10013):53-60 [FREE Full text] [doi: 10.1016/S0140-6736(15)00056-2]
40. Molina JM, Capitant C, Spire B, Pialoux G, Chidiac C, Charreau I. On Demand PrEP With Oral TDF-FTC in MSM: Results of the ANRS Ipergay Trial. 2015 Presented at: Conference on Retroviruses and Opportunistic Infections; 2015; Boston, MA.
41. Statement on PrEP from community organisations working on HIV prevention. URL: http://www.prepaccess.org.uk/ [accessed 2016-06-08] [WebCite Cache ID 6i7BfXczU]
42. The Lancet HIV. PrEP: why are we waiting? The Lancet HIV 2015 Oct;2(10):e401. [doi: 10.1016/S2352-3018(15)00185-X]
43. PrEP FAQs. Prepster URL: http://prepster.info/prep-faqs/ [accessed 2016-06-08] [WebCite Cache ID 6i7Bv5AXc]
44. I want PrEP now. 2015. URL: http://www.iwantprepnow.co.uk/ [accessed 2016-06-08] [WebCite Cache ID 6i7C4RIUi]
45. Jaccard J, McDonald R, Wan CK, Dittus PJ, Quinlan S. The Accuracy of Self-Reports of Condom Use and Sexual Behavior. J Appl Social Pyschol 2002 Sep;32(9):1863-1905. [doi: 10.1111/j.1559-1816.2002.tb00263.x]
46. Couper M. Designing effective Web surveys. Cambridge, MA: Cambridge University Press; 2008.
47. Elford J, Bolding G, Davis M, Sherr L, Hart G. Web-based behavioral surveillance among men who have sex with men: a comparison of online and offline samples in London, UK. J Acquir Immune Defic Syndr 2004 Apr 1;35(4):421-426. [Medline: 15097159]
48. Grov C, Cain D, Whitfield THF, Rendina HJ, Pawson M, Ventuneac A, et al. Recruiting a U.S. national sample of HIV-negative gay and bisexual men to complete at-home self-administered HIV/STI testing and surveys: Challenges and Opportunities. Sex Res Social Policy 2016 Mar 1;13(1):1-21. [doi: 10.1007/s13178-015-0212-y] [Medline: 26858776]
49. Vital Statistics - The Gay Men's Sex Survey SIGMA research. URL: http://sigmaresearch.org.uk/projects/item/project21 [accessed 2016-06-08] [WebCite Cache ID 6i7CmvJMs]
50. Public Health England. HIV and STIs in men who have sex with men in London. 2014. PHE publications gateway number: 2014339 URL: https://www.gov.uk/government/publications/hiv-and-stis-in-men-who-have-sex-with-men-in-london [accessed 2016-06-08] [WebCite Cache ID 6i7D1H52w]
51. Phillips AN, Cambiano V, Miners A, Lampe FC, Rodger AJ, Nakagawa F, et al. Potential impact on HIV incidence of higher HIV testing rates and earlier antiretroviral therapy initiation in MSM. AIDS 2015 Sep 10;29(14):1855-1862. [doi: 10.1097/QAD.0000000000000767] [Medline: 26372391]
52. Cambiano V, Miners A, Dunn D, McCormack S, Gill N, Nardone A, et al. Is pre-exposure prophylaxis for hiv prevention cost-effective in men who have sex with men who engage in condomless sex in the uk? Sex Transm Infect 2015 May 18;91(Suppl 1):A1.1-A1A1. [doi: 10.1136/sextrans-2015-052126.1]

Abbreviations

AIDS: acquired immune deficiency syndrome
ART: antiretroviral therapy
GUM: genito-urinary medicine
HIV: human immunodeficiency virus
HIVST: human immunodeficiency virus self-testing
MSM: men who have sex with men
NHS: National Health Service
Pep: post exposure prophylaxis
PrEP: pre-exposure prophylaxis
STI: sexually transmitted infection
TasP: treatment as prevention

Edited by G Eysenbach; submitted 29.01.16; peer-reviewed by G Prestage, C Grov; comments to author 18.02.16; revised version received 29.02.16; accepted 16.03.16; published 15.06.16.

Please cite as:
Sewell J, Speakman A, Phillips AN, Cambiano V, Lampe FC, Gilson R, Asboe D, Nwokolo N, Clarke A, Ogilvy A, Collins S, Rodger AJ
Attitudes to and Understanding of Risk of Acquisition of HIV Over Time: Design and Methods for an Internet-based Prospective Cohort Study Among UK Men Who Have Sex With Men (the AURAH2 Study)
JMIR Res Protoc 2016;5(2):e128
URL: http://www.researchprotocols.org/2016/2/e128/
doi:10.2196/resprot.5582
PMID:27307218

Protocol

Vascular Health Assessment of The Hypertensive Patients (VASOTENS) Registry: Study Protocol of an International, Web-Based Telemonitoring Registry for Ambulatory Blood Pressure and Arterial Stiffness

Stefano Omboni[1*], MD[‡]; Igor N Posokhov[2*], MD, PhD; Gianfranco Parati[3], MD; Alberto Avolio[4], BE, PhD; Anatoly N Rogoza[5], DSc; Yulia V Kotovskaya[6], MD, PhD; Giuseppe Mulè[7], MD; Maria Lorenza Muiesan[8], MD; Iana A Orlova[9], MD, PhD; Elena A Grigoricheva[10], MD, PhD; Ernesto Cardona Muñoz[11], MD; Parounak H Zelveian[12], MD; Telmo Pereira[13], MSc, PhD; João Manuel Peixoto Maldonado[14], MD

[1]Italian Institute of Telemedicine, Clinical Research Unit, Solbiate Arno, Italy

[2]Hemodynamic Laboratory Ltd, Nizhniy Novgorod, Russian Federation

[3]Department of Cardiology and Department of Medicine and Surgery, Istituto Auxologico Italiano and University of Milano-Bicocca, Milano, Italy

[4]Faculty of Medicine and Health Sciences, Department of Biomedical Sciences, Macquarie University, Sydney, Australia

[5]Russian Cardiology Research and Production Complex, Department of New Diagnostic Methods, Moscow, Russian Federation

[6]Peoples' Friendship University of Russia, Department of Internal Medicine Propaedeutics, Moscow, Russian Federation

[7]Centro di Riferimento Regionale per l'Ipertensione Arteriosa, Policlinico Paolo Giaccone, Unità Operativa di Nefrologia ed Ipertensione, Palermo, Italy

[8]Spedali Civili and University of Brescia, Dipartimento di Scienze Mediche e Chirurgiche and Medicina 2, Brescia, Italy

[9]Lomonosov Moscow State University Clinic, Moscow, Russian Federation

[10]South Ural State Medical University, Department of Outpatient Therapy and Clinical Pharmacology, Chelyabinsk, Russian Federation

[11]University of Guadalajara, Department of Physiology, Guadalajara, Mexico

[12]L.A. Ohanesyan Institute of Cardiology, Center of Preventive Cardiology, Yerevan, Armenia

[13]Escola Superior de Tecnologia da Saúde de Coimbra , Instituto Politécnico de Coimbra, Coimbra, Portugal

[14]Clínica da Aveleira, Instituto de Investigação e Formação Cardiovascular, Coimbra, Portugal

[‡]VASOTENS Registry Study Group

[*]these authors contributed equally

Corresponding Author:
Stefano Omboni, MD
Italian Institute of Telemedicine
Clinical Research Unit
Via Colombera 29
Solbiate Arno, 21048
Italy
Phone: 39 0331984176
Fax: 39 0331984176
Email: stefano.omboni@iitelemed.org

Abstract

Background: Hypertension guidelines recommend ambulatory blood pressure (ABP), central aortic pressure (CAP), and pulse wave velocity (PWV) as parameters for estimating blood pressure (BP) control and vascular impairment. Recent advances in technology have enabled devices to combine non-invasive estimation of these parameters over the 24-hour ABP monitoring. However, currently there is limited evidence on the usefulness of such an approach for routine hypertension management.

Objective: We recently launched an investigator-initiated, international, multicenter, observational, prospective study, the Vascular health Assessment Of The Hypertensive patients (VASOTENS) Registry, aimed at (1) evaluating non-invasive 24-hour ABP and arterial stiffness estimates (through 24-hour pulse wave analysis, PWA) in hypertensive subjects undergoing ambulatory blood pressure monitoring (ABPM) for clinical reasons; (2) assessing the changes in estimates following treatment; (3) weighing

the impact of 24-hour PWA on target organ damage and cardiovascular prognosis; (4) assessing the relationship between arterial stiffness, BP absolute mean level and variability, and prognosis; and (5) validating the use of a 24-hour PWA electronic health (e-health) solution for hypertension screening.

Methods: Approximately 2000 subjects, referred to 20 hypertension clinics for routine diagnostic evaluation and follow-up of hypertension of any severity or stage, will be recruited. Data collection will include ABPM, performed with a device allowing simultaneous non-invasive assessment of 24-hour CAP and arterial stiffness (BPLab), and clinical data (including cardiovascular outcomes). As recommended by current guidelines, each patient will be followed-up with visits occurring at regular intervals (ideally every 6 months, and not less than once a year depending on disease severity). A Web-based telemedicine platform (THOLOMEUS) will be used for data collection. The use of the telemedicine system will allow standardized and centralized data collection, data validation by experts and counseling to remote centers, setup and maintenance of the Registry, and prompt data analysis.

Results: First follow-up results are expected to be available in the next 2 years.

Conclusions: The results of the VASOTENS Registry will help define the normalcy thresholds for current and future indices derived from 24-hour PWA, according to outcome data, and will also provide supporting evidence for the inclusion of this type of evaluation in hypertension management.

Trial registration: Clinicaltrials.gov NCT02577835; https://clinicaltrials.gov/ct2/show/NCT02577835 (Archived by WebCite at http://www.Webcitation.org/6hzZBKY2Q)

(JMIR Res Protoc 2016;5(2):e137) doi:10.2196/resprot.5619

KEYWORDS

blood pressure telemonitoring; arterial stiffness; pulse wave velocity; augmentation index; central aortic pressure; hypertension

Introduction

Literature Review

Central aortic pressure (CAP) and pulse wave velocity (PWV) are independent predictors for the development of cardiovascular (CV) diseases [1-3]. Due to the large amount of epidemiological evidence for its predictive value for CV events, carotid-femoral PWV is currently highly indicated and useful for stratification of total CV risk, and considered the "gold standard" measurement of arterial stiffness [1,4,5]. Pulse-wave analysis (PWA), including evaluation of CAP, and Augmentation Index (AIx), may also provide additional information concerning wave reflections and may be useful for risk stratification and evaluation of the effectiveness of treatment, but more evidence is needed before recommending the routine clinical use of these vascular indices [1,5].

The most widely adopted methods for evaluating pulse waveforms are those based on applanation tonometry and transfer functions [1,6,7]. Notwithstanding the consistent evidence for superior and independent prognostic value, with respect to conventional office BP of either indices of central hemodynamics and stiffness assessed in controlled office condition at rest [2,3,8,9], currently there are no studies that evaluated the long-term predictive ability for CV events of vascular indices (ie, PWV, AIx, and CAP), measured in dynamic conditions over the 24-hours by ambulatory blood pressure monitoring (ABPM). However, some incomplete evidence is available from cross-sectional studies. For example, in 629 patients with diabetes, 24-hour aortic systolic blood pressure (SBP) was higher than in the 86 control patients, and increased with diabetic complications, being more strongly associated to complications than peripheral 24-hour SBP [10]. In the SAFAR Study [11,12], both 24-hour aortic and brachial SBP were superior to conventional office BP measurements in predicting BP-related cardiac damage (left ventricular hypertrophy and left ventricular diastolic dysfunction) in 230 subjects (75% having arterial hypertension). In the same study, 24-hour ambulatory central SBP was also more closely associated with left ventricular hypertrophy than 24-hour ambulatory brachial SBP. With respect to arterial stiffness, Aissopou et al [13] found that ambulatory aortic PWV, estimated by an operator-independent method, provided additional information to carotid-femoral PWV regarding the association of arterial stiffness with the retinal vessel calibers. Elsurer and Afsar [14] found that in 339 hypertensive patients with chronic kidney disease, serum uric acid was significantly correlated with both 24-hour PWV and AIx. However, serum uric acid was independently associated with AIx only. Maloberti and colleagues [15] studied 19 children with Williams-Beuren syndrome, a genetic disorder involving the elastin gene and adversely affecting arterial function and found that sick children showed higher heart rate and AIx values at night than age-matched controls, suggesting an abnormal sympathetic cardiovascular control and an increase in small arteries resistance. The limited evidence from the literature is completed by two longitudinal studies. The Ambulatory Central Aortic Pressure (AmCAP) study described a significant CAP lowering effect on both day-time and night-time with a 12-week treatment based on either aliskiren (300 mg) or telmisartan (80 mg) administered once-daily [16]. Interestingly, this study also showed relatively higher values of nocturnal aortic than brachial BP. Karpetas et al [17] and Koutroumbas et al [18] showed a gradual interdialytic increase in ambulatory CAP and AIx, and to less extent in PWV, in 153 patients with end stage renal disease treated with dialysis.

There is previous evidence that non-invasive assessment of 24-hour arterial stiffness and central hemodynamics in daily life conditions measured by the device used in this study (BPLab device, BPLab GmbH, Schwalbach am Taunus, Hessen,

Germany) may help in assessing the arterial function impairment in hypertensive patients. We recently showed larger 24-hour CAP and peripheral AIx values in 661 patients with hypertension compared to 142 normotensive controls [19]. In a subgroup of 137 patients with hypertension, a significantly positive correlation was found between 24-hour PWV and left ventricular mass index (LVMI) [20]. In another study, Kuznetsova et al [21] provided age- and gender-specific reference diagnostic values for 24-hour PWV, AIx, and CAP in 467 normotensive volunteers. Minyukhina and colleagues [22] observed a reduction in 24-hour PWV one week after kidney transplantation in 41 patients with end-stage renal disease, with a return to pre-transplant values after 20 weeks. Finally, in another study the combination of hypertension and chronic obstructive pulmonary disease was associated with an increased ambulatory peripheral and central aortic pressure, while this was not the case for isolated essential hypertensive subjects and normotensive controls [23].

Rationale

Recent advances in technology enabled devices to combine non-invasive estimation of CAP and arterial stiffness in ambulatory conditions over the 24-hours, based on the oscillometric method [24-28]. Such techniques are affordable and may allow a comfortable, accurate, repeated, and prolonged estimation of arterial stiffness and central hemodynamics over the 24-hours in daily life conditions by ABPM. Recent studies seem to indicate reliability and feasibility of ambulatory arterial stiffness and hemodynamics evaluation based on analysis of brachial oscillograms [8,29,30]. However, at present, there is limited evidence on the clinical usefulness of such an approach and much has to be done to prove its actual benefit in the daily clinical management of hypertension. In particular, there are very few data on the long-term prognostic and clinical value of 24-hour ambulatory CAP and arterial stiffness estimation, since most studies performed so far were not sufficiently long lasting or had a cross-sectional design [11-23]. At the moment, some associations with CV complications have been demonstrated for 24-hour CAP, but not for PWV and AIx. In addition, since different algorithms are used by the different ambulatory devices, non-invasive estimation of central hemodynamics and arterial stiffness appears to be device- and/or technique-dependent, and thus results obtained with one or the other device cannot be easily confronted and interpreted.

To provide further insight on the matter, we created a large database (or registry) of ABPM recordings obtained with the BPLab monitor, which is able to determine CAP, PWV, and AIx, over the 24-hours, based on a clinically validated technology of PWA of oscillometric BP measurements [26-28]. The choice of this device was made not only because of its proved accuracy and clinical reliability, but also because of its compatibility with the Web-based telemedicine platform THOLOMEUS (Biotechmed Ltd., Somma Lombardo, Varese Italy) [31], which enables easy data collection and communication within such a large worldwide network of study centers.

This paper summarizes the study protocol (final version, dated 20/02/2015, available as an online supplement to this paper) (Multimedia Appendix 1) that has been prepared following the recommendations contained in the SPIRIT statement [32], the most appropriate checklist for the publication of protocol papers of observational, non-randomized, prospective studies in the initial stage (Multimedia Appendix 2).

Study Objectives

The VASOTENS (Vascular health Assessment Of The Hypertensive patients) Registry aims at evaluating the clinical value and the prognostic impact of 24-hour ambulatory non-invasive estimation of arterial stiffness and central hemodynamics by PWA in patients with hypertension undergoing an ABPM for clinical reasons in hypertension clinics. Specific study objectives include (1) the evaluation of 24-hour PWV, AIx and CAP in hypertensive patients over consecutive ABPMs performed at regular intervals, as recommended by current guidelines, for a minimum of 2 years (main study objective); (2) the evaluation of the changes in BP and arterial stiffness estimates following treatment initiation or modification, according to current guidelines; (3) the assessment of the impact of non-invasive arterial stiffness estimation on cardiac, vascular and renal damage and patient's CV prognosis (fatal and non-fatal events); (4) the definition of the normal thresholds for PWV, AIx and CAP, in hypertensive patients, according to outcome data; and (5) the definition of the relationship between arterial stiffness, BP absolute level and BP variability, and outcomes.

The outcome-based results provided by the VASOTENS Registry will help establish a worldwide network of certified centers performing ambulatory PWA and will help validate and foster the use of the 24-hour PWA electronic health (e-health) solution for hypertension screening and follow-up. Ultimately, the study-based evidence of the clinical relevance of 24-hour non-invasive central arterial stiffness and hemodynamics assessment may help favor the inclusion of such evaluations among the standard procedures made available in hypertension centers, as well as practical recommendations for improving hypertension management and control.

Trial Design

The VASOTENS Registry is an international, multicenter, observational, non-randomized, prospective study.

Methods

Study Setting

A minimum of 20 hypertension centers will be involved worldwide, each providing at least 100 participants, in order to allow recruitment of a sufficiently consistent sample size able to demonstrate the study objectives. A list of participating centers grouped by countries is shown in Multimedia Appendix 3. Initially, hospitals from Italy and Russia will be enrolled because of their proximity to the study coordinators. Attempts will be made to select investigators among active members of international and national hypertension societies, including membership in the bodies specifically dedicated to blood pressure and arterial stiffness measurement. This will ensure high quality standards of data collection and facilitate the dissemination of information on the project and its findings.

Eligibility Criteria

Participants referred to the study centers for routine diagnostic evaluation of hypertension or established hypertensive patients will be eligible for inclusion in the study. Individuals fulfilling eligibility criteria (Textbox 1), whose data are contained in existing databases collected by the participating centers, and who are regularly followed-up at the center will have priority for enrolment.

Textbox 1. Study eligibility criteria.

Criteria

- Inclusion criteria
  - Male and female
  - Age ≥18 years
  - Participants referred to routine diagnostic evaluation for hypertension of any severity or stage, or established hypertensive patients
  - Good quality ABPM performed for clinical reasons with a BPLab device
    - Availability of individual measurements for ABPM on a bpw file (BPLab format)
    - Data directly uploaded on the telemedicine platform of the study
  - Availability of basic clinical information (see Textbox 2)
  - Availability of a signed informed consent form
- Exclusion criteria
- Age <18 years
- Atrial fibrillation, frequent ectopic beats, second or third degree atrioventricular blocks, or other conditions which might make difficult or unreliable the automatic BP measurement with the oscillometric technique
- Upper arm circumference <22 cm
- Pregnancy

However, naïve hypertensive participants will also be enrolled, provided that an ABPM is required for evaluating their potential hypertension status, according to current recommendations [5,33]. Once enrolled, participants will be visited every 6 or 12 months at the study centers (dependant on disease severity) for a minimum follow-up of 2 years, and submitted to the procedures detailed in the next sections.

Study Procedures

The project will not involve any type of diagnostic evaluation or pharmacological intervention and the investigators will be free to manage the patients included in the Registry according to the requirements of clinical practice and current guidelines [5]. However, as guidelines recommend, each patient will be followed-up with visits occurring at regular intervals: ideally every 6 months, and not less than once a year, for a minimum follow-up of 2 years. The investigators will also be free to use the information yielded by the ABPM tests for the clinical management of their patients. At each study visit, an ABPM by the BPLab device will be performed and patient's clinical data, such as family history, anthropometric data, habits, past and current diseases, therapies, office BP, and laboratory tests, including evaluation of target organ damage, will be collected and entered on the electronic case report form (e-CRF) located on the study website. A detailed list of the clinical data to be collected during the study is itemized in Textbox 2.

Textbox 2. Basic demographic and clinical information to be collected during the study.

Demographic and clinical information

- Age
- Gender
- Height (cm)
- Weight (kg)
- Ethnicity
- Superficial distance between jugulum and symphysis (surrogate of aortic length; cm)
- Waist circumference (cm)
- Smoking status
- Alcohol drinking
- Coffee or tea drinking
- Dyslipidemia (yes/no and indication on treatment)
- Diabetes (yes/no and indication on treatment)
- Diagnosis of hypertension (yes/no and indication on treatment)
- Family history of premature CV disease
- Medical history with particular regard to previous and/or concurrent CV diseases
- Office BP (mmHg) and heart rate (bpm) obtained in the same treatment condition as ABPM
- Electrocardiogram (ECG) indication on left ventricular hypertrophy, Sokolow–Lyon and Cornell index)
- Left ventricular mass index (LVMI, as g/m^2) at echocardiogram
- When available, diameter of the aorta (aortic annulus, root and sinotubular junction, in cm) and/or cardiac output (as L/min), assessed by the echocardiogram
- Intima-media thickness (IMT, mm) at carotid ultrasonography
- When available, ankle-brachial index
- Microalbuminuria (as mg/24h) or albumin-creatinine ratio (mg/g), and serum creatinine (g/dL), with subsequent calculation of estimated glomerular filtration rate (eGFR) by the Cockroft-Gault equation
- When available, PWV (m/s), Aix (%), and CAP (mmHg) taken during the office visit with a validated device different from the BPLab device (eg, Sphygmocor or Complior)

Ambulatory Blood Pressure Monitoring

Twenty-four hour ABPM will be performed with the BPLab device, which has been found to be accurate for estimation of both BP and vascular indices in properly conducted validation studies [26,27,34-36]. A description of the technique used to non-invasively assess central hemodynamics and arterial stiffness by the BPLab device is detailed in a separate section.

Current guidelines will be followed for proper recording performance [33,37,38]. In order to reduce patient's discomfort and to ensure a reliable minimum number of BP measurements for the subsequent data analysis (particularly for the evaluation of BP variability), the device will be programmed to measure BP at least every 20 minutes during the day (providing a minimum of 3 readings per hour) and at least 30 minutes during the night (providing a minimum of 2 readings per hour). Whenever possible, recordings will start between 8 am and 11 am, in order to standardize data collection and comparisons. The monitoring cuff will be placed on the non-dominant arm, the lower edge 2 cm above elbow bend, with the bladder centered on the upper arm, to ensure uniform compression and decompression during inflation and deflation. In order to allow the proper evaluation of PWV, the length of the aorta will be derived by measuring the distance from the sternal notch (jugulum) to the upper edge of the pubic bone (symphysis). In the case of obese patients, this superficial morphological distance will be adjusted by using the frontal projection in standing position. Up to 2 BP test readings will be triggered manually before the device is activated for automatic measurements in order to test its proper functioning. Two sequential conventional (office) BP and heart rate readings will also be taken in the sitting position at the time of ABPM placement (with the same BPLab device or with a validated automatic or manual BP measuring device), and recorded on the e-CRF. Patients will be instructed to keep the arm still and to avoid any movement during each automatic BP measurement. Patients will be free to attend to their usual daily activities during ABPM (avoiding strenuous exercise). They will have to complete a diary in which daily activities (ie, time of sleeping, time of meals) will be reported together with the time of occurrence of unusual events or poor night sleep quality. The patient will come back to the outpatient clinic on the second

day of the recording (after at least 24 hours) to remove the monitor. Shortly after device removal, the recording will be downloaded to a computer using the telemedicine Web platform of the project. The investigator will obtain the results from the Web-based analysis software and verify each recording for compliance with quality criteria (see below for details). In case of a bad quality recording the investigator will have to repeat the recording as soon as possible, preferably within 2 days.

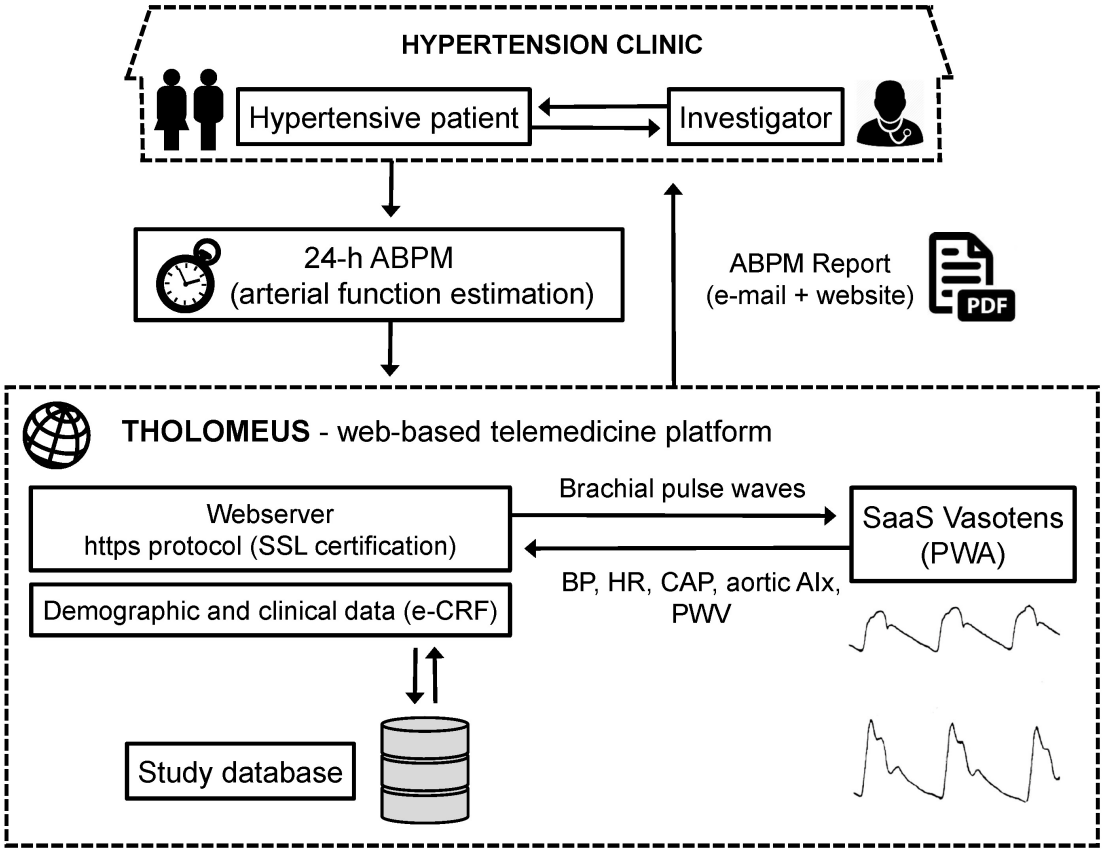
Pulse-Wave Analysis

The oscillometric BPLab device will also allow measurements of ambulatory arterial stiffness and central hemodynamics by recording pulsatile pressure changes at the brachial artery level. Briefly, during BP measurement, the pressure waveforms in the cuff are recorded during a step-by-step deflation and then digitalized and stored in the device memory. When data are uploaded on the Web-based telemedicine platform, the software processes the signal using proprietary mathematical algorithms. These are based on a specially developed hemodynamic model to get the PWV and transfer function that utilizes a modification in a certain frequency range within the acquired pulse signal to derive the aortic pressure wave, and thus to assess CAP and AIx. A detailed description of the methodology may be found elsewhere [26,28,30]. As aforementioned, the accuracy of the BPLab device for the assessment of vascular indices has been validated in studies against a non-invasive gold standard [26,27].

Web-Based Telemedicine Platform

Data contained in existing electronic databases or data of newly enrolled subjects fulfilling the inclusion criteria will be uploaded and entered on the study website. These data will include ABPM measures (peripheral or brachial BP, CAP, and arterial stiffness) obtained with a BPLab device and clinical data. Data collection will be ensured by a certified Web-based telemedicine platform (THOLOMEUS, Biotechmed Ltd., Somma Lombardo, Varese Italy) available on the Tholomeus website [31]. The choice of using an e-health tool for study management is based on the potential of such a solution to allow standardized and centralized data collection, prompt data validation and analysis, effective study monitoring and auditing, easy and real-time distribution of software updates, and bug corrections. It will also help provide advanced screening options for the patients with hypertension through a worldwide network of expert centers connected together. ABPM data will be uploaded on the website as bpw files (original file format of the standard analysis software of BPLab device, for centers already using such software) or by plugging the ABPM device to the computer through a *Universal Serial Bus* (USB) cable. ABPM data will be transmitted to the website and analyzed in real-time with production of an electronic report (as an Acrobat Reader pdf file) sent by email to the investigator and simultaneously published on the user-restricted area of the website. The Web-based telemedicine platform is complemented by an e-CRF, which will allow entering main patient's clinical data into the study database. Access to the website and e-CRF will be granted through authentication with username and password according to local data protection and privacy regulations. A schematic diagram of the workflow of the Web-based telemedicine platform is shown in Figure 1.

Figure 1. Workflow of the THOLOMEUS Web-based telemedicine system used in the VASOTENS Registry.



Ethics

The study will be conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki [39]. The data collection will start in each center only after approval or notification (depending on local laws) of the study protocol and amendments (if any) by the independent ethics committees of the centers. All participants meeting inclusion criteria and not meeting exclusion criteria will be fully informed about the study design and purposes, and asked to give a written informed consent if willing to participate. All patient-related information is subject to medical confidentiality and to the local data protection acts. Data will be pseudonymized before any aggregate analysis. This means that main data useful to identify the patient will be replaced with a unique number and thus the patient's identity will not be disclosed to third parties, except the promoter.

Data Quality Control

Given its observational nature, no formal monitoring of the study is foreseen for this study. However, electronic data verification will be done remotely by a data manager who will get in touch with the investigators and, when needed, will ask the investigator to correct the erroneous data or complete missing data on the e-CRF. The investigator will be required to verify and check that the information provided on the e-CRF is as precise and accurate as possible. The procedures for data monitoring and verification will be ensured by the presence of logical checks and range (defined a priori) for the different variables and by automatic identification of inconsistencies by the e-CRF used to manage the database. The controls and related corrections will be made on the e-CRF directly by the investigator on the website. Since no standardized or centralized analysis of laboratory tests will be done, except for ABPM, particular attention will be dedicated to check the congruency of data collected through ultrasonography, ECG, and biochemistry.

Dissemination Activities

An important part of the study-related activities will be aimed at disseminating the knowledge on the correct use of ambulatory CAP and arterial stiffness estimation in clinical practice and in research, and thus at achieving a possibly standardized and widespread use of this integrated technology. Manuscripts reporting main study results and documents embedding specific recommendations on the use of the technique will be developed. All publications related to the study results will be prepared by the study coordinators with the support of the scientific committee and will include any investigator significantly contributing to the success of the study. A complete list of investigators will be provided at the end of each manuscript. The original study protocol (with appendices) can be downloaded from, and any future study results will be published on the VASOTENS study website.

Statistical Methods

Primary Outcome Measures

The primary study endpoint will consist of the calculations of the average 24-hour values of PWV, CAP, and AIx during the study. The main time points will be the baseline versus the end of the study, corresponding to 2 years following enrolment, but averages will be computed for each study visit occurring during the follow-up.

Secondary Outcome Measures

The endpoints considered secondary study variables and evaluated according to the same timeline applied to the primary outcome measures are shown in Textbox 3.

Textbox 3. Secondary outcome measures.

Outcome measures

- Average 24-hour brachial (or peripheral) SBP and DBP
- 24-hour brachial SBP and DBP variability estimated by:
  - Unweighted standard deviation: the standard deviation of 24-hour mean value of brachial SBP and DBP [40]
  - Weighted standard deviation: the standard deviation of the average of all brachial SBP and DBP values during day-time and night-time, with weights corresponding to the duration of day-time and night-time [41]
  - Average real variability (ARV): the mean of the successive absolute differences between adjacent brachial SBP and DBP values over the 24-hours [42]
- Cardiac damage, defined by the presence of cardiac hypertrophy, as determined by echocardiography (LVMI >115 g/m^2 in men and >95 g/m^2 in women according to the recommendations of the American Society of Echocardiography) [43,44] or ECG (Sokolow-Lyon index >3.5 mV + R in aVL >1.1 mV or Cornell voltage duration product >244 mV*ms) [5]
- Vascular damage, defined by the presence of carotid wall thickening or plaque (intima media thickness, IMT >0.9 mm) at ultrasonography and, if available, by an ankle-brachial index (ABI) <0.9 [5]
- Renal damage, defined by microalbuminuria (30-300 mg/24 h) or albumin–creatinine ratio (30–300 mg/g) (preferentially on morning spot urine) or reduced estimated glomerular filtration rate (eGFR <60 ml/min/1.73 m^2) [5]
- Cardiovascular fatal or non-fatal events: death or hospitalization for congestive heart failure, myocardial infarction, angina, stroke or cerebrovascular accident, renal failure, or other cardiovascular diseases

Sample Size

Given the observational nature of the study and the lack of precedent studies with a similar design and objectives, it is difficult to define a proper sample size. According to the number of subjects enrolled and followed-up in previous cross-sectional or prospective trials [10,11,14-21], and considering the number of participants usually needed to collect a sufficient number of clinical outcomes in longitudinal population studies based on ABPM [45], a minimum number of 2000 participants has been considered for the present study. Ideally, such a sample size will be able to provide consistent outcome-based information on the clinical relevance of 24-hour PWA.

Statistical Analysis

Analysis will be performed on all participants with valid ABPM recordings at study entry and during the follow-up. Principal derived ABPM variables and arterial stiffness measures will be immediately calculated once the data will be uploaded on the website and their quality verified. Analysis of 24-hour recordings will be preceded by removal of artifacts according to previously described editing criteria [37,38]. Valid recordings will be considered those with (1) an interval between measurements not exceeding 30 minutes during the whole 24-hours; (2) a recording duration of at least 24-hours; (3) at least 70% of expected number of readings; and (4) at least 20 valid readings during the day-time and 7 during the nigh-time. Average brachial and central SBP and DBP, and arterial stiffness indices (PWV and AIx) will be computed by averaging all the individual readings over the 24-hours, and separately for the day-time and night-time subperiods, and for each hour of the recording. Measures of BP variabilities (unweighted standard deviation, weighted standard deviation and ARV) will also be computed based on individual readings. Other ABPM variables of interest (eg, nocturnal BP fall, morning surge, etc) will be subsequently defined in the framework of sub-analyses based on the Registry data and calculated according to procedures specifically defined.

Basic descriptive statistics will be provided for all variables with calculations of absolute and relative frequencies for categorical variables and calculation of average value, standard deviation, and minimum and maximum for continuous variables. The relationship between BP and arterial stiffness estimates, and organ damage and prognosis will be evaluated by appropriate parametric or non parametric tests, depending on the type of data distribution (normal or non-normal). The occurrence of any cardiovascular event during the study will be evaluated by the Kaplan-Meier method. Time-to-event curves will be drawn and the survival analysis will be performed according to the Cox proportional hazard model to analyze predictors of outcomes. Data management and analysis will be carried out by SPSS for Windows version 20. A $P<0.05$ will be considered as the minimum level of statistical significance.

Results

Enrolment of patients in the first study centers started in October 2015. The first data analysis is expected to be performed by the end of 2017 or early 2018.

Discussion

The VASOTENS Registry is an international, multicenter, observational, non-randomized, prospective study devised to evaluate the clinical impact and usefulness of 24-hour PWA for hypertension management.

Expected Contributions

With respect to all of the studies briefly reviewed in this paper, our Registry may offer, for the first time, the possibility to shed light on the role of 24-hour ambulatory central hemodynamics and stiffness as predictors of cardiovascular outcomes. The study results may help determine whether the clinical value of ABPM might be further increased by incorporating information on ambulatory CAP and stiffness. The results of the VASOTENS Registry will help define the normalcy thresholds for current and future indices derived from 24-hour PWA, according to outcome data. They will also provide supporting evidence for the inclusion of such evaluations in recommendations on hypertension management and its possible impact on the general population health state. Thanks to this study, an important lack of knowledge will be worked-out and the foundation for future studies with a more robust design could be hopefully laid.

Limitations

The non-randomized uncontrolled nature of the study and the rather wide selection criteria may increase the risk of obtaining heterogeneous and poorly powered results. In addition, the fact that patients will be recruited in hypertension centers may result in a potential selection bias: the sample being unrepresentative or not fully representative of the general population of patients with hypertension. Despite these important limitations, we think that since the study is carried out in a real-life setting and that it is a longitudinal long-term outcome-driven study, it represents an important added value.

Dissemination Strategy

An important component of this study is disseminating the knowledge on correct use of ambulatory CAP and arterial stiffness estimation and to help create an e-health network for a standardized and widespread use of this hypertension screening tool. In order to achieve this, apart from data collection, several disseminating activities are required. An exchange of knowledge between participating centers will be achieved by the cooperation of investigators in preparing a possibly unified methodology of ABPM data collection and analysis and by jointly addressing methodological issues that may arise during the project. Data collected in the Registry will foster the performance of studies aimed at optimizing a possible clinical application of non-invasive ambulatory arterial stiffness estimation. The study will help provide instructions on appropriate ambulatory arterial stiffness monitoring methodology to other physicians, particularly to intermediate level centers, not necessarily experts in ABPM use and arterial stiffness determination. A major task of the consortium will be to provide these participants with accurate information on correct methodology and interpretation of such data, in order to support them in case of difficulties and to monitor the

correctness of the use of the methodology in these centers during the project. The study findings will favor preparation of specific recommendations on the use and clinical application of ABPM integrated with arterial stiffness evaluation. The study will also ensure cooperation between international and national scientific societies in the area related to ABPM and arterial stiffness monitoring. This will facilitate the dissemination of information on the project and its findings and will also allow an interaction with writing committees involved in the preparation of guidelines pertinent to this area

Conclusions

The results of the data collected at baseline and during regular follow-up of hypertensive patients in the VASOTENS Registry will help define the normalcy thresholds for current and future indices derived from 24-hour PWA, according to outcome data. They will also provide supporting evidence on the clinical usefulness of such a technological approach, based on telemedicine, for the screening and follow-up of the vascular function status of the patients with hypertension.

Acknowledgments

This is an investigator-initiated study, endorsed by the Russian and Italian Societies of Hypertension. The study coordinator, Italian Institute of Telemedicine, is the promoter and main sponsor of the study, and makes available its resources and facilities for conducting the trial. BPLab GmbH provides the ambulatory blood pressure devices, and Biotechmed Ltd provides the Web-based telemedicine platform used for data collection, at no cost. These funding sources had no role in the design of the study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results. For this study, no additional funding source is available.

Authors' Contributions

SO conceived the study and defined the study design with INP. SO and INP wrote the protocol. SO, INP, GP, and ANR contributed to refinement of the study protocol. All authors approved the final manuscript.

Conflicts of Interest

SO is scientific consultant of Biotechmed Ltd. The other authors do not declare any conflicts of interest.

Multimedia Appendix 1

VASOTENS Registry Study Protocol.

[PDF File (Adobe PDF File), 451KB - resprot_v5i2e137_app1.pdf]

Multimedia Appendix 2

Updated SPIRIT checklist.

[PDF File (Adobe PDF File), 241KB - resprot_v5i2e137_app2.pdf]

Multimedia Appendix 3

List of centers.

[PDF File (Adobe PDF File), 35KB - resprot_v5i2e137_app3.pdf]

References

1. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, European Network for Non-invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006 Nov;27(21):2588-2605 [FREE Full text] [doi: 10.1093/eurheartj/ehl254] [Medline: 17000623]
2. McEniery CM, Cockcroft JR, Roman MJ, Franklin SS, Wilkinson IB. Central blood pressure: current evidence and clinical importance. Eur Heart J 2014 Jul;35(26):1719-1725 [FREE Full text] [doi: 10.1093/eurheartj/eht565] [Medline: 24459197]
3. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol 2010 Mar 30;55(13):1318-1327 [FREE Full text] [doi: 10.1016/j.jacc.2009.10.061] [Medline: 20338492]
4. Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. J Am Coll Cardiol 2014 Feb 25;63(7):636-646 [FREE Full text] [doi: 10.1016/j.jacc.2013.09.063] [Medline: 24239664]
5. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension

(ESH) and of the European Society of Cardiology (ESC). J Hypertens 2013 Jul;31(7):1281-1357. [doi: 10.1097/01.hjh.0000431740.32696.cc] [Medline: 23817082]
6. Kim DH, Braam B. Assessment of arterial stiffness using applanation tonometry. Can J Physiol Pharmacol 2013 Dec;91(12):999-1008. [doi: 10.1139/cjpp-2013-0010] [Medline: 24289069]
7. Nelson MR, Stepanek J, Cevette M, Covalciuc M, Hurst RT, Tajik AJ. Noninvasive measurement of central vascular pressures with arterial tonometry: clinical revival of the pulse pressure waveform? Mayo Clin Proc 2010 May;85(5):460-472 [FREE Full text] [doi: 10.4065/mcp.2009.0336] [Medline: 20435839]
8. Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. Eur Heart J 2010 Aug;31(15):1865-1871 [FREE Full text] [doi: 10.1093/eurheartj/ehq024] [Medline: 20197424]
9. Zhang Y, Agnoletti D, Safar ME, Wang J, Topouchian J, Xu Y, et al. Comparison study of central blood pressure and wave reflection obtained from tonometry-based devices. Am J Hypertens 2013 Jan;26(1):34-41. [doi: 10.1093/ajh/hps031] [Medline: 23382325]
10. Theilade S, Lajer M, Hansen TW, Joergensen C, Persson F, Andrésdottir G, et al. 24-hour central aortic systolic pressure and 24-hour central pulse pressure are related to diabetic complications in type 1 diabetes - a cross-sectional study. Cardiovasc Diabetol 2013;12:122 [FREE Full text] [doi: 10.1186/1475-2840-12-122] [Medline: 23978271]
11. Protogerou AD, Argyris AA, Papaioannou TG, Kollias GE, Konstantonis GD, Nasothimiou E, et al. Left-ventricular hypertrophy is associated better with 24-h aortic pressure than 24-h brachial pressure in hypertensive patients: the SAFAR study. J Hypertens 2014 Sep;32(9):1805-1814. [doi: 10.1097/HJH.0000000000000263] [Medline: 24999798]
12. Zhang Y, Kollias G, Argyris AA, Papaioannou TG, Tountas C, Konstantonis GD, et al. Association of left ventricular diastolic dysfunction with 24-h aortic ambulatory blood pressure: the SAFAR study. J Hum Hypertens 2015 Jul;29(7):442-448. [doi: 10.1038/jhh.2014.101] [Medline: 25391758]
13. Aissopou EK, Argyris AA, Nasothimiou EG, Konstantonis GD, Tampakis K, Tentolouris N, et al. Ambulatory aortic stiffness is associated with narrow retinal arteriolar caliber in hypertensives: the SAFAR study. Am J Hypertens 2016 May;29(5):626-633. [doi: 10.1093/ajh/hpv145] [Medline: 26304958]
14. Elsurer R, Afsar B. Serum uric acid and arterial stiffness in hypertensive chronic kidney disease patients: sex-specific variations. Blood Press Monit 2014 Oct;19(5):271-279. [doi: 10.1097/MBP.0000000000000056] [Medline: 24892881]
15. Maloberti A, Cesana F, Hametner B, Dozio D, Villa P, Hulpke-Wette M, et al. Increased nocturnal heart rate and wave reflection are early markers of cardiovascular disease in Williams-Beuren syndrome children. J Hypertens 2015 Apr;33(4):804-9; discussion 809. [doi: 10.1097/HJH.0000000000000454] [Medline: 25915885]
16. Williams B, Lacy PS, Baschiera F, Brunel P, Düsing R. Novel description of the 24-hour circadian rhythms of brachial versus central aortic blood pressure and the impact of blood pressure treatment in a randomized controlled clinical trial: the Ambulatory Central Aortic Pressure (AmCAP) study. Hypertension 2013 Jun;61(6):1168-1176 [FREE Full text] [doi: 10.1161/HYPERTENSIONAHA.111.00763] [Medline: 23630950]
17. Karpetas A, Sarafidis PA, Georgianos PI, Protogerou A, Vakianis P, Koutroumpas G, et al. Ambulatory recording of wave reflections and arterial stiffness during intra- and interdialytic periods in patients treated with dialysis. Clin J Am Soc Nephrol 2015 Apr 7;10(4):630-638 [FREE Full text] [doi: 10.2215/CJN.08180814] [Medline: 25635033]
18. Koutroumbas G, Georgianos PI, Sarafidis PA, Protogerou A, Karpetas A, Vakianis P, et al. Ambulatory aortic blood pressure, wave reflections and pulse wave velocity are elevated during the third in comparison to the second interdialytic day of the long interval in chronic haemodialysis patients. Nephrol Dial Transplant 2015 Dec;30(12):2046-2053. [doi: 10.1093/ndt/gfv090] [Medline: 25920919]
19. Omboni S, Posokhov IN, Rogoza AN. Evaluation of 24-hour arterial stiffness indices and central hemodynamics in healthy normotensive subjects versus treated or untreated hypertensive patients: a feasibility study. Int J Hypertens 2015;2015:601812 [FREE Full text] [doi: 10.1155/2015/601812] [Medline: 25692032]
20. Posokhov IN, Kulikova NN, Starchenkova IV, Grigoricheva EA, Evdokimov VV, Orlov AV, et al. The “Pulse Time Index of Norm” highly correlates with the left ventricular mass index in patients with arterial hypertension. Vasc Health Risk Manag 2014;10:139-144 [FREE Full text] [doi: 10.2147/VHRM.S58351] [Medline: 24672245]
21. Kuznetsova TY, Korneva VA, Bryantseva EN, Barkan VS, Orlov AV, Posokhov IN, et al. The 24-hour pulse wave velocity, aortic augmentation index, and central blood pressure in normotensive volunteers. Vasc Health Risk Manag 2014;10:247-251 [FREE Full text] [doi: 10.2147/VHRM.S61978] [Medline: 24812515]
22. Minyukhina IE, Lipatov KS, Posokhov IN. Analysis of 24-hour pulse wave velocity in patients with renal transplantation. Int J Nephrol Renovasc Dis 2013;6:125-129 [FREE Full text] [doi: 10.2147/IJNRD.S47011] [Medline: 23843699]
23. Aksenova TA, Gorbunov VV, Parkhomenko IV. [24-hour monitoring central aortic pressure in patients with hypertensive disease and concomitant chronic obstructive pulmonary disease]. Klin Med (Mosk) 2013;91(7):43-47. [Medline: 24437169]
24. Wassertheurer S, Kropf J, Weber T, van der Giet M, Baulmann J, Ammer M, et al. A new oscillometric method for pulse wave analysis: comparison with a common tonometric method. J Hum Hypertens 2010 Aug;24(8):498-504 [FREE Full text] [doi: 10.1038/jhh.2010.27] [Medline: 20237499]

25. Luzardo L, Lujambio I, Sottolano M, da Rosa A, Thijs L, Noboa O, et al. 24-h ambulatory recording of aortic pulse wave velocity and central systolic augmentation: a feasibility study. Hypertens Res 2012 Oct;35(10):980-987. [doi: 10.1038/hr.2012.78] [Medline: 22622282]
26. Rogoza AN, Kuznetsov AA. Central aortic blood pressure and augmentation index: comparison between Vasotens and SphygmoCor technology. RRCC 2012 May;3:27-33. [doi: 10.2147/RRCC.S30994]
27. Kotovskaya YV, Kobalava ZD, Orlov AV. Validation of the integration of technology that measures additional “vascular” indices into an ambulatory blood pressure monitoring system. Med Devices (Auckl) 2014;7:91-97 [FREE Full text] [doi: 10.2147/MDER.S61839] [Medline: 24833924]
28. Posokhov IN. Pulse wave velocity 24-hour monitoring with one-site measurements by oscillometry. Med Devices (Auckl) 2013;6:11-15 [FREE Full text] [doi: 10.2147/MDER.S42082] [Medline: 23549868]
29. Protogerou AD, Argyris A, Nasothimiou E, Vrachatis D, Papaioannou TG, Tzamouranis D, et al. Feasibility and reproducibility of noninvasive 24-h ambulatory aortic blood pressure monitoring with a brachial cuff-based oscillometric device. Am J Hypertens 2012 Aug;25(8):876-882. [doi: 10.1038/ajh.2012.63] [Medline: 22673021]
30. Ageenkova OA, Purygina MA. Central aortic blood pressure, augmentation index, and reflected wave transit time: reproducibility and repeatability of data obtained by oscillometry. Vasc Health Risk Manag 2011;7:649-656 [FREE Full text] [doi: 10.2147/VHRM.S24877] [Medline: 22140314]
31. THOLOMEUS (TelemedicineHOme teLemOnitoring for MEdical sUrveillance of chronic diSeases). URL: https://www.tholomeus.net/Default.aspx [accessed 2016-06-14] [WebCite Cache ID 6iFPwmTBF]
32. Chan A, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013 Feb 5;158(3):200-207. [doi: 10.7326/0003-4819-158-3-201302050-00583] [Medline: 23295957]
33. O'Brien E, Parati G, Stergiou G, Asmar R, Beilin L, Bilo G, European Society of Hypertension Working Group on Blood Pressure Monitoring. European Society of Hypertension position paper on ambulatory blood pressure monitoring. J Hypertens 2013 Sep;31(9):1731-1768. [doi: 10.1097/HJH.0b013e328363e964] [Medline: 24029863]
34. Koudryavtcev SA, Lazarev VM. Validation of the BPLab(®) 24-hour blood pressure monitoring system according to the European standard BS EN 1060-4:2004 and British Hypertension Society protocol. Med Devices (Auckl) 2011;4:193-196 [FREE Full text] [doi: 10.2147/MDER.S25800] [Medline: 22915946]
35. Dorogova IV, Panina ES. Comparison of the BPLab® sphygmomanometer for ambulatory blood pressure monitoring with mercury sphygmomanometry in pregnant women: validation study according to the British Hypertension Society protocol. Vasc Health Risk Manag 2015;11:245-249 [FREE Full text] [doi: 10.2147/VHRM.S82381] [Medline: 25926739]
36. Ledyaev MY, Stepanova OV, Ledyaeva AM. Validation of the BPLab(®) 24-hour blood pressure monitoring system in a pediatric population according to the 1993 British Hypertension Society protocol. Med Devices (Auckl) 2015;8:115-118 [FREE Full text] [doi: 10.2147/MDER.S78515] [Medline: 25674018]
37. Parati G, Omboni S, Palatini P, Rizzoni D, Bilo G, Valentini M, et al. Italian society of hypertension guidelines for conventional and automated blood pressure measurement in the office, at home and over 24 hours. High Blood Press Cardiovasc Prev 2008 Oct;15(4):283-310. [doi: 10.2165/0151642-200815040-00008] [Medline: 23355131]
38. Omboni S, Palatini P, Parati G, Working Group on Blood Pressure Monitoring of the Italian Society of Hypertension. Standards for ambulatory blood pressure monitoring clinical reporting in daily practice: recommendations from the Italian Society of Hypertension. Blood Press Monit 2015 Oct;20(5):241-244. [doi: 10.1097/MBP.0000000000000135] [Medline: 26049213]
39. World MA. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013 Nov 27;310(20):2191-2194. [doi: 10.1001/jama.2013.281053] [Medline: 24141714]
40. Mancia G, Ferrari A, Gregorini L, Parati G, Pomidossi G, Bertinieri G, et al. Blood pressure and heart rate variabilities in normotensive and hypertensive human beings. Circ Res 1983 Jul;53(1):96-104 [FREE Full text] [Medline: 6861300]
41. Bilo G, Giglio A, Styczkiewicz K, Caldara G, Maronati A, Kawecka-Jaszcz K, et al. A new method for assessing 24-h blood pressure variability after excluding the contribution of nocturnal blood pressure fall. J Hypertens 2007 Oct;25(10):2058-2066. [doi: 10.1097/HJH.0b013e32829c6a60] [Medline: 17885548]
42. Mena L, Pintos S, Queipo NV, Aizpúrua JA, Maestre G, Sulbarán T. A reliable index for the prognostic significance of blood pressure variability. J Hypertens 2005 Mar;23(3):505-511. [Medline: 15716690]
43. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. Circulation 1977 Apr;55(4):613-618. [Medline: 138494]
44. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Chamber Quantification Writing Group, American Society of Echocardiography's GuidelinesStandards Committee, European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005 Dec;18(12):1440-1463. [doi: 10.1016/j.echo.2005.10.005] [Medline: 16376782]
45. Gu Y, Thijs L, Li Y, Asayama K, Boggia J, Hansen TW, International Database on Ambulatory blood pressure in relation to Cardiovascular Outcomes (IDACO) Investigators. Outcome-driven thresholds for ambulatory pulse pressure in 9938

participants recruited from 11 populations. Hypertension 2014 Feb;63(2):229-237 [FREE Full text] [doi: 10.1161/HYPERTENSIONAHA.113.02179] [Medline: 24324050]

Abbreviations

ABP: ambulatory blood pressure
ABPM: ambulatory blood pressure monitoring
AIx: Augmentation Index
BP: blood pressure
CAP: central aortic pressure
CV: cardiovascular
ECG: electrocardiogram
e-CRF: electronic case report form
LVMI: left ventricular motility injury
PWA: pulse-wave analysis
PWV: pulse wave velocity
SBP: systolic blood pressure
VASOTENS: Vascular health ASsessment Of The HypertENSive Patients

Edited by G Eysenbach; submitted 08.02.16; peer-reviewed by A Protogerou, G Paré, I Kiss; comments to author 23.03.16; revised version received 01.05.16; accepted 04.05.16; published 29.06.16.

Please cite as:
Omboni S, Posokhov IN, Parati G, Avolio A, Rogoza AN, Kotovskaya YV, Mulè G, Muiesan ML, Orlova IA, Grigoricheva EA, Cardona Muñoz E, Zelveian PH, Pereira T, Peixoto Maldonado JM
Vascular Health Assessment of The Hypertensive Patients (VASOTENS) Registry: Study Protocol of an International, Web-Based Telemonitoring Registry for Ambulatory Blood Pressure and Arterial Stiffness
JMIR Res Protoc 2016;5(2):e137
URL: http://www.researchprotocols.org/2016/2/e137/
doi:10.2196/resprot.5619
PMID:27358088

Original Paper

A Registry for Evaluation of Efficiency and Safety of Surgical Treatment of Cartilage Defects: The German Cartilage Registry (KnorpelRegister DGOU)

Julia Maurer[1*], MA; Birgit Grotejohann[1*], DPhil; Carolin Jenkner[1*]; Carla Schneider[1*]; Thomas Flury[1*], Dr. rer. nat.; Adrian Tassoni[1*]; Peter Angele[2,3*], Prof. Dr. med.; Jürgen Fritz[4*], MD; Dirk Albrecht[5*], MD; Philipp Niemeyer[6*], Prof. Dr. med.

[1]Clinical Trials Unit, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg im Breisgau, Germany

[2]Department Trauma Surgery, University Hospital Regensburg, Regensburg, Germany

[3]Sporthopaedicum, Straubing, Berlin, Regensburg, München, Germany

[4]Orthopädisch Chirurgisches Centrum Tübingen, Tübingen, Germany

[5]Klinik im Kronprinzenbau Reutlingen, Reutlingen, Germany

[6]Department of Orthopedics and Trauma Surgery, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg im Breisgau, Germany

[*]all authors contributed equally

Corresponding Author:
Julia Maurer, MA
Clinical Trials Unit
Medical Center - University of Freiburg
Faculty of Medicine, University of Freiburg
Elsaesser Str 2
Freiburg im Breisgau, 79110
Germany
Phone: 49 761 270 ext 77830
Fax: 49 761 270 73730
Email: julia.maurer@uniklinik-freiburg.de

Abstract

Background: The need for documentation in cartilage defects is as obvious as in other medical specialties. Cartilage defects can cause significant pain, and lead to reduced quality of life and loss of function of the affected joint. The risk of developing osteoarthritis is high. Therefore, the socioeconomic burden of cartilage defects should not be underestimated.

Objective: The objective of our study was to implement and maintain a registry of all patients undergoing surgical treatment of cartilage defects.

Methods: We designed this multicenter registry for adults whose cartilage defects of a knee, ankle, or hip joint are treated surgically. The registry consists of two parts: one for the physician and one for the patient. Data for both parts will be gathered at baseline and at 6-, 12-, 24-, 36-, 60-, and 120-month follow-ups.

Results: To date, a wide range of German, Swiss, and Austrian trial sites are taking part in the German Cartilage Registry, soon to be followed by further sites. More than 2124 (as of January 31, 2016) cases are already documented and the first publications have been released.

Conclusions: The German Cartilage Registry addresses fundamental issues regarding the current medical care situation of patients with cartilage defects of knee, ankle, and hip joints. In addition, the registry will help to identify various procedure-specific complications, along with putative advantages and disadvantages of different chondrocyte products. It provides an expanding large-scale, unselected, standardized database for cost and care research for further retrospective studies.

Trial Registration: German Clinical Trials Register: DRKS00005617; https://drks-neu.uniklinik-freiburg.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00005617 (Archived by WebCite at http://www.webcitation.org/6hbFqSws0)

(JMIR Res Protoc 2016;5(2):e122) doi:10.2196/resprot.5895

KEYWORDS

ankle joint; cartilage defect; chondral defect; hip joint; knee joint; patient registry

Introduction

Isolated cartilage defects are common orthopedic disorders in middle-aged patients that are typically associated with pain, reduced quality of life, and loss of function of the affected joint [1,2]. In fact, chondral defects have been described in 34% to 62% of knee arthroscopies [3-6]. They tend to progress to osteoarthritis, as spontaneous healing is rare, and can therefore be considered a potential risk factor or precondition for joint degeneration [7].

As of 2008, nearly 27 million US adults aged 25 and older have clinical osteoarthritis [8]. Osteoarthritis is the fourth most frequent cause of hospital admission in the United States and the leading cause of joint replacement surgery [9]. In 2009, in the United States 905,000 knee or hip replacements were conducted, resulting in treatment costs of US $42.3 billion [9]. In sum, osteoarthritis is one of the major causes of global disability and is a socioeconomic burden that will most likely soon become a substantial problem for global health systems [10,11]. Therefore, it is very important to cure cartilage defects in the first place.

Concerning cartilage repair techniques, several therapies have been established, which can be divided into two major groups: bone marrow stimulation techniques and transplantation techniques [12,13]. Despite the fact that the number of randomized controlled trials (RCTs) on cartilage repair has increased significantly over the years, RCTs aim only at direct comparison between two surgical procedures, such as the comparison between arthroscopic microfracturing and autologous chondrocyte implantation [14-18]. In addition, only a highly selected patient population is considered in these trials. Real-life clinical data are hardly ever considered.

The group of Engen et al [11] published a study on this issue and came to the final conclusion that only approximately 4.5% of patients with cartilage defects are represented by RCTs. Jakobsen et al [19] stated that promising results of cartilage repair studies have to be interpreted carefully due to their low methodological quality. Against this background and based on the fact that some scientific questions, such as a detailed analysis of surgical complication, and the influence of sex, overweight, and other factors, cannot be investigated in RCTs, many experts think that RCTs should be supplemented by well-designed observational studies [20-24]. Thus, we have initiated this multicenter patient registry to 1) systematically describe the current medical care situation of patients undergoing surgical treatment of their cartilage defect, 2) compare competing cartilage therapies regarding their outcomes, procedure-specific complication rates, and symptom relief by collecting real-life clinical data, 3) identify putative advantages and disadvantages of various chondrocyte products in daily clinical care, 4) develop new hypotheses on cartilage repair techniques as a basis for future RCTs and to test outcomes of former RCTs in a larger and more representative population, and 5) evaluate the efficiency and safety of surgically treated cartilage defects of knee, hip, and ankle joints, independent of strict patient characteristics or surgical procedure.

Here we describe the study design and layout of the German Cartilage Registry, which is to our knowledge the first patient registry for this indication worldwide.

Methods

Study Design

The German Cartilage Registry is an observational and international multicenter registry that was initiated by the *Arbeitsgemeinschaft Klinische Geweberegeneration* (Working Group Clinical Tissue Regeneration) of the German Society for Orthopaedics and Trauma (DGOU) in 2013. It is a purely scientifically motivated project and as a consequence independent of the interests of industrial partners. The study is conducted in accordance with the Declaration of Helsinki and registered at germanctr.de (DRKS00005617).

The registry investigates the efficiency and safety of surgical treatment of cartilage defects in patients under real-life conditions. In October 2013, the assessment started with the documentation of cartilage defects of the knee. The modules for cartilage defects of the ankle and hip joint were implemented 1 year later.

Ethics Approval

Depending on individual state's law, investigators consult the responsible ethics committee before starting the study at their site. At their request, investigators are supported by the Clinical Trials Unit (CTU; Medical Center - University of Freiburg, Freiburg, Germany) in preparing the essential documents for submission (first approval in Freiburg on March 13, 2013, internal number 105/13). So far, 33 ethics committees have welcomed the implementation of the German Cartilage Registry in their jurisdiction.

After consulting the ethics committee, investigators are allowed to take part in the German Cartilage Registry.

Study Population

All patients aged ≥18 years who meet the following criteria are eligible to take part in the German Cartilage Registry: 1) they have had surgical treatment of cartilage defects of a knee, ankle, or hip joint at a participating site, 2) they have given written informed consent, 3) they have a personal email address.

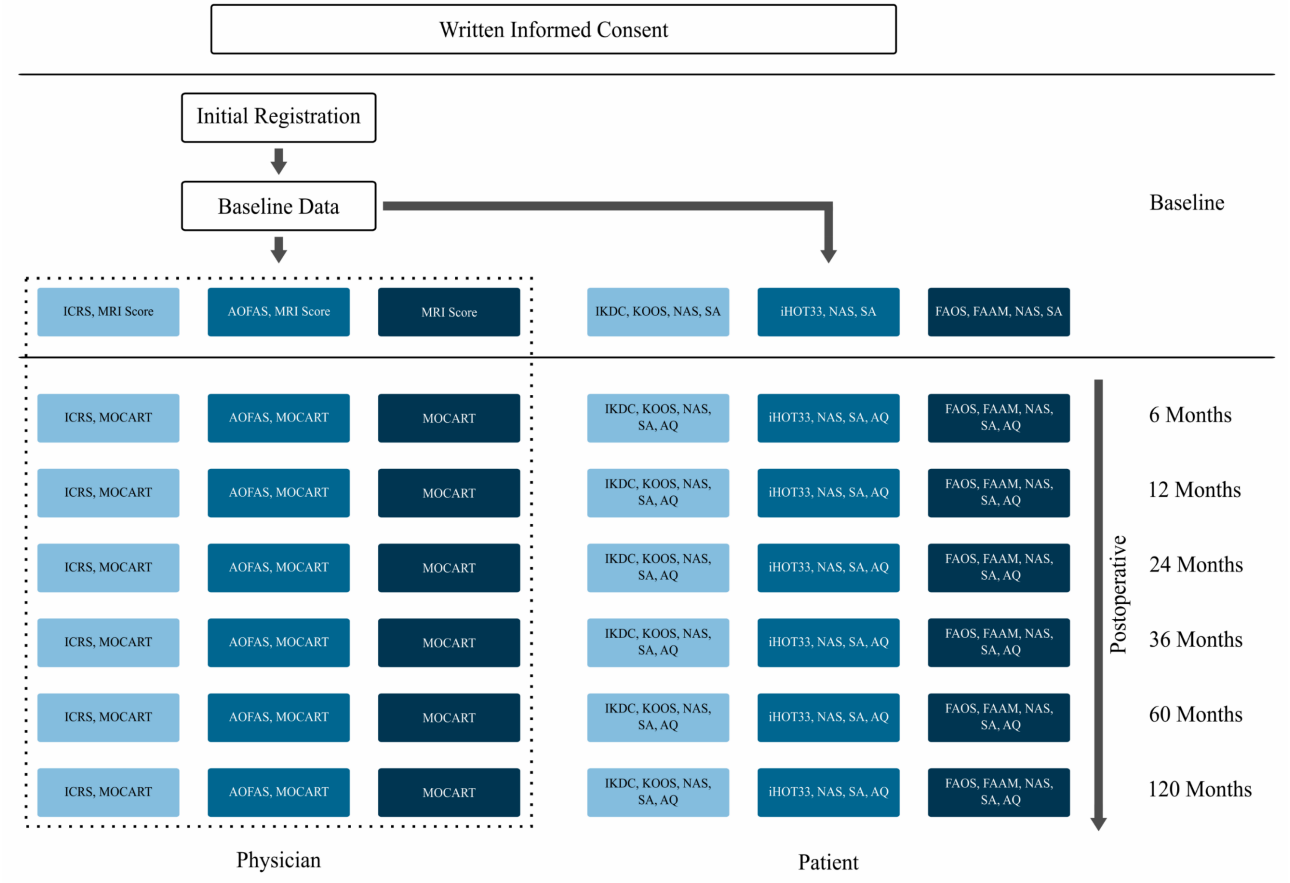
Procedure and Data Collection

Only after the patient has signed the written informed consent the investigator is allowed to register the patient in the database. We recommend that this registration procedure takes place immediately after the surgery is completed. Thus, the investigator can type in the following mandatory baseline data

at the same time: initially, the date of surgery, the patient's identification, and the patient's email address to generate a new case; and subsequently, basic information concerning patient history and treatment technique. In the course of 6-, 12-, 24-, 36-, 60-, and 120-month follow-ups, the physician can document further optional data.

The day following initial data entry by the physician, the patient automatically receives an email inviting him or her to fill in a questionnaire for baseline data. Additionally, the patient receives an invitational email at 6-, 12-, 24-, 36-, 60-, and 120-month follow-ups to complete the questionnaire. If the patient does not complete the form within a given time limit, an email reminder is sent automatically. If the patient still does not fill in the questionnaire, the trial site seeks personal contact. Figure 1 shows the flow chart of the German Cartilage Registry in detail, naming all deployed questionnaires. Light blue represents all questionnaires that are used in the knee part, medium blue shows the questionnaires deployed in the hip part, and dark blue displays all questionnaires used in the ankle part of the German Cartilage Registry. Completion of the questionnaires shown in the dotted box is optional. Answering all other questionnaires is mandatory.

Figure 1. Flow chart of the German Cartilage Registry and questionnaires deployed to physicians and patients. AOFAS: American Orthopaedic Foot & Ankle Society; AQ: additional questions; FAAM: Foot and Ankle Ability Measure; FAOS: Foot and Ankle Outcome Score; ICRS: International Cartilage Repair Society; iHOT33: International Hip Outcome Tool-33; IKDC: International Knee Documentation Committee; KOOS: Knee injury and Osteoarthritis Outcome Score; MOCART: magnetic resonance observation of cartilage repair tissue; MRI: magnetic resonance imaging; NAS: numeric analog scale for pain description; SA: sports activities.



Instruments

The German Cartilage Registry consists of two parts: one for the physician and one for the patient. At baseline, the physician section includes mandatory information on patient-specific characteristics (age, sex, smoking behavior, weight and height, as well as varus or valgus malalignment), the preliminary operation(s), all surgical procedures performed on the injured joint (including defect-specific characteristics), and therapy characteristics.

Furthermore, the physician can fill in a premagnetic resonance imaging score (similar to the magnetic resonance observation of cartilage repair tissue, or MOCART, score), as well as joint-specific scores, such as the International Cartilage Repair Society (ICRS) score (equal to International Knee Documentation Committee, IKDC, objective score) for the knee joint and American Orthopaedic Foot & Ankle Society (AOFAS) for the ankle joint [25,26]. Investigator's data entry at 6-, 12-, 24-, 36-, 60-, and 120-month follow-ups is optional. But there is the opportunity to document joint-specific scores, such as MOCART [27,28], AOFAS, and ICRS (see Figure 1).

At all times, the patient's questionnaire consists of a numeric analog scale for pain description, a few questions about sports activities, and joint-specific, validated, and standardized instruments, such as IKDC subjective score and Knee injury and Osteoarthritis Outcome Score (for the knee part) [29-33], International Hip Outcome Tool-33 (hip part) [34,35], Foot and

Ankle Outcome Score, and Foot and Ankle Ability Measure (ankle part) [36-38]. At 6-, 12-, 24-, 36-, 60-, and 120-month follow-ups, 3 additional questions ask about the patient's satisfaction with the surgical treatment at baseline and further surgeries (see Figure 1).

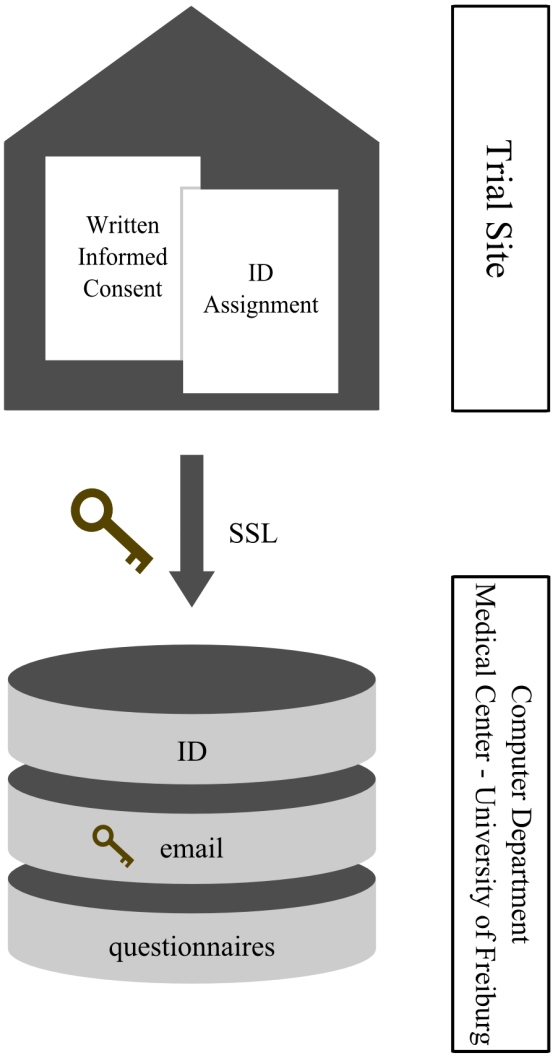
Data Entry

The Web-based remote data entry system called RDE-LIGHT was developed by the CTU of the Medical Center - University of Freiburg as an electronic data entry interface and data management system for clinical studies and other projects in clinical research. Data are collected paperless and directly on site via an Internet browser. The RDE-LIGHT system displays the questionnaires in a structured view in the main window, indicating the status of the questionnaires as traffic light colors. Questionnaires are based on HTML. RDE-LIGHT is available in various languages and validated according to GAMP 5 (ISPE, Tampa, FL, USA). Furthermore, it fulfills all requirements of good clinical practice.

The RDE-LIGHT system applies established security standards such as cryptographic security protocols (secure socket layer/transport layer security), user authentication protocols, and authorization concepts. For example, investigators can access data only of their own site, while the system denies unauthorized access. Data transfer to the database is encrypted and secured. The server is located in the Medical Computer Department of the Medical Center - University of Freiburg, with strict access control. Hence, common concepts of data protection are implemented. Changes to the database and the underlying system are logged, saved, and archived regularly to ensure end-to-end tracking.

When working with personal data, the CTU encourages involved researchers to use pseudonyms to prohibit the identification of their patients. The patients' names and contact details (email address) will be kept confidential and are available to the research team only for contact purposes. Any data presented publically will ensure participants' anonymity. In order to be able to automatically send emails to the patients when new questionnaires have to be completed, it is necessary to access the patients' email addresses in the system's database. As the email address is part of the patients' personal information, it is stored in an encrypted way in the database using password-based encryption with MD5 and Triple Data Encryption Standard. Figure 2 illustrates the data storage location and clearly shows that the email addresses are separated from the physicians' and patients' questionnaires, as well as the patients' identification, in a well-protected way.

Figure 2. Data storage location for the German Cartilage Registry. ID: identification; SSL: secure socket layer.



Statistical Analysis

After approval from the *Arbeitsgemeinschaft Klinische Geweberegeneration* (Working Group Clinical Tissue Regeneration), every participating physician is allowed to publish the full set of anonymized data available at that time. Data will always be prepared by an experienced biostatistician of the CTU. We are planning several descriptive analyses concerning the structure and composition of the registry. Analyses will be done by first specifying several different research questions (eg, efficacy of certain therapies in real-life datasets) and prespecifying inclusion criteria for these specific questions. Independently, every investigator is allowed to download his or her own data set for anonymized statistical evaluations. However, it is important to keep in mind that registry data need special care in the analysis, as populations are unbalanced and several sources of bias can be present, such as in confounding variables. Therefore, the results must be interpreted very carefully.

Quality Assurance

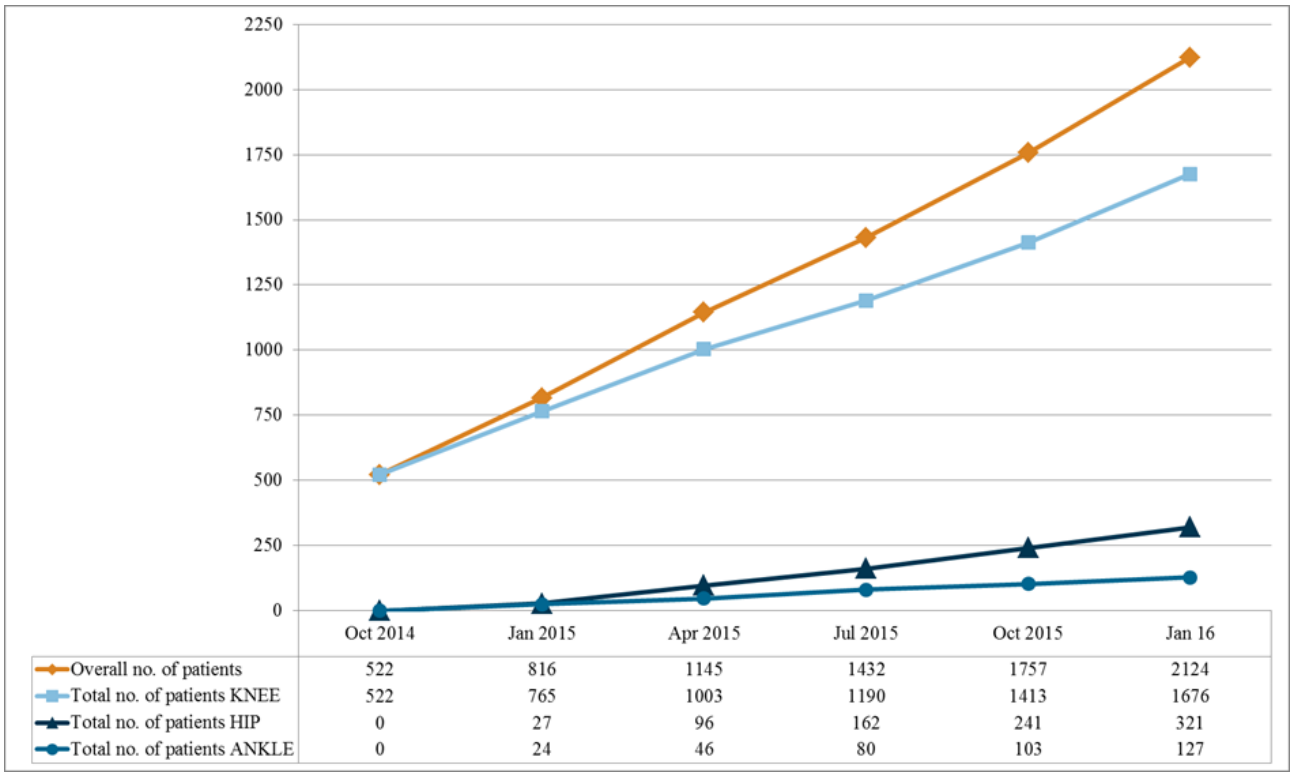
The registry is being implemented and maintained by the CTU of the Medical Center- University of Freiburg. The CTU is member of the network of coordinating centers for clinical trials in Germany [39] and offers profound expertise in all areas of clinical trial planning, conduct, and analysis, in both universities and industry. The CTU is involved in about 250 trials a year.

Skilled and experienced staff of the CTU offer email and telephone support for any emerging problems. Additionally, documents, user manuals, and Web-based instructions via video may help to assist physicians and other personnel at the site. A query management system helps to identify patients and physicians who did not fill in the mandatory questionnaires.

Results

At time of data collection for this paper, 100 German trial sites and 5 trial sites in Austria and Switzerland are taking part in the German Cartilage Registry. Among these are university medical centers and private hospitals, doctors' surgeries, and outpatient surgical centers. As of January 31, 2016, a total of 2124 patients have been registered (see Figure 3) and the first clinical results have been published [40-42].

Figure 3. Total number of patients in the German Cartilage Registry as of January 31, 2016.



Discussion

The primary aim of this multicenter registry is to assess the efficiency and safety of surgically treated cartilage defects of knee, hip, and ankle joints and to subsequently provide future patients with their best treatment option. Therefore, we are collecting as much valuable information as possible on a preferably heterogeneous group of people who have been treated in day-to-day clinical practice.

In the following section we highlight the strengths of the German Cartilage Registry and discuss the known limitations to this project.

Complementing Data from RCTs

In recent years, there has been a focus on RCTs in cartilage repair, since they still are the highest level of clinical research [43]. Nevertheless, due to strict inclusion and exclusion criteria, study populations in many RCTs do not completely represent clinical routine and the entire population of patients with cartilage defects. In fact, the number of patients who are eligible

for RCTs in the field of cartilage defects is estimated to be only around 4.5% [11]. Hence, the vast majority of patients are not represented by RCTs, since they do not qualify for different reasons, such as an increased body mass index or concomitant pathologies. In addition, important patient-related factors such as smoking and being overweight have been proven to significantly influence the outcome of cartilage repair techniques, but they cannot be analyzed by RCTs for methodological reasons [44-46]. This also applies to pathology-related parameters such as the influence of defect size or detailed defect location [46]. Furthermore, concomitant pathologies are considered to be exclusion criteria in most RCTs but are frequently present in cartilage repair patients. All of these factors underline the necessity of not exclusively relying on findings of RCTs, but to complement the results of RCTs with data from well-designed observational studies (eg, registries), and, therefore, to reassess findings of RCTs in daily clinical use.

Selection Bias

Due to organizational or other limitations, we cannot guarantee that every single patient with a surgically treated chondral defect of a knee, hip, or ankle joint will be documented in the system. For instance, for small- or medium-sized medical health providers, the additional workload for data input may seem too high. But we tried to keep the administrative effort as small as possible by allowing the physicians to register a patient immediately after surgery has been completed, although the first patient questionnaire refers to the complaints before surgery. In this way, the physician can record all mandatory data at once. Furthermore, we tried to include as many patient characteristics as possible that are thought to affect outcomes.

Data Quality

No onsite clinical monitoring is provided to assure the quality of entered data, and the respective sites are solely responsible for data input. Nevertheless, quality parameters need to be established and carefully applied. For instance, we have to observe the follow-up rate, which is crucial in any type of clinical research. Therefore, a validation study of recorded data will have to follow.

Expansion of the Registry

Additional sites in German-speaking countries, namely Austria and Switzerland, have already been affiliated and others will be approached to join the registry.

Further information is available on the KnorpelRegister website [47].

Acknowledgments

We thank all participating sites and the Arbeitsgemeinschaft Klinische Geweberegeneration (Working Group Clinical Tissue Regeneration) of the German Society for Orthopaedics and Trauma who have contributed to the successful implementation of the German Cartilage Registry. Special thanks to Deutsche Arthrose-Hilfe e.V. and Stiftung Oskar-Helene-Heim, who supported this registry financially.

The article processing charge was funded by the German Research Foundation (DFG) and the Albert-Ludwigs University Freiburg in the funding program Open Access Publishing.

Conflicts of Interest

None declared.

References

1. Heir S, Nerhus TK, Røtterud JH, Løken S, Ekeland A, Engebretsen L, et al. Focal cartilage defects in the knee impair quality of life as much as severe osteoarthritis: a comparison of knee injury and osteoarthritis outcome score in 4 patient categories scheduled for knee surgery. Am J Sports Med 2010 Feb;38(2):231-237. [doi: 10.1177/0363546509352157] [Medline: 20042546]
2. Solheim E, Krokeide AM, Melteig P, Larsen A, Strand T, Brittberg M. Symptoms and function in patients with articular cartilage lesions in 1,000 knee arthroscopies. Knee Surg Sports Traumatol Arthrosc 2014 Dec 13:1-7. [doi: 10.1007/s00167-014-3472-9] [Medline: 25502829]
3. Arøen A, Løken S, Heir S, Alvik E, Ekeland A, Granlund OG, et al. Articular cartilage lesions in 993 consecutive knee arthroscopies. Am J Sports Med 2004;32(1):211-215. [Medline: 14754746]
4. Curl WW, Krome J, Gordon ES, Rushing J, Smith BP, Poehling GG. Cartilage injuries: a review of 31,516 knee arthroscopies. Arthroscopy 1997 Aug;13(4):456-460. [Medline: 9276052]
5. Hjelle K, Solheim E, Strand T, Muri R, Brittberg M. Articular cartilage defects in 1,000 knee arthroscopies. Arthroscopy 2002 Sep;18(7):730-734. [Medline: 12209430]
6. Widuchowski W, Widuchowski J, Trzaska T. Articular cartilage defects: study of 25,124 knee arthroscopies. Knee 2007 Jun;14(3):177-182. [doi: 10.1016/j.knee.2007.02.001] [Medline: 17428666]
7. Cicuttini F, Ding C, Wluka A, Davis S, Ebeling PR, Jones G. Association of cartilage defects with loss of knee cartilage in healthy, middle-age adults: a prospective study. Arthritis Rheum 2005 Jul;52(7):2033-2039 [FREE Full text] [doi: 10.1002/art.21148] [Medline: 15986359]

8. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 2008 Jan;58(1):26-35 [FREE Full text] [doi: 10.1002/art.23176] [Medline: 18163497]
9. Murphy L, Helmick CG. The impact of osteoarthritis in the United States: a population-health perspective. Am J Nurs 2012 Mar;112(3 Suppl 1):S13-S19. [doi: 10.1097/01.NAJ.0000412646.80054.21] [Medline: 22373741]
10. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis 2014 Jul;73(7):1323-1330. [doi: 10.1136/annrheumdis-2013-204763] [Medline: 24553908]
11. Engen CN, Engebretsen L, Årøen A. Knee cartilage defect patients enrolled in randomized controlled trials are not representative of patients in orthopedic practice. Cartilage 2010 Oct;1(4):312-319 [FREE Full text] [doi: 10.1177/1947603510373917] [Medline: 26069562]
12. Niemeyer P, Kreuz PC, Steinwachs M, Südkamp NP. [Operative treatment of cartilage lesions in the knee joint]. Sportverletz Sportschaden 2007 Mar;21(1):41-50. [doi: 10.1055/s-2007-963030] [Medline: 17385104]
13. Cole BJ, Pascual-Garrido C, Grumet RC. Surgical management of articular cartilage defects in the knee. J Bone Joint Surg Am 2009 Jul;91(7):1778-1790. [Medline: 19571102]
14. Basad E, Ishaque B, Bachmann G, Stürz H, Steinmeyer J. Matrix-induced autologous chondrocyte implantation versus microfracture in the treatment of cartilage defects of the knee: a 2-year randomised study. Knee Surg Sports Traumatol Arthrosc 2010 Apr;18(4):519-527. [doi: 10.1007/s00167-009-1028-1] [Medline: 20062969]
15. Vanlauwe J, Saris DB, Victor J, Almqvist KF, Bellemans J, Luyten FP, TIG/ACT/01/2000&EXT Study Group. Five-year outcome of characterized chondrocyte implantation versus microfracture for symptomatic cartilage defects of the knee: early treatment matters. Am J Sports Med 2011 Dec;39(12):2566-2574. [doi: 10.1177/0363546511422220] [Medline: 21908720]
16. Saris D, Price A, Widuchowski W, Bertrand-Marchand M, Caron J, Drogset JO, et al. Matrix-applied characterized autologous cultured chondrocytes versus microfracture: two-year follow-up of a prospective randomized trial. Am J Sports Med 2014 Jun;42(6):1384-1394. [doi: 10.1177/0363546514528093] [Medline: 24714783]
17. Saris DB, Vanlauwe J, Victor J, Almqvist KF, Verdonk R, Bellemans J, TIG/ACT/01/2000&EXT Study Group. Treatment of symptomatic cartilage defects of the knee: characterized chondrocyte implantation results in better clinical outcome at 36 months in a randomized trial compared to microfracture. Am J Sports Med 2009 Nov;37 Suppl 1:10S-19S. [doi: 10.1177/0363546509350694] [Medline: 19846694]
18. Saris DB, Vanlauwe J, Victor J, Haspl M, Bohnsack M, Fortems Y, et al. Characterized chondrocyte implantation results in better structural repair when treating symptomatic cartilage defects of the knee in a randomized controlled trial versus microfracture. Am J Sports Med 2008 Feb;36(2):235-246. [doi: 10.1177/0363546507311095] [Medline: 18202295]
19. Jakobsen RB, Engebretsen L, Slauterbeck JR. An analysis of the quality of cartilage repair studies. J Bone Joint Surg Am 2005 Oct;87(10):2232-2239. [doi: 10.2106/JBJS.D.02904] [Medline: 16203888]
20. Concato J, Lawler EV, Lew RA, Gaziano JM, Aslan M, Huang GD. Observational methods in comparative effectiveness research. Am J Med 2010 Dec;123(12 Suppl 1):e16-e23. [doi: 10.1016/j.amjmed.2010.10.004] [Medline: 21184862]
21. Ligthelm RJ, Borzì V, Gumprecht J, Kawamori R, Wenying Y, Valensi P. Importance of observational studies in clinical practice. Clin Ther 2007 Jun;29(6 Pt 1):1284-1292. [doi: 10.1016/j.clinthera.2007.07.004] [Medline: 18036390]
22. Hannan EL. Randomized clinical trials and observational studies: guidelines for assessing respective strengths and limitations. JACC Cardiovasc Interv 2008 Jun;1(3):211-217 [FREE Full text] [doi: 10.1016/j.jcin.2008.01.008] [Medline: 19463302]
23. Silverman SL. From randomized controlled trials to observational studies. Am J Med 2009 Feb;122(2):114-120. [doi: 10.1016/j.amjmed.2008.09.030] [Medline: 19185083]
24. Black N. Why we need observational studies to evaluate the effectiveness of health care. BMJ 1996 May 11;312(7040):1215-1218 [FREE Full text] [Medline: 8634569]
25. Kitaoka HB, Alexander IJ, Adelaar RS, Nunley JA, Myerson MS, Sanders M. Clinical rating systems for the ankle-hindfoot, midfoot, hallux, and lesser toes. Foot Ankle Int 1994 Jul;15(7):349-353. [Medline: 7951968]
26. Kostuj T, Schaper K, Baums M, Lieske S. Eine Validierung des AOFAS-Ankle-Hindfoot-Scale für den deutschen Sprachraum. Fuß & Sprunggelenk 2014 Jun;12(2):100-106. [doi: 10.1016/j.fuspru.2014.02.002]
27. Marlovits S, Striessnig G, Resinger CT, Aldrian SM, Vecsei V, Imhof H, et al. Definition of pertinent parameters for the evaluation of articular cartilage repair tissue with high-resolution magnetic resonance imaging. Eur J Radiol 2004 Dec;52(3):310-319. [doi: 10.1016/j.ejrad.2004.03.014] [Medline: 15544911]
28. Marlovits S, Singer P, Zeller P, Mandl I, Haller J, Trattnig S. Magnetic resonance observation of cartilage repair tissue (MOCART) for the evaluation of autologous chondrocyte transplantation: determination of interobserver variability and correlation to clinical outcome after 2 years. Eur J Radiol 2006 Jan;57(1):16-23. [doi: 10.1016/j.ejrad.2005.08.007] [Medline: 16203119]
29. Irrgang JJ, Anderson AF, Boland AL, Harner CD, Kurosaka M, Neyret P, et al. Development and validation of the international knee documentation committee subjective knee form. Am J Sports Med 2001;29(5):600-613. [Medline: 11573919]

30. Anderson AF, Irrgang JJ, Kocher MS, Mann BJ, Harrast JJ, International Knee Documentation Committee. The International Knee Documentation Committee Subjective Knee Evaluation Form: normative data. Am J Sports Med 2006 Jan;34(1):128-135. [doi: 10.1177/0363546505280214] [Medline: 16219941]
31. Higgins LD, Taylor MK, Park D, Ghodadra N, Marchant M, Pietrobon R, International Knee Documentation Committee. Reliability and validity of the International Knee Documentation Committee (IKDC) Subjective Knee Form. Joint Bone Spine 2007 Dec;74(6):594-599. [doi: 10.1016/j.jbspin.2007.01.036] [Medline: 17888709]
32. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. J Orthop Sports Phys Ther 1998 Aug;28(2):88-96. [doi: 10.2519/jospt.1998.28.2.88] [Medline: 9699158]
33. Kessler S, Lang S, Puhl W, Stöve J. [The Knee Injury and Osteoarthritis Outcome Score--a multifunctional questionnaire to measure outcome in knee arthroplasty]. Z Orthop Ihre Grenzgeb 2003;141(3):277-282. [doi: 10.1055/s-2003-40083] [Medline: 12822074]
34. Baumann F, Weber J, Zeman F, Müller M, Lahner M, Nerlich M, et al. Validation of a German version of the International Hip Outcome Tool (G-iHOT33) according to the COSMIN checklist: how much improvement is clinically relevant? Arch Orthop Trauma Surg 2016 Jan;136(1):83-91. [doi: 10.1007/s00402-015-2336-1] [Medline: 26419895]
35. Mohtadi NG, Griffin DR, Pedersen ME, Chan D, Safran MR, Parsons N, Multicenter Arthroscopy of the Hip Outcomes Research Network. The development and validation of a self-administered quality-of-life outcome measure for young, active patients with symptomatic hip disease: the International Hip Outcome Tool (iHOT-33). Arthroscopy 2012 May;28(5):595-605. [doi: 10.1016/j.arthro.2012.03.013] [Medline: 22542433]
36. van Bergen CJ, Sierevelt IN, Hoogervorst P, Waizy H, van Dijk CN, Becher C. Translation and validation of the German version of the foot and ankle outcome score. Arch Orthop Trauma Surg 2014 Jul;134(7):897-901. [doi: 10.1007/s00402-014-1994-8] [Medline: 24748232]
37. Nauck T, Lohrer H. Translation, cross-cultural adaption and validation of the German version of the Foot and Ankle Ability Measure for patients with chronic ankle instability. Br J Sports Med 2011 Aug;45(10):785-790. [doi: 10.1136/bjsm.2009.067637] [Medline: 19955163]
38. Martin RL, Irrgang JJ, Burdett RG, Conti SF, Van Swearingen JM. Evidence of validity for the Foot and Ankle Ability Measure (FAAM). Foot Ankle Int 2005 Nov;26(11):968-983. [Medline: 16309613]
39. KKS Netzwerk. Koordinierungszentren für Klinische Studien. Cologne, Germany: KKS Netzwerk URL: http://www.kks-netzwerk.de/ [accessed 2016-05-19] [WebCite Cache ID 6hcmuiC67]
40. Niemeyer P, Schweigler K, Grotejohann B, Maurer J, Angele P, Aurich M, et al. [The German Cartilage Registry (KnorpelRegister DGOU) for evaluation of surgical treatment for cartilage defects: experience after six months including first demographic data]. Z Orthop Unfall 2015 Feb;153(1):67-74. [doi: 10.1055/s-0034-1383222] [Medline: 25723583]
41. Spahn G, Fritz J, Albrecht D, Hofmann GO, Niemeyer P. Characteristics and associated factors of Klee cartilage lesions: preliminary baseline-data of more than 1000 patients from the German cartilage registry (KnorpelRegister DGOU). Arch Orthop Trauma Surg 2016 Mar 21:1-6. [doi: 10.1007/s00402-016-2432-x] [Medline: 27001180]
42. Niemeyer P, Feucht MJ, Fritz J, Albrecht D, Spahn G, Angele P. Cartilage repair surgery for full-thickness defects of the knee in Germany: indications and epidemiological data from the German Cartilage Registry (KnorpelRegister DGOU). Arch Orthop Trauma Surg 2016 Apr 9:1-7. [doi: 10.1007/s00402-016-2453-5] [Medline: 27062375]
43. Obremskey WT, Pappas N, Attallah-Wasif E, Tornetta P3, Bhandari M. Level of evidence in orthopaedic journals. J Bone Joint Surg Am 2005 Dec;87(12):2632-2638. [doi: 10.2106/JBJS.E.00370] [Medline: 16322612]
44. Jaiswal PK, Bentley G, Carrington RW, Skinner JA, Briggs TW. The adverse effect of elevated body mass index on outcome after autologous chondrocyte implantation. J Bone Joint Surg Br 2012 Oct;94(10):1377-1381. [doi: 10.1302/0301-620X.94B10.29388] [Medline: 23015564]
45. Jaiswal PK, Macmull S, Bentley G, Carrington RW, Skinner JA, Briggs TW. Does smoking influence outcome after autologous chondrocyte implantation?: A case-controlled study. J Bone Joint Surg Br 2009 Dec;91(12):1575-1578. [doi: 10.1302/0301-620X.91B12.22879] [Medline: 19949119]
46. Niemeyer P, Salzmann GM, Hirschmüller A, Südkamp NP. [Factors that influence clinical outcome following autologous chondrocyte implantation for cartilage defects of the knee]. Z Orthop Unfall 2012 Feb;150(1):83-88. [doi: 10.1055/s-0030-1270894] [Medline: 21526464]
47. KnorpelRegister DGOU, AG Klinische Geweberegeneration. KnorpelRegister DGOU. Berlin, Germany: Deutsche Gesellschaft für Orthopädie und Unfallchirurgie; 2016. URL: http://www.knorpelregister-dgou.de/start.html [accessed 2016-05-19] [WebCite Cache ID 6hcnMZYuO]

Abbreviations

AOFAS: American Orthopaedic Foot & Ankle Society
CTU: Clinical Trials Unit
DGOU: German Society for Orthopaedics and Trauma
ICRS: International Cartilage Repair Society

IKDC: International Knee Documentation Committee
MOCART: magnetic resonance observation of cartilage repair tissue
RCT: randomized controlled trial

Edited by G Eysenbach; submitted 21.04.16; peer-reviewed by E Solheim; accepted 06.05.16; published 29.06.16.

Please cite as:
Maurer J, Grotejohann B, Jenkner C, Schneider C, Flury T, Tassoni A, Angele P, Fritz J, Albrecht D, Niemeyer P
A Registry for Evaluation of Efficiency and Safety of Surgical Treatment of Cartilage Defects: The German Cartilage Registry (KnorpelRegister DGOU)
JMIR Res Protoc 2016;5(2):e122
URL: http://www.researchprotocols.org/2016/2/e122/
doi:10.2196/resprot.5895
PMID:27357998

Original Paper

Usefulness of a Tailored eHealth Service for Informal Caregivers and Professionals in the Dementia Treatment and Care Setting: The eHealthMonitor Dementia Portal

Sandra Schaller[1], Dipl.-Sozw.; Velislava Marinova-Schmidt[1], Dipl.-Psych.; Manuela Setzer[1], MSc; Haridimos Kondylakis[2], MSc; Lena Griebel[3], MSc; Martin Sedlmayr[3], Dr.; Elmar Graessel[4], Prof. Dr. med.; Juan Manuel Maler[5], PD Dr. med.; Stefan Kirn[6], Prof. Dr.; Peter L Kolominsky-Rabas[1], Prof. Dr. med., MBA

[1]Interdisciplinary Centre for Health Technology Assessment (HTA) and Public Health, Friedrich-Alexander-University of Erlangen-Nürnberg, Erlangen, Germany

[2]Institute of Computer Science, Foundation for Research and Technology - Hellas (FORTH), Heraklion, Greece

[3]Chair of Medical Informatics Friedrich-Alexander-University of Erlangen-Nürnberg, Erlangen, Germany

[4]Centre for Health Services Research in Medicine, Department of Psychiatry and Psychotherapy, University Hospital Erlangen, Friedrich-Alexander-University of Erlangen-Nürnberg, Erlangen, Germany

[5]Department of Psychiatry and Psychotherapy, Friedrich-Alexander-University of Erlangen-Nürnberg, Erlangen, Germany

[6]Institut für Health Care & Public Management, Information Systems 2, University of Hohenheim, Hohenheim, Germany

Corresponding Author:
Sandra Schaller, Dipl.-Sozw.
Interdisciplinary Centre for Health Technology Assessment (HTA) and Public Health, Friedrich-Alexander-University of Erlangen-Nürnberg
Schwabachanlage 6
Erlangen, 91054
Germany
Phone: 49 9131 8534167
Fax: 49 9131 8535854
Email: sandra.schaller@uk-erlangen.de

Abstract

Background: The European eHealthMonitor project (eHM) developed a user-sensitive and interactive Web portal for the dementia care setting called the eHM Dementia Portal (eHM-DP). It aims to provide targeted support for informal caregivers of persons with dementia and professionals.

Objective: The objective of this study was to assess the usefulness and impact of the eHM-DP service in the dementia care setting from two user perspectives: informal caregivers and professionals.

Methods: The evaluation study was conducted from June to September 2014 and followed a before-after, user-participatory, mixed-method design with questionnaires and interviews. The used intervention was the eHM-DP: an interactive Web portal for informal caregivers and professionals that was tested for a 12-week period. Primary outcomes for caregivers included empowerment, quality of life, caregiver burden, decision aid, as well as perceived usefulness and benefits of the eHM-DP. Primary outcomes for professionals involved decision aid, perceived usefulness, and benefits of the eHM-DP.

Results: A total of 25 informal caregivers and 6 professionals used the eHM-DP over the 12-week study period. Both professionals and informal caregivers indicated perceived benefits and support by the eHM-DP. In total, 65% (16/25) of informal caregivers would use the eHM-DP if they had access to it. Major perceived benefits were individualized information acquisition, improved interaction between informal caregivers and professionals, access to support from home, and empowerment in health-related decisions (PrepDM Score: 67.9). Professionals highlighted the improved treatment and care over the disease course (83%, 5/6) and improved health care access for people living in rural areas (67%, 4/6). However, there was no improvement in caregiver burden (Burden Scale for Family Caregivers) and quality of life (EuroQol-5D-5L) over the study period.

Conclusions: Our study provides insight into the different user perspectives on an eHealth support service in the dementia treatment and care setting. These results are of importance for future developments and the uptake of eHealth solutions in the dementia domain and reinforce the importance of early user involvement. Turning to the primary target of the eHM-DP service,

our findings suggest that the eHM-DP service proved to be a valuable post-diagnostic support service, in particular for the home-based care setting. Further research on a larger scale is needed to enhance the implementation in existing health care infrastructures.

(JMIR Res Protoc 2016;5(2):e47) doi:10.2196/resprot.4354

KEYWORDS

eHealth; web portal; decision aid; personalized support; dementia; Alzheimer's disease; informal caregiver; medical professional

Introduction

Planning for the treatment and care provision of increasing numbers of persons with dementia (PwD) and their informal caregivers has become an urgent global health service task. Need for care in dementia starts early and increases with disease severity, affecting multiple dimensions such as medical treatment and care, support for household, financial, and social activities, up to almost constant supervision in the severe stage. Thus, dementia has a high impact on PwDs, families (informal caregivers), and health care systems [1]. On average, 70% of persons with dementia are cared for at home. In particular, spouses and children provide extensive care and communicate with professionals, while facing many challenges. They often suffer from higher physical and emotional burden [1-7] in contrast to informal caregivers caring for a person without dementia [8]. In addition, the personal burden of informal care is one of the main reasons for nursing home transfers [9,10]. Given that there is currently no cure for dementia, care concepts and services that provide assistance for persons with dementia are essential. Although several support services exist, they are highly underutilized. Brodaty et al [11] identified the following four major reasons for non-use of support services: caregivers do not perceive the need of the services, reluctance to use the services, the service characteristics, and the lack of information regarding the availability of support services. A recent review highlights the importance of tailoring support services to the needs of caregivers as well as improving access to services [12]. Against this background and due to the projected increase in the number of PwD worldwide [13], there is an urgent need for cost-effective support services for informal caregivers. In this context, several studies highlight the potential of eHealth services, due to the increasing availability of Internet access and the benefit of flexibility, facilitated accessibility, and personalization of the service [14-19].

Therefore, the European eHealthMonitor project (eHM) developed a user-sensitive and interactive Web portal for dementia care: the eHM Dementia Portal (eHM-DP). By providing information and access for local support services from home and information that is tailored to the needs of the users, the eHM-DP aims to increase the use of support services. It aims to provide targeted and personalized support for both informal caregivers of persons with dementia in a home-based care setting and professionals [20]. Especially during the course of the disease, medical professionals play an important role with regard to treatment and care for the PwD and communication with informal caregivers is crucial in order to provide the appropriate treatment and care.

Currently, the majority of Internet-based, supportive interventions for informal caregivers in dementia are websites or specific educational programs. A recent review identified six (of 14) interventions that included a professional [21]. However, only a minority of studies that were identified in two recent reviews [21,22] were similar to the eHM-DP with respect to provision of context-sensitive information [23,24] or interaction functionalities [25-27]. In comparison, the eHM-DP is unique by combining individualized (need-tailored) information and interaction functionalities for both informal caregivers and professionals. Overall, the eHM-DP differs from previous eHealth service solutions for informal caregivers of PwD by a combination of seven major aspects, which were identified based on current reviews [21,22] and the involvement of users in the initial development of the program: (1) interactive and personalized portal with own account, (2) computerized communication between professionals and informal caregivers, (3) tailored support services according to user-specific entries in caregiving diaries, (4) focus on caregiver empowerment and decision aid, (5) the perspectives of medical professionals, (6) provision of individual and longitudinal data about the home-based care setting and course of the disease of the PwD (ie, symptoms, medication, well-being), and (7) provision of individual and longitudinal data of caregiving tasks and caregiver burden. A further advantage of the eHM-DP is the professionals' access to information from health care parameters of PwDs and caregiver burden of informal caregivers.

The purpose of this study was to assess the usefulness and impact of the eHM-DP. The focus was on perceived usefulness that was assessed by the attitude toward using, perceived benefits, concerns, and recommendations of informal caregivers and professionals. In addition, the impact on informal caregivers (quality of life, caregiver burden) was explored.

Methods

Description of the eHM Dementia Portal

We designed a Personal eHealth Knowledge Space (PeKS) as an aggregation of all knowledge sources relevant for the provision of individualized personal eHealth services, featuring individualized support and a personalized Web portal that enables interactions with professionals.

Findings of a recent review from Boots et al [22] indicated that multicomponent interventions, combining tailored information with interaction, are the most promising. The technical design of the eHM-DP was realized by service-oriented architecture based on the open source Web platform, Liferay; modeling and semantic knowledge engineering methods; and multiagent systems (MAS) [28,29]. Based on the aforementioned

technologies and a rapid and iterative design process between technical and medical partners, the caregivers' needs were integrated based on (1) a caregiver focus group, (2) interviews with three medical professional experts in the field, and (3) reviews of current scientific literature [2,3,5,21,22,30-33]. Based on these findings, we decided to involve two important professional groups within the eHM-DP: medical and social professionals. Whereas medical professionals are important for medical treatment and care for the PwD (focus on PwD), social professionals from caregiver counseling institutions take care of the caregiving situation and informal caregivers needs (focus on informal caregivers). The eHM-DP aims to provide access to relevant and comprehensive information for both professional groups in order to improve treatment and care and to prevent caregiver burden.

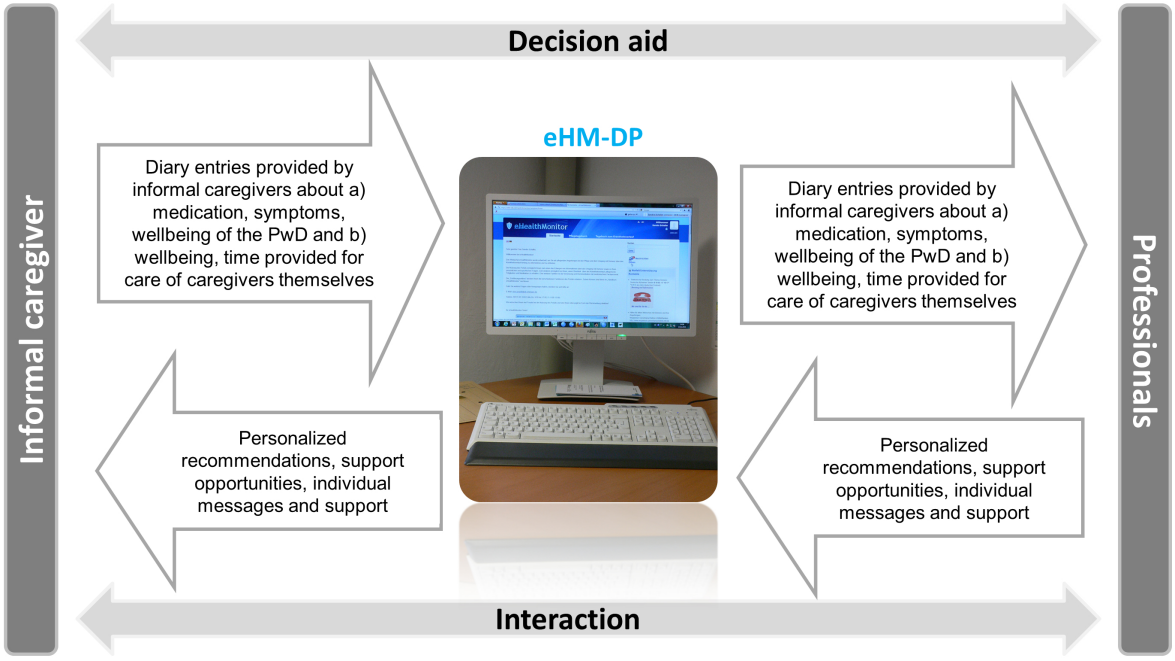
Before the final implementation and evaluation in a field trial, the eHM-DP was piloted in a pretest by 31 informal caregivers and 11 professionals [34]. Based on the pretest findings, the eHM-DP was revised. Major revisions were made on the following aspects: improved interaction functionality for communication between informal caregivers and professionals, the possibility for professionals to list patients based on priority levels (eg, worse health status), a revision of the medication plan, a print option for diaries and design aspects.

In the evaluation study, user access to the eHM-DP was realized via a customizable personal account for informal caregivers and professionals. Thus, the provision of individualized support services by means of a user-specific profile and user-specific diary entries (by informal caregivers) were enabled. This is important, as caregiver needs are multifaceted and complex in nature [16]. There are four major roles that are relevant for the eHM-DP:

1. Informal caregiver with own user account: provision of information about medical data and health status (symptoms, well-being) of the PwD (external assessment) as well as about their own caregiving situation and well-being (caregiver burden).
2. Person with dementia without personal eHM-DP account: PwD is not directly involved in the eHM-DP, but is indirectly via external assessment from informal caregivers and recommendations/advice from medical and social professionals with the aim to improve treatment, care, and well-being for the PwD.
3. Medical professional with personal eHM-DP account: acquisition of "hard-to-access" information about the PwD (improved decision making, improved treatment and care), timely reactions to health status changes of the PwD via the eHM-DP or directly.
4. Social professional with personal eHM-DP account: acquisition of "hard-to-access" information about the caregiving situation (prevention of caregiver burden), timely reactions to health status changes of the informal caregiver via the eHM-DP or directly.

The eHM-DP is personalized and interactive and provides two major functionalities (see Figure 1): (1) interactive and individualized provision of information and knowledge, and (2) communication with domain experts in dementia. First, the portal provided individualized, timely, and situation-specific information to informal caregivers and professionals based on an individual registration profile as well as the electronic diary entries provided by informal caregivers (ie, caregiving diary, course-of-disease diary about PwD, medication diary about PwD). Informal caregivers received tailored information consisting of approved guidelines and documents (eg, factsheets of German Alzheimer Association, Ministry of Health, local dementia institutions/groups) and of recommendations from professionals via the message functionality of the eHM-DP. Second, the eHM-DP sought to facilitate and enable close communication and interaction between informal caregivers and professionals. Thus, its aim was to empower informal caregivers and prevent caregiver burden as well as to improve treatment and care for the PwD. From the perspective of professionals, the eHM-DP facilitated information acquisition of individual "hard-to-access" information and sought to improve the management, treatment, and care for PwDs (based on diary entries from caregivers about symptoms and medication of the PwD) and the well-being of informal caregivers (based on diary entries from caregivers about the caregiving situation and caregiver burden). Based on these individual diary entries provided by informal caregivers as well as specific questions (free text), professionals were informed by the eHM-DP (eg, alerts) and were able to provide support either via the portal (messaging feature) or directly (appointment, telephone call).

Figure 1. Schematic representation of the eHM-DP.

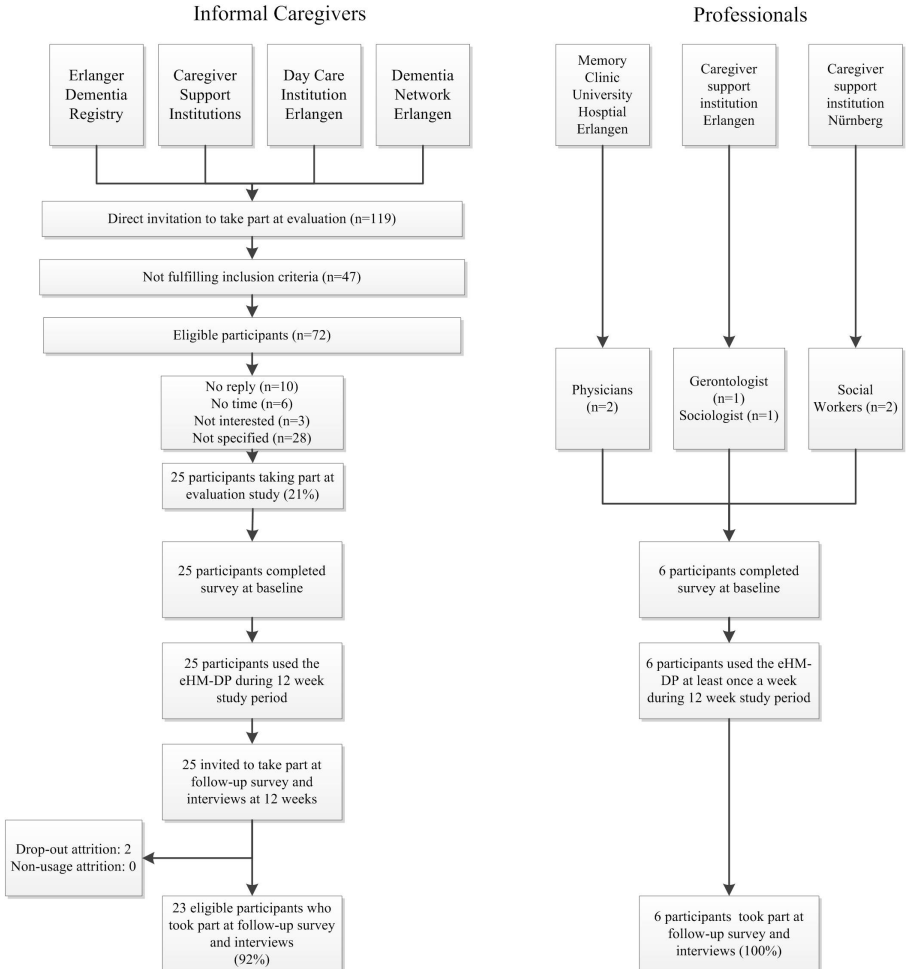


Participants and Evaluation Design

The Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online TeleHealth (CONSORT-EHEALTH) provided guidance for the development of our evaluation [35]. According to Eysenbach [35], these guidelines may also be used for other evaluation methods. Our evaluation study sought to assess the usefulness and impact of the final implementation of the eHM-DP in order to optimize the platform before starting a large-scale randomized controlled trial. This is in agreement with previous studies, which emphasized the need to conduct early evaluation studies such as “proof-of-principle-studies” before the realization of studies on a larger scale [36].

Our study was conducted from June 1-September 30, 2014, and followed a before-after study with 12-week follow-up to investigate the eHM-DPs impact on informal caregivers and professionals. Study participants accessed the Web portal from home (informal caregivers) or from their workplace (professionals) and used the Web portal at least once a week over the 12-week study period. A convenience sampling strategy was used to recruit study participants: informal caregivers, medical professionals, and social professionals. Informal caregivers were recruited from a Hospital Memory Clinic, a district hospital, and two caregiver support institutions from the metropolitan region of Erlangen-Nürnberg. Eligibility criteria included (1) primary responsibility as an informal caregiver for a person with dementia (International Statistical Classification of Diseases and Related Health Problems, ICD-10, F00-F03) who is living at home, (2) is aged over 18 years, (3) is able to speak, read, and write German, and (4) has Internet access from home. In addition, 2 medical professionals were recruited from a Hospital Memory Clinic and 4 social professionals from caregiver support institutions. The participant flowchart (see Figure 2) describes the recruitment and inclusion process in detail. The evaluation study was approved by the local ethics committee of the Friedrich-Alexander University Erlangen-Nürnberg (Germany). All study participants were informed about the objectives and the scope of the study and gave written, informed consent for participation. Data were collected confidentially in written face-to-face interviews by trained interviewers. Personal contact data (ie, name, address, institution) were used only for the second contact (follow-up interview) and related questionnaires were coded based on an identification number. The data analysis and interpretation were based on two separate datasets (informal caregivers and professionals) and conducted confidentially by 2 independent researchers.

Figure 2. Schematic representation of the eHM-DP evaluation participant flowchart.



Procedure

The eHM-DP was introduced to study participants by trained persons according to the Standard Operating Procedure of eHealthMonitor's evaluation [37]. The content of the introduction included a detailed explanation of all the features and functionalities of the eHM Portal and was supported with additional materials, such as videos and written information material. Support for study participants was provided throughout the whole study period (ie, telephone help desk, email). The non-usage attrition (discontinuation of services) [38] was minimized by "push" factors such as reminders and telephone calls.

Measures

A user participatory research design based on a mixed-method approach was applied to investigate the different user perspectives of the eHM-DP at baseline and follow-up (after 12 weeks). This approach has been recommended in previous reviews and studies on eHealth interventions [21,39,40]. The questionnaire was developed according to our research questions and consisted of instruments assessing the perceived usefulness of the eHM-DP with regard to decision aid, the attitude toward using it, perceived benefits and concerns, as well as recommendations of both informal caregivers and professionals. In addition, the impact on informal caregivers' quality of life and burden was explored.

Further, sociodemographic data as well as informal caregivers' eHealth literacy, using the eHEALS scale [41], and needs, using the Carers' Needs Assessment for Dementia (CNA-D) [30], were assessed at baseline.

Quantitative Measures

Usefulness: Empowerment (Informal Caregivers)

The empowerment of informal caregivers was assessed via 13 relevant categories of the CNA-D instrument and rated on a 5-point Likert scale (1=strongly agree to 5=not agree at all). Although the CNA-D was designed to assess carers' needs, its relevant areas of need were chosen to assess whether the eHM-DP contributes to address these needs and is able to empower caregivers in these specific areas of need.

Usefulness: Decision Aid (Informal Caregivers, Professionals)

The "Preparation for Decision Making Scale" (PrepDM) [42] was used to assess the informal caregivers' and professionals' perception of the eHM-DP with regard to decision support. Based on 10 items, the preparation for decision making is rated on a 5-point Likert scale (5=a great deal, 1=not at all). The score ranges from 0 (no perceived preparation for decision making) to 100 (highest perceived level of preparation for decision making).

Usefulness: Attitude Toward Using (Informal Caregivers, Professionals)

The attitude toward using the eHM-DP was assessed via the item "I think that eHM is a good concept" and intention to use via the item, "If I had access, I would use eHM." Both were rated on a 5-point Likert scale (1=strongly agree to 5=not agree at all). In addition, users were asked about the frequency of use of the eHM-DP.

Usefulness: Perceived Benefits (Informal Caregivers, Professionals)

The benefits for each user group were assessed via specific items that were rated on a 5-point Likert scale (1=strongly agree to 5=not agree at all). The questionnaire items were derived from current literature as well as pretest results of the eHM-DP [34].

Impact: Quality Of Life (Informal Caregivers)

Health-related quality of life was measured via the EQ-5D-5L instrument [43], which captures five dimensions: mobility, self-care, activity, pain, and anxiety. The labels for each of the dimensions are no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems. Utility values range from 1 (best possible health) to 0 (worst possible health).

Impact: Caregiver Burden (Informal Caregivers)

Caregiver burden was assessed via the short form of the Burden Scale for Family Caregivers (BSFC) [44], which measures the subjective caregiver burden of informal caregivers. It consists of 10 items rated on a scale (3=strongly agree, 2=agree, 1=disagree to 0=strongly disagree). The score ranges from 0-30 (0-9: low burden; 10-20: moderate burden; 21-30: severe burden).

Qualitative Interviews

In addition to the quantitative data, the perceived usefulness was explored through a semistructured interview focusing on users' experiences in terms of perceived benefits, major concerns, and further desired functionalities and improvements. The rationale was to assess the impact on users' perception of the eHM-DP. The semistructured, written interviews lasted approximately 60 minutes. All interviews were performed by a trained interviewer (3 interviewers were involved in the study) at baseline and follow-up. Interviews were conducted either at the study participants' home (informal caregivers) or at work (professionals).

Data Analysis

Descriptive analysis methods for quantitative data were applied using SPSS Statistics 21.0 software. Paired sample *t* tests were used to analyze changes in caregiver burden and quality of life from baseline to 12 weeks. Written qualitative data was captured electronically and structured by the method of an inductive category development according to Mayring [45]. The summary content analysis technique was applied in order to reduce the material to core contents or aspects. Therefore, the following steps were applied: (1) paraphrasing of content-bearing text passages, (2) generalization to the required level of abstraction (category definition), (3) first reduction through selection, and (4) second reduction [45]. At the end of this reduction phase, exact checking took place to ascertain whether the new statements collated as a category system still represent the base material. An intercoder check by 2 coders was performed to assure quality of the data analysis. The software MAXQDA was used to conduct the content analysis.

Results

User Statistics

A total of 119 informal caregivers were invited to take part in the evaluation study. Of those, 47 (39.5%) did not meet the inclusion criteria (eg, no Internet access), and 25 (35%) of the 72 caregivers who were qualified for the study were interested in taking part in the study. The main reason for non-participation was "no time," which often was due to the fact that informal caregivers were already stressed by the caregiving situation. This fact has to be taken into account when interpreting our conclusions and when planning further studies in the field. Informal caregivers were aged 29-80 years. Mean age was 58 years (SD 13.0, median 61 years) and almost half (48%, 12/25) of informal caregivers were female. Informal caregivers were mainly spouses (44%, 11/25) or children (36%, 9/25) of the PwD. Table 1 provides detailed information for the 25 informal caregivers.

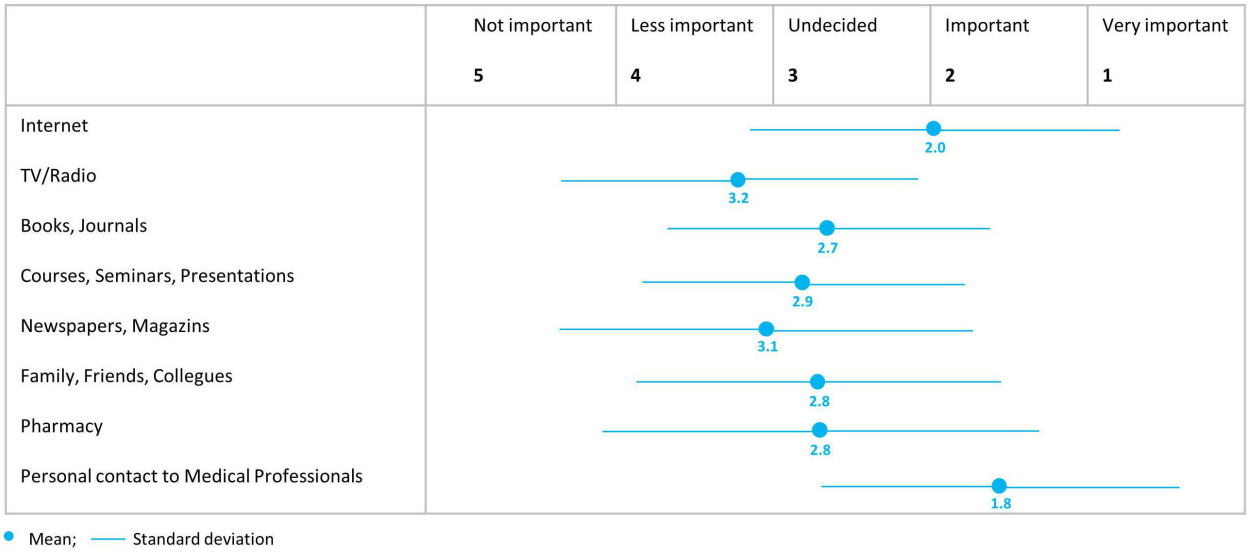
Table 1. Informal caregivers' characteristics (N=25).

	Participants, n (%)	Median; Min, Max
Age		Median 61; min=29, max=80
Time caring for PwD (years)		4 (3); min=1, max=12
Sex		
Female	12 (48)	
Male	13 (52)	
Relationship to PwD		
Spouse	11 (44)	
Child	9 (36)	
Relative	5 (20)	
Living situation		
Living together with PwD	14 (56)	
Living NOT together with PwD	11 (44)	
Living area		
Urban	16 (64)	
Rural	9 (36)	
Professional status		
Full-time employed	9 (36)	
Part-time employed	4 (16)	
Retired	10 (40)	
Other	2 (8)	
Caregiver burden		
Low	11 (44)	
Moderate	8 (32)	
Severe	6 (24)	

At baseline, the health information source "Internet" was rated as "very important" by 48% (12/25) and as "important" by 24% (6/25) of informal caregivers. It is rated as the second most important information source (mean 2.0, SD 1.2), directly after the personal contact to professionals (mean 1.8, SD 1.1) (see Figure 3). eHealth literacy competence at baseline was measured by the eHEALS Scale [41] and indicated a mean value of 19.9 (SD 9.0) on a scale from 8-40. On average, 37% of informal caregivers expressed needs for one of the 18 categories of the CNA-D instrument. The mean value for the number of reported needs is 6.6 (SD 5.3).

Mean age of professionals was 43 years (SD 13.2; min=31; max=58) and half of them were female (3/6). In total, 29 study participants (23 informal caregivers and 6 professionals) took part in the follow-up study (two drop-out attritions within the group of informal caregivers; reasons: 1 PwD died, 1 informal caregiver was sent to hospital) [38].

Figure 3. Importance of information sources for health-related aspects.

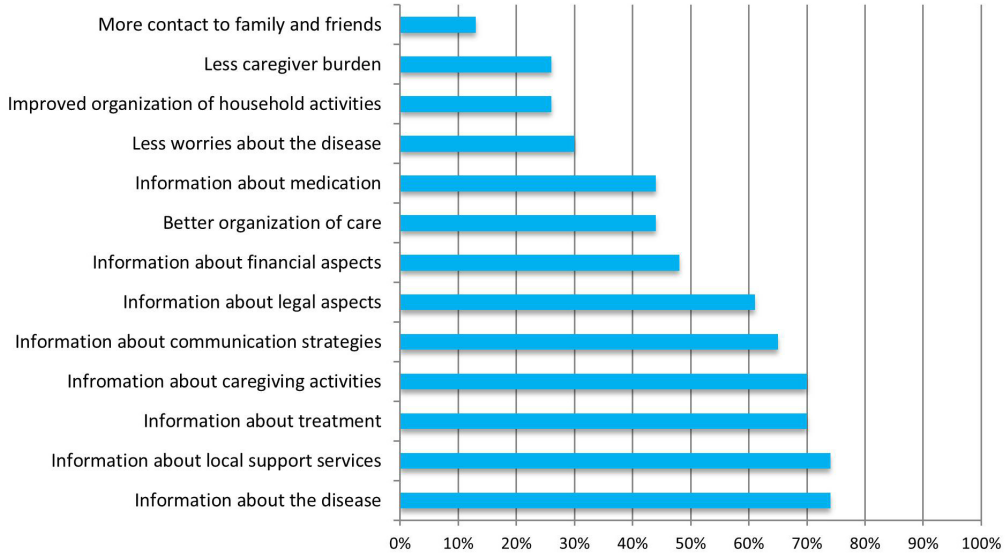


Quantitative Findings

Usefulness: Empowerment (Informal Caregivers)

The empowerment of informal caregivers was assessed via 13 relevant categories of the CNA-D instrument (see Figure 4).

Figure 4. Empowerment via the eHM-DP (Informal caregivers, n=23).

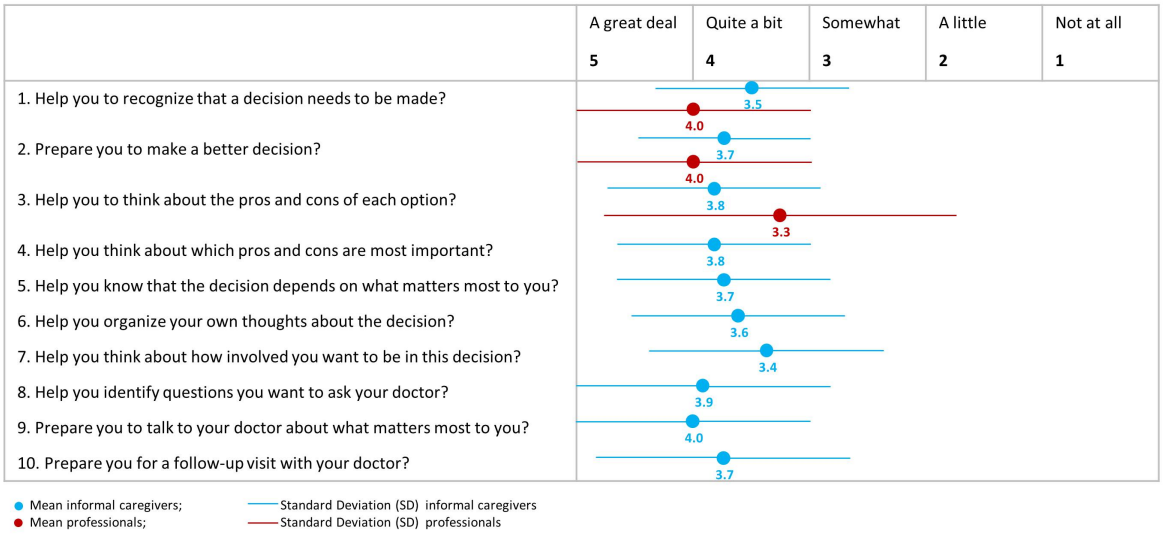


The most perceived empowerment was received via information acquisition for several topics (disease, local services, treatment, caregiving activities, and communication strategies). About a third agreed that the eHM-DP contributed to fewer worries about the disease or to less caregiver burden.

Usefulness: Decision Aid (Informal Caregivers, Professionals)

The score of 67.9 (min=38.9; max=100.0) of the PrepDM instrument indicates the perceived decision aid of the eHM-DP for informal caregivers. Highest decision support was perceived for “Prepares me to talk to my doctor about what matters most to me” (mean 4.0, SD 1.0), followed by “Helps me to identify questions I want to ask my doctor” (mean 3.9, SD 1.1). Professionals pointed out that eHM-DP specifically helps them to recognize that a decision has to be made (mean 4.0, SD 1.0) and prepares them to make a better decision (mean 4.0, SD 1.0). Figure 5 illustrates the perceived decision support of the eHM-DP.

Figure 5. Preparation for decision making by the eHM-DP service.



Usefulness: Attitude Toward Using (Informal Caregivers, Professionals)

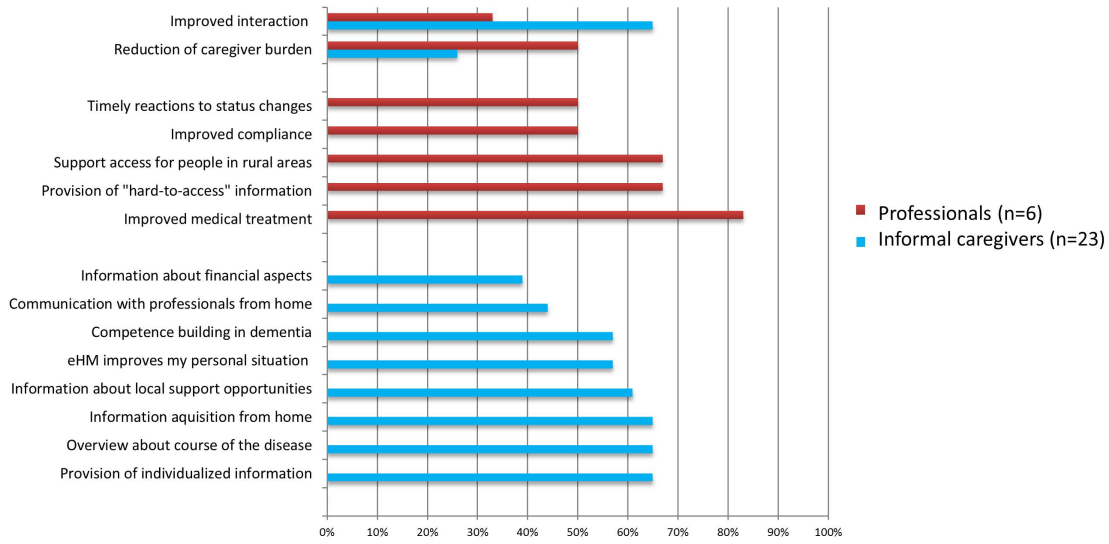
Two thirds (65%, 15/25) of informal caregivers indicated that they would use the eHM-DP service if they had access to it. In total, 83% (19/25) of caregivers and 67% (4/6; 2 medical professionals, 2 social professionals) of professionals think that eHM-DP is a good concept. Further, 2 social professionals were not convinced that eHM-DP is a good concept; however, they suggested further functionalities that would make the eHM-DP unique for them (eg, involvement and connection of all relevant stakeholders within the dementia treatment and care process via the eHM-DP). With regard to the informal caregivers' frequency of use, 22% (5/25) indicated 2-3 times per week, 57% (13/25) weekly, and 13% (3/15) monthly. Half of the professionals prefer to use the eHM-DP at least once a week.

Usefulness: Perceived Usefulness (Informal Caregivers, Professionals)

Although there were no pre-post changes in quality of life, the user-specific questionnaires suggest that over half of the informal caregivers perceived an improvement of their individual situation (see Figure 6). Over one third highlighted an improvement in communication with professionals (especially from home), the provision of individualized information, an overview about course of the disease (symptoms, care), as well as the information acquisition from home. In addition, the provision of information about local support opportunities, the improved individual situation as an informal caregiver and the competence-building in dementia were mentioned. A resulting consequence for 26% (6/25) of informal caregivers is a reduction of caregiver burden. From the perspective of professionals, the eHM-DP contributes to an improved medical treatment of the PwD (83%, 5/6) and improved compliance (50%, 3/6). One major aspect that contributed was the provision of "hard-to-access" information (home-based care setting, symptoms over disease course). This resulted in faster response time to status changes and thus also to a reduction of caregiver burden (50%, 3/6), and overall improved interaction with informal caregivers (33%, 2/6). A third aspect that is highlighted is the improved access to support, especially for mobility-impaired persons and for people living in rural areas (67%, 4/6). In addition, professionals indicated that eHM-DP contributes to active medical decision making for PwD and informal caregivers, timely reaction to changes in the disease course (67%, 4/6), as well as the prevention of the deterioration of the disease (50%, 3/6).

Overall, medical professionals emphasized the possibility of timely reactions to status changes, whereas social professionals highlighted the improved access to care and support for caregivers who are living in rural areas. Both groups showed a high level of consistency with regard to an improved medical treatment of the PwD.

Figure 6. Perceived usefulness of the eHM-DP.



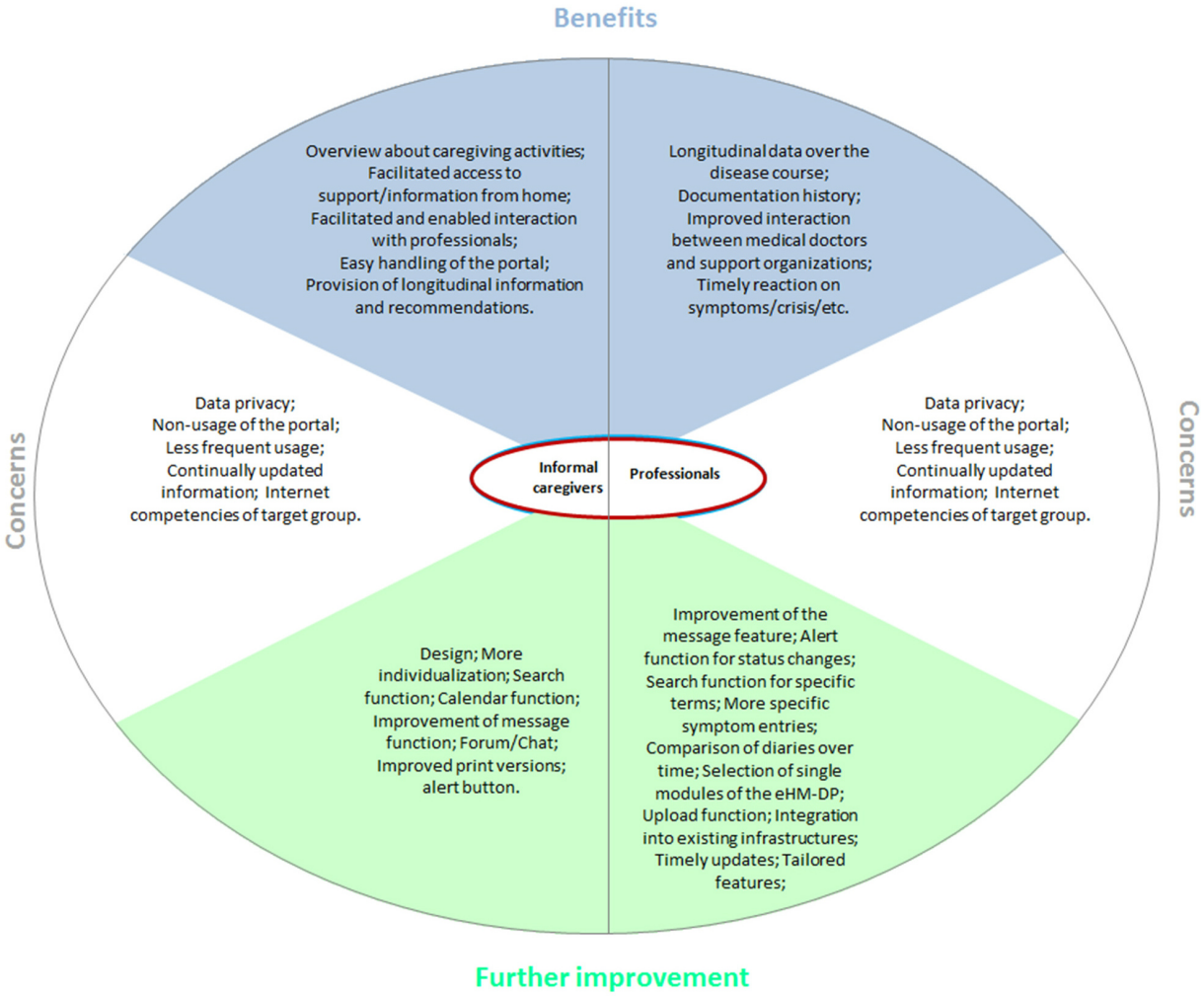
Impact: Quality of Life and Caregiver Burden (Informal Caregivers)

After 12 weeks of eHM-DP usage, there were no improvements on primary informal caregiver outcomes (BSFC and EQ-5D-5L).

Qualitative Findings

The content analysis of the 29 interviews (23 informal caregivers and 6 professionals) resulted in 18 categories across three domains (ie, perceived benefits, concerns, further improvement), which are presented below (see Figure 7).

Figure 7. Results of qualitative content analysis: Benefits, concerns, improvements.



Perceived Benefits (8 Categories)

Informal caregiver reported the following five major benefits: saved time, 24-hour access, facilitated communication with professionals, easily operated portal, and overview about individual caregiving activities.

A major benefit for informal caregivers was saved time (eg, communication with professionals from home, provision of individualized information), which was predominantly expressed by employed informal caregivers. Another perceived benefit was 24-hour facilitated access to support and information, due to access from home or work. A further perceived benefit resulted from the facilitated and increased communication with professionals. In addition, the overview about individual caregiving activities resulted in increased awareness of personal tasks and support areas. The easily operated portal also accounted for frequent use from users.

For the professionals, the following four major benefits were identified: provision of longitudinal data over the disease course, documentation history, improved interaction between professional institutions and support organizations, and timely reaction to status changes.

Provision of longitudinal data over the disease course and documentation history were essential and beneficial factors of the eHM-DP. In addition, the professionals mentioned an improved interaction between professional institutions and support organizations. The latter factors contributed also to an improved and faster response time to behavioral symptoms, adverse events, or crisis.

Concerns (4 Categories)

We identified the following categories: concerns of data privacy, risk of non-usage of the portal, assurance of provision of up-to-date information, and insufficient Internet competence of informal caregivers. Both informal caregivers and professionals expressed concerns about data privacy (eg, who will access the entered data?). In addition, they mentioned the risk of non-usage or insufficiently frequent usage, which is the precondition to realize the eHM-DP's benefits and interaction between both sides. Further, they emphasized that all provided information has to be up to date and professionals stated that the target group of informal caregivers is hard to reach and often has less competence with the Internet.

Further Improvement (6 Categories)

The following categories for the domain "further improvement" were identified: improved design of the portal, more specific individualization of the portal, further functionalities, improvement/extension of specific functionalities, selection of certain functionalities of the portal for professionals, and integration of the eHM-DP into existing infrastructures.

Informal caregivers reported the following comments for further improvements. First, they suggested an improved design of the eHM-DP (eg, the presentation of tables and graphs, the main menu, the selective use of colors, or the presentation of videos). In addition, they emphasized the need for even more specific individualization of the eHM-DP (eg, according to the caregiver status to the patient [spouse or child] or for specific topics). The possibility of searching for specific terms, information about local events (eg, based on a calendar), print version for whole diaries, and the integration of an alert button were warranted. Further, the need to improve the message feature for communication with professionals was expressed by both informal caregivers and professionals (eg, display of a message history, read confirmation). In addition to the interaction with professionals, informal caregivers wanted to have an integration of a forum or chat for informal caregivers themselves.

The professionals mentioned the benefit of an improved alert function for status changes of the patient or caregiver, which helps them react in a timely fashion to status changes. In addition, the possibility of making more specific symptom entries and caregiving entries within the diaries and the integration of a search functionality for specific terms was expressed. Professionals would also benefit from the option to compare diary entries (over time). A selection of single modules of the eHM-DP service would help professionals choose the most important functionalities of the service and tailor the eHM-DP features and modules to specific professions (eg, physician, caregiver counseling institution, psychologists, care service). Also the possibility of uploading specific documents like blood parameters or diagnostic findings would facilitate patient management.

Finally, the need for integration of the eHM-DP into existing software infrastructures as well as the need for timely updates of provided information was highly warranted.

Discussion

Principal Findings

This study describes the perceived usefulness and impact of a personalized eHealth service (eHM-DP) that aims to support informal caregivers and professionals in the dementia treatment and care setting. Our results reveal that the eHM-DP is promising in addressing needs of both informal caregivers [2,3,30,31,33] and professionals [32] in the dementia treatment and care setting. Those were addressed by five major factors: individualized information acquisition, decision support, facilitated access to care and support infrastructures, interaction between professionals and informal caregivers, and provision of longitudinal data about the disease course and medication history ("hard-to-access" information). Although pre-post changes in caregiver burden (BFSC) and quality of life (EQ-5D-5L) for informal caregivers were not observed, the perceived usefulness of the eHM-DP and qualitative interview data of both study participant groups are encouraging. They indicated perceived benefits and a positive impact of the eHM-DP with respect to increased knowledge in certain topics (PrepDM, CNA-D), as well as the facilitated interaction with professionals. These results are also evident in a recent review from Boots et al (2014) [22], concluding that multicomponent interventions that combine tailored information with interaction are the most promising approaches [22].

One factor that contributed to these results is that both user groups have been involved early in the development process of the eHM-DP, which has proven to be valuable in previous studies [46-48]. Further, the combination of comprehensive information provision within the eHM-DP of informal caregivers and of PwDs was relevant for tailoring information and support.

From the perspective of professionals, the eHM-DP provided benefits for improved medical treatment of dementia patients, improved compliance, and interaction with informal caregivers. Although no significant changes in the reduction of caregiver burden were measured, half of the professionals considered that the eHM-DP is able to reduce caregiver burden. The latter aspects are encouraging with regard to the reduction of hospitalizations and institutionalizations (positive health economic impact), as especially caregiver burden is one of the main predictors for nursing home referrals [9,10,49]. A major factor that led to these perceived benefits was the timely provision of "hard-to-access" information (eg, home-based care situation, symptoms over disease course, medication, subjective informal caregiver burden, health status of informal caregiver and PwD). This is a major advantage as informal caregivers are often the only information source for professionals at (regular) checkups but are not able to provide quantified long-term details. However, professionals expressed doubts about whether the informal caregivers would be motivated to use the eHM-DP regularly. This concern could not be confirmed within our study; however, participants were reminded and motivated to use the eHM-DP. The physicians from the memory clinic mainly benefited from the course of disease diary with timely, quantified, and longitudinal information about cognitive status, activities of daily living, mood, behavioral symptoms, and social behavior, followed by the medication diary with information of all medications and reported side effects. This is especially important because PwDs are often elderly persons with more than one disease who are in contact with several physicians [50]. The latter diaries enable an overview of all prescriptions, side effects, and comorbidities of the PwD. In contrast to physicians, caregiver counseling institutions emphasized the comprehensive (PwD and informal caregiver status, needs) and timely information provision that helps prevent caregiver burden and provides additional benefits (eg, optimized counseling, improved accessibility for target group) to the usual face-to-face support. The eHM-DP provided them additional and timely insight into actual carers' needs and, thus, contributes to prevention of caregiver burden and early crisis intervention. This is crucial, as informal caregivers often wait until a crisis situation occurred or they become exhausted before seeking

support [51]. Regular contact with professionals can help prevent such crisis situations.

From the perspective of informal caregivers, the provision of individualized information for the specific care situation of the informal caregiver contributed to caregiver empowerment. The importance of tailoring information to informal caregivers' needs was highlighted in previous studies [21,23,33,52,53]. Within the eHM-DP, modifying information based on the symptoms and status of the PwD, in addition to informal caregivers' health status and needs, proved to be important for individual information provision and interaction with professionals. In addition to provided information from the eHM-DP, professionals gave individual recommendations based on diary entries via the portal message feature. A number of the informal caregivers reported that information about specific topics triggered reflection about their own caregiver role and situation and, thus, provided a useful decision aid. In contrast to experienced caregivers, "new" caregivers of recently diagnosed PwDs reported a high perceived benefit with regard to individual information acquisition.

Overall, a recent review indicated that informal caregivers often receive little or unclear information about dementia, especially after the diagnosis disclosure [54]. This leads to another determinant that contributed to empowerment of informal caregivers: the facilitated access to information and support. It is evident that the accessibility of services is a major predictor for its utilization [11,55]. The overall empowerment of informal caregivers via knowledge acquisition about local support options is crucial, as the lack of knowledge about existing services and dementia infrastructures contributes to one of four major reasons for non-use of services [10]. The eHM-DP contributes to increased autonomy in the sense of awareness and offers the chance to choose between different support services as demonstrated by Schüz et al [56]. In particular, informal caregivers from rural areas, non-mobile informal caregivers or full-time employed informal caregivers emphasized the facilitated interaction and information acquisition from home. In addition, it can reach informal caregivers, who are either not motivated (eg, persons who do not want to travel to the next town) or not able to use (eg, no public transport) traditional services like caregiver counseling. This is especially true for people living in rural and remote areas [18,51,57]. These findings are in line with previous studies, where time constraints, transportation, and health issues have been identified as predictors for non-participation in face-to-face support services [12,51].

Limitations

Although the findings of our study provided essential insight into the usefulness of eHealth support services for informal caregivers of PwD and professionals, some limitations need to be considered. Our study confirmed that introducing eHealth services to elderly people is challenging, as computer competencies and Internet access are important prerequisites, which narrows the potential number of study participants. The objective was to conduct a comprehensive proof of principle study with a demonstrator in order to improve the eHM-DP before evaluating effects on a larger scale and in a (randomized) controlled group design. This approach has been recommended in previous studies [36]. However, the fact that no control group was included is a limitation and the realization of a controlled study is needed. The first limitation was the small sample size of study participants. The convenience sample had rather lower levels of caregiver burden, which has to be taken into account when interpreting results for further studies on a larger scale, as well as the reach of the intervention. Additionally, the positive feedback of the eHM-DP from 83% of caregivers may be overestimated due to the convenience sample that agreed to take part in the study.

Another limitation is the short 12-week study period, which likely explains the non-significant changes in quality of life and caregiver burden. Furthermore, an apparent discrepancy between the non-significant pre-post outcome measures (BSFC, EQ-5D-5L) and the positive results on perceived usefulness of both user groups is present. This can be explained by the small number of study participants and the testing period of 12 weeks. However, an advantage of our study is the focus on post-outcome measurements and qualitative interviews (mixed-method design) that provided promising results for the eHM-DP service and emphasizes the need for further controlled studies on a larger scale.

Future Directions

Our study contributes to scientific research by providing insight into the different user perspectives of eHealth support services in the dementia treatment and care setting. These results are crucial for future developments and the use of eHealth solutions in the dementia domain and reinforce the importance of early user involvement. The perceived benefits and willingness to use the system combined with an increasing number of adults who use the Internet regularly, emphasizes the potential of personalized and Web-based support services for informal caregivers. This is especially true for our aging societies and limited expenditures for health care services.

Based on our findings, the following aspects are decisive for implementing eHealth services in the dementia treatment and care context: a comprehensive introduction into the eHM-DP with all its functionalities, the provision of informational material and the provision of a contact person for seeking advice or help. These aspects proved to be important to ensure competent handling of the eHM-DP service. In addition, the latter aspects are suitable for addressing concerns of both study participants (non-usage of the portal, Internet competencies of target group, data privacy). Furthermore, the provision of technical support is essential, in particular for participants with low computer competence. In the future, the introduction and support could be provided by, for example, the professional organization itself or by trained, voluntary caregivers. The use of reminders (eg, messages, phone calls) to use the eHM-DP has proven to be valuable.

Another important success factor of the eHM-DP is the facilitated and enabled computerized interaction between informal caregivers and professionals. Future developments of the eHM-DP should concentrate on linking more than one stakeholder via the eHM-DP (eg, informal caregiver, social worker, physician, professional caregiver) because a

well-functioning, interprofessional, and interorganizational communication in dementia care is important [58]. Overall, further controlled studies on a larger scale, focusing on cost-effectiveness and usability are crucial to embed the eHM-DP into existing health care infrastructures. In addition, the future eHM-DP development should exploit potential synergy effects between existing systems with similar intentions, such as InformCare [59] as well as complementary systems such as Ambient Assisted Living (AAL)-systems (eg, ALLADIN [60]), educational online courses (eg, Mastery over Dementia [61]), or chatrooms (eg, ALZConnected [62], ANKER [63]).

In particular, different priorities and needs of professional organizations (eg, hospitals versus counseling institutions or professional caregivers) have to be considered carefully. Valuable tips for professional organizations were already provided in the results section. In addition, more research with regard to different informal caregiver types (eg, according to gender, relationship to PwD, employment status, rural areas, and ethnicity) and related needs is necessary. This was also emphasized in the qualitative study results, where informal caregivers expressed the wish for more individualization.

Turning to the primary target of the eHM-DP service, our findings suggest that the eHM-DP service proved to be a valuable post-diagnostic eHealth support service for the home-based care setting. It revealed several benefits for families (informal caregivers), professionals, and health care systems, which are the basis for further studies and future health care policy planning in dementia.

Acknowledgments

We express our special thanks to all family caregivers who contributed to this study by giving their opinions and ideas to the design and functionalities of the eHM-DP. The staff of the regional offices of the Alzheimer's Society, caregiver counseling services (S Engel, V Stein, C Lottes, A Ober, HD Mückschel, B Kuhn, B Lischka, P Mönius-Gittelbauer, H Volkmann), and the Memory Clinic of the University Hospital Erlangen are also acknowledged for their support.

Furthermore, we express special thanks to V De La Rosa and B Häupler for several revisions to the manuscript. Finally, we would like to express our thanks to all the eHealthMonitor consortium partners.

This study was financed by the European Commission, FP7-project eHealthMonitor (ID 287509) and supported by the Emerging Fields Initiative (EFI), Project Human Rights in Healthcare, of the Friedrich-Alexander-University Erlangen-Nürnberg.

This work was performed in partial fulfillment of the requirements for obtaining the degree "Dr. rer. biol. hum." for author SS.

Authors' Contributions

SS designed the study; coordinated, prepared (interviewer training), and organized data collection; and was responsible for the statistical design and data analysis (qualitative and quantitative study) as well as for the preparation of the manuscript. SS, VM-S, and MS were responsible for the data collection and interviews and contributed to data preparation and analysis (qualitative and quantitative data). MS and LG were responsible for designing the study from the perspective of a medical technician with a focus on the relationship between technical features and perceived benefits. Both gave important tips for interpretation and discussion of study results. HK was responsible for the development of Sematic Infrastructure of the eHM-DP and the description of the technical infrastructure. EG and JM contributed to the pilot study by providing expert advice from the perspective of a professional in the dementia care setting and gave important hints for interpretation and discussion of study results. The eHM project coordinator SK was responsible for the development and provision of the eHM-DP demonstrator and gave important advice for the realization of the study and discussion of the study results from a technical perspective. PK-R supervised and designed the study. All authors have read the paper and contributed to the discussion of the study results.

Conflicts of Interest

None declared.

References

1. World Health Organization. Dementia - a public health priority. Geneva: World Health Organization; 2012.
2. Zwaanswijk M, Peeters JM, van Beek AP, Meerveld JH, Francke AL. Informal caregivers of people with dementia: problems, needs and support in the initial stage and in subsequent stages of dementia: a questionnaire survey. Open Nurs J 2013;7:6-13 [FREE Full text] [doi: 10.2174/1874434601307010006] [Medline: 23346266]
3. Black BS, Johnston D, Rabins PV, Morrison A, Lyketsos C, Samus QM. Unmet needs of community-residing persons with dementia and their informal caregivers: findings from the maximizing independence at home study. J Am Geriatr Soc 2013 Dec;61(12):2087-2095 [FREE Full text] [Medline: 24479141]
4. Gräßel E, Adabbo R. Perceived Burden of Informal Caregivers of a Chronically ill Older Family Member. GeroPsych 2011;24(3):143-154.
5. Brodaty H, Donkin M. Family caregivers of people with dementia. Dialogues Clin Neurosci 2009;11(2):217-228 [FREE Full text] [Medline: 19585957]

6. Wimo A, Jönsson L, Bond J, Prince M, Winblad B, Alzheimer DI. The worldwide economic impact of dementia 2010. Alzheimers Dement 2013 Jan;9(1):1-11.e3. [doi: 10.1016/j.jalz.2012.11.006] [Medline: 23305821]
7. Schaller S, Mauskopf J, Kriza C, Wahlster P, Kolominsky-Rabas PL. The main cost drivers in dementia: a systematic review. Int J Geriatr Psychiatry 2015 Feb;30(2):111-129. [doi: 10.1002/gps.4198] [Medline: 25320002]
8. Graessel E. Belastung und gesundheitliche Situation der Pflegenden. Quer-schnittuntersuchung zur häuslichen Pflege bei chronischem Hilfs- oder Pflege-bedarf im Alter 1998.
9. Eska K, Graessel E, Donath C, Schwarzkopf L, Lauterberg J, Holle R. Predictors of institutionalization of dementia patients in mild and moderate stages: a 4-year prospective analysis. Dement Geriatr Cogn Dis Extra 2013;3(1):426-445 [FREE Full text] [doi: 10.1159/000355079] [Medline: 24348504]
10. Gallagher D, Ni MA, Crosby L, Ryan D, Lacey L, Coen RF, et al. Determinants of the desire to institutionalize in Alzheimer's caregivers. Am J Alzheimers Dis Other Demen 2011 May;26(3):205-211. [doi: 10.1177/1533317511400307] [Medline: 21378063]
11. Brodaty H, Thomson C, Thompson C, Fine M. Why caregivers of people with dementia and memory loss don't use services. Int J Geriatr Psychiatry 2005 Jun;20(6):537-546. [doi: 10.1002/gps.1322] [Medline: 15920707]
12. Phillipson L, Jones SC, Magee C. A review of the factors associated with the non-use of respite services by carers of people with dementia: implications for policy and practice. Health Soc Care Community 2014 Jan;22(1):1-12. [doi: 10.1111/hsc.12036] [Medline: 23530738]
13. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement 2013 Jan;9(1):63-75.e2. [doi: 10.1016/j.jalz.2012.11.007] [Medline: 23305823]
14. Bujnowska-Fedak MM, Pirogowicz I. Support for e-health services among elderly primary care patients. Telemed J E Health 2014 Aug;20(8):696-704 [FREE Full text] [doi: 10.1089/tmj.2013.0318] [Medline: 24359252]
15. Chiu TML, Eysenbach G. Stages of use: consideration, initiation, utilization, and outcomes of an internet-mediated intervention. BMC Med Inform Decis Mak 2010;10:73 [FREE Full text] [doi: 10.1186/1472-6947-10-73] [Medline: 21092275]
16. Chiu TML, Eysenbach G. Theorizing the health service usage behavior of family caregivers: a qualitative study of an internet-based intervention. Int J Med Inform 2011 Nov;80(11):754-764. [doi: 10.1016/j.ijmedinf.2011.08.010] [Medline: 21958550]
17. McKechnie V, Barker C, Stott J. The effectiveness of an Internet support forum for carers of people with dementia: a pre-post cohort study. J Med Internet Res 2014;16(2):e68 [FREE Full text] [doi: 10.2196/jmir.3166] [Medline: 24583789]
18. Blusi M, Dalin R, Jong M. The benefits of e-health support for older family caregivers in rural areas. J Telemed Telecare 2014 Mar;20(2):63-69. [doi: 10.1177/1357633X13519901] [Medline: 24446251]
19. Grässel E, Bleich S, Meyer-Wegener K, Schmid U, Kornhuber J, Prokosch H. [The internet as an information source for family caregivers of dementia patients]. Psychiatr Prax 2009 Apr;36(3):115-118. [doi: 10.1055/s-2008-1067550] [Medline: 18924061]
20. Schaller S, Kriza C, Niederländer C, Wahlster P, Kolominsky-Rabas P. Developing an Individualized E-Health Decision Support System for Dementia Treatment and Care: The FP7 EU-Project E-Health Monitor (eHM). Value in Health 2013;16(7):2.
21. McKechnie V, Barker C, Stott J. Effectiveness of computer-mediated interventions for informal carers of people with dementia-a systematic review. Int Psychogeriatr 2014 Oct;26(10):1619-1637 [FREE Full text] [doi: 10.1017/S1041610214001045] [Medline: 24989249]
22. Boots LMM, de Vugt ME, van Knippenberg RJM, Kempen GIJM, Verhey FRJ. A systematic review of Internet-based supportive interventions for caregivers of patients with dementia. Int J Geriatr Psychiatry 2014 Apr;29(4):331-344. [doi: 10.1002/gps.4016] [Medline: 23963684]
23. van der Roest HG, Meiland FJM, Jonker C, Dröes RM. User evaluation of the DEMentia-specific Digital Interactive Social Chart (DEM-DISC). A pilot study among informal carers on its impact, user friendliness and, usefulness. Aging Ment Health 2010 May;14(4):461-470. [doi: 10.1080/13607860903311741] [Medline: 20455122]
24. Beauchamp N, Irvine AB, Seeley J, Johnson B. Worksite-based internet multimedia program for family caregivers of persons with dementia. Gerontologist 2005 Dec;45(6):793-801. [Medline: 16326661]
25. Chiu T, Marziali E, Colantonio A, Carswell A, Gruneir M, Tang M, et al. Internet-based caregiver support for Chinese Canadians taking care of a family member with alzheimer disease and related dementia. Can J Aging 2009 Dec;28(4):323-336. [doi: 10.1017/S0714980809990158] [Medline: 19925698]
26. Glueckauf RL, Ketterson TU, Loomis JS, Dages P. Online support and education for dementia caregivers: overview, utilization, and initial program evaluation. Telemed J E Health 2004;10(2):223-232. [doi: 10.1089/tmj.2004.10.223] [Medline: 15319052]
27. Magnusson L, Hanson E. Supporting frail older people and their family carers at home using information and communication technology: cost analysis. J Adv Nurs 2005 Sep;51(6):645-657. [doi: 10.1111/j.1365-2648.2005.03541.x] [Medline: 16129015]

28. Kondylakis H, Plexousakis D, Hrgovcic V, Woitsch R, Premm M, Schuele M. Agents, Models and Semantic Integration in Support of Personal eHealth Knowledge Spaces. In: Web Information Systems Engineering. Switzerland: Springer International Publishing; 2014:496-511.
29. Kondylakis H, Plexousakis D, Hrgovcic V, Woitsch R, Premm M, Schuele M. Personal eHealth Knowledge Spaces though Models, Agents and Semantics. In: Advances in Conceptual Modeling. Switzerland: Springer International Publishing; 2014:293-297.
30. Wancata J, Krautgartner M, Berner J, Alexandrowicz R, Unger A, Kaiser G, et al. The Carers' Needs Assessment for Dementia (CNA-D): development, validity and reliability. Int Psychogeriatr 2005 Sep;17(3):393-406. [Medline: 16252373]
31. Ducharme F, Kergoat M, Coulombe R, Lévesque L, Antoine P, Pasquier F. Unmet support needs of early-onset dementia family caregivers: a mixed-design study. BMC Nurs 2014;13(1):49 [FREE Full text] [doi: 10.1186/s12912-014-0049-3] [Medline: 25550685]
32. Komarahadi FL, Ruf D, Hüll M, Härter M. [Information needs of physicians, professional carers and family carers for an evidence-based dementia website]. Psychiatr Prax 2012 Jan;39(1):34-39. [doi: 10.1055/s-0031-1276837] [Medline: 21796578]
33. Vaingankar JA, Subramaniam M, Picco L, Eng GK, Shafie S, Sambasivam R, et al. Perceived unmet needs of informal caregivers of people with dementia in Singapore. Int Psychogeriatr 2013 Oct;25(10):1605-1619. [doi: 10.1017/S1041610213001051] [Medline: 23845530]
34. Schaller S, Marinova-Schmidt V, Gobin J, Criegee-Rieck M, Griebel L, Engel S, et al. Tailored e-Health services for the dementia care setting: a pilot study of 'eHealthMonitor'. BMC Med Inform Decis Mak 2015;15:58 [FREE Full text] [doi: 10.1186/s12911-015-0182-2] [Medline: 26215731]
35. Eysenbach G, CONSORT- E. CONSORT-EHEALTH: improving and standardizing evaluation reports of Web-based and mobile health interventions. J Med Internet Res 2011;13(4):e126 [FREE Full text] [doi: 10.2196/jmir.1923] [Medline: 22209829]
36. Makai P, Perry M, Robben SHM, Schers HJ, Heinen MM, Olde Rikkert MG, et al. Evaluation of an eHealth intervention in chronic care for frail older people: why adherence is the first target. J Med Internet Res 2014;16(6):e156 [FREE Full text] [doi: 10.2196/jmir.3057] [Medline: 24966146]
37. Kolominsky-Rabas P, Schaller S, Griebel L. Standard Operating Procedure (SOP) for evaluation of eHealthMonitor. Standard Operating Procedures eHM 2014:1-10.
38. Eysenbach G. The law of attrition. J Med Internet Res 2005;7(1):e11 [FREE Full text] [doi: 10.2196/jmir.7.1.e11] [Medline: 15829473]
39. Lilford RJ, Foster J, Pringle M. Evaluating eHealth: how to make evaluation more methodologically robust. PLoS Med 2009 Nov;6(11):e1000186 [FREE Full text] [doi: 10.1371/journal.pmed.1000186] [Medline: 19956674]
40. Van Der Meijden MJ, Tange HJ, Troost J, Hasman A. Determinants of success of inpatient clinical information systems: a literature review. J Am Med Inform Assoc 2003;10(3):235-243 [FREE Full text] [doi: 10.1197/jamia.M1094] [Medline: 12626373]
41. Norman CD, Skinner HA. eHEALS: The eHealth Literacy Scale. J Med Internet Res 2006;8(4):e27 [FREE Full text] [doi: 10.2196/jmir.8.4.e27] [Medline: 17213046]
42. Bennett C, Graham ID, Kristjansson E, Kearing SA, Clay KF, O'Connor AM. Validation of a preparation for decision making scale. Patient Educ Couns 2010 Jan;78(1):130-133. [doi: 10.1016/j.pec.2009.05.012] [Medline: 19560303]
43. Hinz A, Kohlmann T, Stöbel-Richter Y, Zenger M, Brähler E. The quality of life questionnaire EQ-5D-5L: psychometric properties and normative values for the general German population. Qual Life Res 2014 Mar;23(2):443-447. [doi: 10.1007/s11136-013-0498-2] [Medline: 23921597]
44. Grau H, Graessel E, Berth H. The subjective burden of informal caregivers of persons with dementia: extended validation of the German language version of the Burden Scale for Family Caregivers (BSFC). Aging Ment Health 2015;19(2):159-168. [doi: 10.1080/13607863.2014.920296] [Medline: 24914762]
45. Mayring P. Qualitative Content Analysis. In: Theoretical Foundation, Basic Procedures and Software Solution. Austria: Klagenfurt; 2014.
46. Meiland FJM, Hattink BJJ, Overmars-Marx T, de Boer M ME, Jedlitschka A, Ebben PWG, et al. Participation of end users in the design of assistive technology for people with mild to severe cognitive problems; the European Rosetta project. Int Psychogeriatr 2014 May;26(5):769-779. [doi: 10.1017/S1041610214000088] [Medline: 24507571]
47. Orpwood R. User Involvement in Dementia Product Development. Dementia 2004 Oct 01;3(3):263-279. [doi: 10.1177/1471301204045160]
48. Wherton J, Monk A. Technological opportunities for supporting people with dementia who are living at home. International Journal of Human-Computer Studies 2008 Aug;66(8):571-586. [doi: 10.1016/j.ijhcs.2008.03.001]
49. Gaugler JE, Yu F, Krichbaum K, Wyman JF. Predictors of nursing home admission for persons with dementia. Med Care 2009 Feb;47(2):191-198. [doi: 10.1097/MLR.0b013e31818457ce] [Medline: 19169120]
50. Bunn F, Burn A, Goodman C, Rait G, Norton S, Robinson L, et al. Comorbidity and dementia: a scoping review of the literature. BMC Med 2014;12:192 [FREE Full text] [doi: 10.1186/s12916-014-0192-4] [Medline: 25358236]
51. Morgan DG, Semchuk KM, Stewart NJ, D'Arcy C. Rural families caring for a relative with dementia: barriers to use of formal services. Soc Sci Med 2002 Oct;55(7):1129-1142. [Medline: 12365526]

52. Pinquart M, Sörensen S. Helping caregivers of persons with dementia: which interventions work and how large are their effects? Int Psychogeriatr 2006 Dec;18(4):577-595. [doi: 10.1017/S1041610206003462] [Medline: 16686964]
53. Raivio M, Eloniemi-Sulkava U, Laakkonen M, Saarenheimo M, Pietilä M, Tilvis R, et al. How do officially organized services meet the needs of elderly caregivers and their spouses with Alzheimer's disease? Am J Alzheimers Dis Other Demen 2007;22(5):360-368. [doi: 10.1177/1533317507305178] [Medline: 17959871]
54. Stokes L, Combes H, Stokes G. The dementia diagnosis: a literature review of information, understanding, and attributions. Psychogeriatrics 2015 Sep;15(3):218-225. [doi: 10.1111/psyg.12095] [Medline: 25515569]
55. Gräßel E, Luttenberger K, Trilling A, Donath C. Counselling for dementia caregivers - predictors for utilization and expected quality from a family caregiver's point of view. European Journal of Ageing 2010;7:111-119.
56. Schüz B, Dräger D, Richter S, Kummer K, Kuhlmey A, Tesch-Römer C. Autonomie trotz Multimorbidität im Alter - Der Berliner Forschungsverbund AMA. Z Gerontol Geriatr 2011;44(2):9-26.
57. Blusi M, Kristiansen L, Jong M. Exploring the influence of Internet-based caregiver support on experiences of isolation for older spouse caregivers in rural areas: a qualitative interview study. Int J Older People Nurs 2015 Sep;10(3):211-220 [FREE Full text] [doi: 10.1111/opn.12074] [Medline: 25425070]
58. Karlsson S, Bleijlevens M, Roe B, Saks K, Martin MS, Stephan A, et al. Dementia care in European countries, from the perspective of people with dementia and their caregivers. J Adv Nurs 2015 Jun;71(6):1405-1416. [doi: 10.1111/jan.12581] [Medline: 25430690]
59. European Association Working for Carers. URL: http://eurocarers.org/InformCare [accessed 2016-03-02] [WebCite Cache ID 6fhz0vRCt]
60. Torkamani M, McDonald L, Saez AI, Kanios C, Katsanou M, Madeley L, et al. A randomized controlled pilot study to evaluate a technology platform for the assisted living of people with dementia and their carers. J Alzheimers Dis 2014;41(2):515-523. [doi: 10.3233/JAD-132156] [Medline: 24643137]
61. Blom M, Zarit S, Groot Zwaaftink RBM, Cuijpers P, Pot A. Effectiveness of an Internet intervention for family caregivers of people with dementia: results of a randomized controlled trial. PLoS One 2015;10(2):e0116622 [FREE Full text] [doi: 10.1371/journal.pone.0116622] [Medline: 25679228]
62. Alzheimer's and Dementia Caregiver Center. ALZConnected. URL: https://www.alzconnected.org/ [accessed 2016-03-02] [WebCite Cache ID 6gXqoyI1f]
63. ANKER - Regionales Online-Netzwerk Demenz. 2015. URL: http://www.anker-netzwerk.net/ [accessed 2016-03-02] [WebCite Cache ID 6gXqwgNkA]

Abbreviations

BSFC: Burden Scale for Family Caregivers
CNA-D: Carers' Needs Assessment for Dementia
eHM: eHealthMonitor
eHM-DP: eHealthMonitor Dementia Portal
ICD: International Statistical Classification of Diseases and Related Health Problems
MAS: multi-agent system
PeKS: Personal eHealth Knowledge Space
PrepDM: Preparation for Decision Making Scale
PwD: person with dementia

Edited by G Eysenbach; submitted 20.02.15; peer-reviewed by M Blusi, F Meiland, V McKechnie; comments to author 05.08.15; revised version received 11.09.15; accepted 04.01.16; published 05.04.16.

Please cite as:
Schaller S, Marinova-Schmidt V, Setzer M, Kondylakis H, Griebel L, Sedlmayr M, Graessel E, Maler JM, Kirn S, Kolominsky-Rabas PL
Usefulness of a Tailored eHealth Service for Informal Caregivers and Professionals in the Dementia Treatment and Care Setting: The eHealthMonitor Dementia Portal
JMIR Res Protoc 2016;5(2):e47
URL: http://www.researchprotocols.org/2016/2/e47/
doi:10.2196/resprot.4354
PMID:27050401

Original Paper

Parental Evaluation of a Nurse Practitioner-Developed Pediatric Neurosurgery Website

Tina Kovacs Vogel[1], RN, NP, BScN, MN; Manal Kleib[1,2], RN, MSN, MBA, PhD; Sandra J Davidson[1], RN, MSN, PhD; Shannon D Scott[1], RN, PhD

[1]Faculty of Nursing, University of Alberta, Edmonton, AB, Canada

[2]Alberta Health Services, Edmonton, AB, Canada

Corresponding Author:
Shannon D Scott, RN, PhD
Faculty of Nursing
University of Alberta
Level 3, Edmonton Clinic Health Academy
11405 87 Avenue
Edmonton, AB, T6G 1C9
Canada
Phone: 1 7804921037
Fax: 1 7804922551
Email: shannon.scott@ualberta.ca

Abstract

Background: Parents often turn to the Internet to seek health information about their child's diagnosis and condition. Information, support, and resources regarding pediatric neurosurgery are scarce, hard to find, and difficult to comprehend. To address this gap, a pediatric nurse practitioner designed a website called the Neurosurgery Kids Fund (NKF). Analyzing the legitimacy of the NKF website for parents seeking health information and fulfilling their social and resource needs is critical to the website's future development and success.

Objective: To explore parental usage of the NKF website, track visitor behavior, evaluate usability and design, establish ways to improve user experience, and identify ways to redesign the website. The aim of this study was to assess and evaluate whether a custom-designed health website could meet parents' health information, support, and resource needs.

Methods: A multimethod approach was used. Google Analytic usage reports were collected and analyzed for the period of April 23, 2013, to November 30, 2013. Fifty-two online questionnaires that targeted the website's usability were collected between June 18, 2014, and July 30, 2014. Finally, a focus group was conducted on August 20, 2014, to explore parents' perceptions and user experiences. Findings were analyzed using an inductive content analysis approach.

Results: There were a total of 2998 sessions and 8818 page views, with 2.94 pages viewed per session, a 56.20% bounce rate, an average session duration of 2 minutes 24 seconds, and a 56.24% new sessions rate. Results from 52 eligible surveys included that the majority of NKF users were Caucasian (90%), females (92%), aged 36-45 years (48%), with a university or college degree or diploma (69%). Half plan to use the health information. Over half reported turning to the Internet for health information and spending 2 to 4 hours a day online. The most common reasons for using the NKF website were to (1) gather information about the 2 summer camps, (2) explore the Media Center tab, and (3) stay abreast of news and events supported by NKF. Parents were unanimous in reporting that the NKF website was pleasing in color and design, very easy to use and navigate, useful, and that they would continue to access it regularly.

Conclusions: Parents perceive the NKF website to be useful and easy-to-use in meeting their health information needs, finding social support, and learning about resources relevant to their child. A custom-designed website can be used to augment parents' health information needs by reinforcing, supplementing, and improving their understanding of their child's medical needs.

(JMIR Res Protoc 2016;5(2):e55) doi:10.2196/resprot.5156

KEYWORDS

Pediatric; neurosurgery; website; evaluation; parents; children; Google analytics; Internet health information needs; knowledge translation.

Introduction

Children who require neurosurgery are a unique population with highly specialized medical needs. Information, support, and resources regarding pediatric neurosurgery are scarce, hard to find, and difficult to understand. Furthermore, connecting with other parents or caregivers whose children are also affected by neurosurgical conditions or illnesses can be even more difficult given the rarity of these diagnoses. Studying the impact and legitimacy of using a custom-designed website, the Neurosurgery Kids Fund (NKF) [1], to support parents' health information needs—as well as their social and support needs—is imperative in bridging these gaps.

Searching for information on the Internet is a common first step for parents to gain knowledge about a child's diagnosis, prognosis, treatment, and support options [2-4]. Once considered passive receivers of care, patients today are active consumers of health care who want to be involved in decision making, in managing their own health care, and in deciding how to mitigate risk factors and complications [5]. eHealth, the use of the Internet as a source of health information, offers many benefits, including data that complements the physician's information, anonymous health information seeking, information exchange, community support, and empowerment in seeking help for and understanding of medical conditions [6]. People use online health information as a source of knowledge for many reasons. These reasons may include: getting immediate answers; learning about the diagnosis, treatment options, and prognosis; supplementing the physician's information; finding support; and sharing with others who have similar experiences [2,6-11]. Parents of sick children report using the Internet to find health information because they worry about their child's health, feel rushed and received limited guidance or advice from doctors, seek convenience and accessibility, and need to connect with others in similar situations [11].

Up until now, knowledge translation efforts have largely focused on ensuring that health care professionals use the latest research to inform their practice; however, initiatives that target health care consumers (eg, parents) can inform parental decision making, expectations, and shape their treatment outcomes [7,12,13]. Parents now have access to what was once privileged health information, potentially changing their understanding of their child's medical condition, treatment options, medical decision-making, and relationships with health care providers [13]. Knowledge translation in child health is unique given family-centered care and the extent and level of parental involvement [14]. It is important to examine knowledge translation interventions such as websites that are developed specifically for parents to address health information needs and to provide resources and support tools (Appendix 1).

Crutzen, Roosjen, and Poelman argued that in contrast to self-reported exposure measures, tracking user behavior (eg, via dedicated software such as Google Analytics [15]) is independent of visitor's memory, interpretation, or social desirability and when combined with qualitative methods, such as interviews, can yield a fuller and richer picture [16]. In Google Analytics, each visitor to the NKF website brings along his own set of data that can be collected, measured, analyzed, and reported and is an effective website evaluation tool guided by an analyst [17]. Similarly, Wilfert asserted that Google Analytics yields only statistical data but when paired with qualitative methods, a narrative unfolds with storylines including "how people got to the site, what they searched for when they were there, what they looked at, and what they did not" [18].

Methods

Design

This study used a multimethods approach including both quantitative and qualitative designs. Firstly, Google Analytics, a sophisticated Web analytics service, was employed to collect statistical data about NKF usage behavior. Secondly, a 20-question online survey questionnaire directed at parents about the usability of the NKF website was designed and collected using determinants of the technology acceptance model (TAM) [19,20]. Lastly, a focus group interview with parents about their experiences using the NKF website was conducted to augment the Google Analytics and online survey questionnaire data. The Google Analytics reports and online survey questionnaire results were used to inform and direct the focus group interview. Distinctions between usability and user experience are needed because the former is the ability of the user to use the website to carry out a task successfully (eg, used the NKF website to meet the health information needs addressed in the survey) and the latter takes a broader look at the individual's interaction with the website, as well as the thoughts, perceptions, and experiences that results from that interaction (eg, reported during the focus group) [21]. Usage refers to the ways a website is used (eg, number of users, number of page views, time spent on page, etc). However, it is noteworthy that usability influences user experience.

Ethical approval was obtained from the University of Alberta Health Research Ethics Board. Consent was not required for Google Analytics as it is an embedded Web tool that collects anonymous grouped data. Participation in the online survey questionnaire and focus group interview was voluntary and signed consent was obtained for the focus group.

Sampling

Recruitment was targeted at parents who have children, aged 0 to 16 years, who have undergone neurosurgery at the Stollery Children's Hospital in Edmonton, Canada. Parents also had to be familiar with the NKF website for inclusion in the online survey questionnaire and focus group interview. Purposeful sampling was used in the focus group to ensure a breadth of age (for both the child and parent); parental education level; their usage of mobile devices, tablets, and/or computers; and their child's neurosurgical diagnosis. Parents were excluded from the study if their English fluency prevented them from completing the survey or conversing in the focus group.

Data Collection

Methodological triangulation was used and 4 sources of data collected: (1) Google Analytics reports, (2) online survey questionnaire results, (3) focus group interview with parents, and (4) field notes. Survey and focus group data were uploaded

and kept secure in the Health Research Data Repository of the Faculty of Nursing at the University of Alberta. First, the Google Analytics data collection and analysis were conducted for the Web analytic and survey phases. With these results, revision of guiding questions for the focus group interview was performed. Google Analytics reports about NKF website usage were obtained from April 23, 2013, to November 30, 2013. This Web analytic tool uses client-sided data collection, called "page-tagging," to collect raw data from the user's browser. Google Analytics turns that raw data, or statistical numbers, into meaningful and usable information. Using a Web analytic tool, such as Google Analytics, removes bias and ensures speed, rigorous structure, and that an abundance of data can be collected [9,22].

The survey consisted of 20 multiple-choice and check-box questions with principals of the TAM underpinning the framing of the questions. The survey was developed after a review of the literature and piloted with 12 parents to ensure content validity and reliability. Developed by Davis, the TAM suggested perceived usefulness and perceived ease of use to be fundamental determinants of system use [19]. To summarize, a system, such as using a website, is more likely to be accepted and used if it is perceived to be useful and easy to use. Questions focused on the usability of the NKF website, namely: how parents seek health information; how and why they accessed the NKF website; whether their information, support, and resources needs were met online; if they discussed any health information found online with their health care provider; and the website's perceived ease of use and usefulness. In addition, demographic data about the parents were collected including age, gender, ethnicity, location of residence, highest level of formal education, and computer usage.

A semistructured interview guide (Appendix 2) was used in the focus group, which lasted approximately 60 to 90 minutes and asked 4 parents about their experiences using the NKF website and its usability. The interview was recorded in real-time by a court reporter [23]. Benefits to using a court reporter to transcribe the focus group interview verbatim include increased data accuracy, timeliness, preserving confidentiality, and affordability [23]. Transcript-based data collection and analysis represents the most rigorous and time-intensive mode of analyzing focus group data [24]. The transcribed interview was cleaned by comparing the audio-recording with the transcript. Any identifiable information in the transcript was removed to preserve anonymity. Field notes were also obtained before, during, and after the interview to capture the context in which the data was collected. The field notes were reflected on during the data analysis to help situate when and how the responses were elicited (eg, nonverbal expressions or linguistic patterns).

Data Analysis

Usage data for the NKF website was analyzed using the Audience, Acquisition, and Behavior reports from Google Analytics. The Audience report offers an overview of the time period selected, including the number of sessions logged, number of users, percentage of new sessions, number of page views, average session duration, bounce rates, number of pages per session, and location and languages used by the user. Reports about what type of browser and operating system were used and a mobile device overview and breakdown were analyzed. The Acquisition report examines how a user arrived at the website, which can reveal their purpose for visiting the website. Traffic analysis examines how well a website is supporting users who come to the site with specific information. Subheads of channels and mediums, all traffic sources, all referrals, and keywords were identified as metrics in this study. Lastly, the Behavior report offers information about what the user actually did when they arrived on the site; data about landing page, time spent on each page, the number of page views, and the percentage of exits and what page they exited from were analyzed.

Survey data were collected and entered into SPSS Statistics version 21 (IBM) from a text file and uploaded into a secure data repository. Data were verified for accuracy and cleaned. Seventy-four surveys were completed. Of those, 21 respondents were not parents or primary guardians of children with neurosurgery and 1 respondent indicated English was a second language with poor fluency; therefore, those surveys were excluded from this study. A total of 52 surveys were used in data analysis. Data were coded and descriptive data were computed for all variables.

The focus group interview data were analyzed using an inductive content analysis approach to address the purpose of the study [25]. The transcript was read as a whole several times and concepts, patterns, and themes were identified. With further immersion in the data, a coding system was developed and subsequent grouping and categorizing of the data into the recurring themes was performed. New codes and themes emerged throughout the analysis period and the data were continuously reexamined. The qualitative analysis software program NVivo 10 (QSR International) was used to assist with data management and analysis. In addition, a classic analysis strategy was used to make analysis a visual and concrete process [26].

Credibility was achieved in this study with methodological triangulation between the quantitative and qualitative data [27,28]. Both qualitative and quantitative methods were used together in an iterative process with neither method being weighted superior to another method [27]. Triangulation also allowed for the use of new research methods, Web analytics, to balance with the other methods in this study.

Credibility of the data was further achieved with transparency using an audit trail of all methodological processes. Reliability was achieved with the audit trail such that the results of this study could be replicated. Equivalence and internal consistency criterion were met because there was 1 researcher who was the only moderator and coder of the focus group data. Validity was enhanced with method triangulation because 2 or more methods demonstrated the same results and strict adherence to principles of qualitative research were followed. Field notes were reviewed to ensure that the findings were reflective of the focus group interview and not a reflection of any personal biases [10].

Results

Google Analytics Reports

Audience Report

For the first 6 months after the NKF website was launched, 2998 sessions and 1686 unique users were logged, with 56.27% (1687/2998) returning visitors. There were 8818 page views with an average of 2.94 pages viewed per session. The site bounce rate was 56.20% and the average session duration was 2 minutes 24 seconds. Using IP addresses to track and measure where a user is located, 90.23% users were from Canada (85.55% were from Alberta with 50.35% of them located in the Edmonton area). The remaining users were from: United States (172/2998, 5.74%), United Kingdom (35/2998, 1.17%), India (15/2998, 0.50%), Australia (8/2998, 0.27%), Ukraine (6/2998, 0.20%), and Philippines, Saudi Arabia, and South Africa (5/2998, 0.17%). The majority of users (2971/2998, 99.11%) viewed the NKF website in English. The remaining users accessed the website in French, German, Mandarin/Cantonese, or Arabic.

Users from the Philippines had the longest average session (4 minutes 5 seconds), followed by Canada (2 minutes 33 seconds) and the United Kingdom (1 minutes 28 seconds). Apple's Safari browser was the most frequently used (1354/2998, 45.16%), followed by Internet Explorer (690/2998, 23.02%), Chrome (360/2998, 12.01%), Safari (app version; 241/2998, 8.04%), Mozilla Firefox (183/2998, 6.10%), and Android (117/2998, 3.90%). The majority of NKF website users (1628/2998, 54.30%) accessed the site using desktop or laptop computers. Mobile users accounted for 31.05% (931/2998) of all sessions and tablet users logged 14.64% (439/2998) of all sessions. Mobile users had the highest bounce rate with 68.74%, whereas computer and tablet users showed bounce rates of 50.06% and 52.39%, respectively.

Acquisition Report

Direct traffic accounted for 42.56% (1276/2998) of total visits to the NKF website. Organic search traffic using Google yielded 32.52% (975/2998) of users. Bing generated only 1.37% (41/2998) of users, and Yahoo brought only 1.03% (31/2998) of users to the NKF website.

Referral traffic accounted for 22.41% (672/2998) of the sessions. Average session duration for referral traffic was 2 minutes 5 seconds, with 2.82 pages viewed per session and a bounce rate of 54.76%. Of significance is that 24.67% (416/1686) of new users to the NKF site were acquired via referral sources. When mobile devices and tablets are combined, 70.09% (471/672) of all referrals were generated from Facebook, with a 50.41% bounce rate and an average of 3.25 pages viewed per session.

Since the NKF does not have any paid AdWords with any search engine company, only organic inbound keywords were analyzed. Organic search traffic yielded 1050 sessions, with an average session duration of 2 minutes 28 seconds, 3.03 pages viewed per session, and a 54.10% bounce rate. Variations of search terms "pediatric," "neurosurgery," "kids," and/or "fund" accounted for 12 of the top 20 organic inbound keyword searches, or 24.86% (261/1050) of sessions. Of note, 48.48% (509/1050) of all sessions did not provide a keyword—this traffic arrived via a referral, used the URL directly, or had bookmarked the NKF website. The highest average session duration, using "www.neurosurgerykids.com" as a keyword, was 9 minutes 12 seconds, a significant outlier. The remaining top 8 keywords were related to specific fundraisers or events that were happening at that time. Only 1 medical term, "arachnoid cyst," was included in the top 20 organic keyword searches. One search included the name of a pediatric neurosurgeon from the Stollery Children's Hospital.

Behavior Report

The All Pages report for the NKF site illustrated a fairly typical distribution of the top 10 page views—the Homepage was the most viewed with 21.05%, followed by other pages that can be accessed from the Homepage with one-click buttons: About NKF (9.55%), Media Centre (7.62%), Join the Community (3.62%), Events (3.40%), Just for Kids (2.98%), Donate (2.88%), and Hope Stone (2.82%). The Media Centre's subcategories of photographs and videos of children attending the NKF Camp or other events garnered the lowest bounce rate (23.53%) on the NKF website.

The NKF Homepage was the top-landing page with 52.97% (1588) of all sessions. Noteworthy are 3 landing pages that are buried further into the NKF site, which each garnered a number of sessions—arachnoid cyst (66), Just for Kids (47), and Hope Stone (45) . The NKF website did not have any significant outliers in the time spent on pages when combined with page views and unique page views. The range difference between page views and unique page views was 14%-38%. The Donate page attracted 216 page views, with 92 of those being unique, and users spent a lot of time there (2 minutes 37 seconds); however, the bounce rate was 85.87%.

Online Survey Questionnaire

Demographic data and computer usage data were collected for 52 parents of children who have undergone neurosurgery. All participants resided in Alberta and a majority were Caucasian (47/52, 90%), female (48/52, 92%), aged 36-45 years (25/52, 48%), and had a university or college degree or diploma (36/52, 69%). Ninety-six percent of parents (50/52) reported accessing the Internet from home and 52% (27/52) spent approximately 2 to 4 hours a day online, with 21% (11/52) going online less than an hour a day and 25% (13/52) surfing the Internet for 5 or more hours a day.

A total of 42% (22/52) of parents reported that accessing health information on a computer as "very easy." This was followed by 25% (13/52) and 21% (11/52) who said it was "somewhat easy" or "neither easy nor difficult," respectively. Only 7.7% (4/52) of parents found accessing health information online to be "somewhat difficult"; however, no parents reported it being "very difficult."

Several health information resources were reportedly used by parents. Ninety-eight percent of parents (51/52) reported relying on health care providers for their health information, followed by 77% (40/52) getting information from family and/or friends and 60% (31/52) going online to health websites. In addition,

one-third (16/52, 31%) of the sample accessed medical journals and another third (18/52, 35%) reported favoring print media to supplement their health information search. One-fifth (19%, 10/52) of parents reported using TV or radio programming. Almost half (24/52, 46%) of the parents found reading health information on a computer compared to a book or pamphlet to be very easy, with 25% (13/52) saying it was somewhat easy, 21% (11/52) reporting it to be neither easy nor difficult, and 8% (4/52) stating it was somewhat difficult.

When parents were asked how they came to learn about the NKF website, 69% (36/52) responded that they learned about the NKF website from medical staff at a clinic or hospital visit, followed by 37% (19/52) hearing about it from family and/or friends, and 14% (7/52) came across it from an Internet search. Two respondents learned about the NKF site via Facebook or a local television or radio program.

Reasons why parents visited the NKF website included: to find more information about Camp Everest and L'il Everest Camp (67%, 35/52), to learn about upcoming media events and news related to the NKF (40%, 21/52), to check out the site in general (33%, 17/52), to find more health information about their child's diagnosis or condition (23%, 12/52), to find social support and resources (21%, 11/52), to get their child a Hope Stone (17%, 9/52), and to make a donation (14%, 7/52).

Parents were also surveyed on how or if they planned to use the health information specifically found on the NKF website. Half of the parents (26/52) have discussed or plan to discuss the health information found on the NKF site with their child's physician, nurse practitioner (NP), or other medical personnel involved in their child's care. Six percent (3/52) of parents reported looking for health information from other sources. One-third (17/52) of the sample will discuss findings with family and friends and have contacted, or plan to contact, a support group. Further, survey results found that approximately 20% (10/52) stated that the health information found on the NKF website may influence future health decisions for their child and has improved their understanding of their child's condition, surgery, or illness. The majority of parents (58%, 30/52) strongly or somewhat agreed that the health information found on the NKF website added to information from their child's physician, NP, or other medical personnel, with 19 (37%) neither agreeing nor disagreeing and 2 (4%) strongly or somewhat disagreeing.

The survey examined parents' perceptions about the ease of reading and understanding health information on the NKF website. Results found that approximately two-thirds of the parents (65%, 34/52) found the NKF website to be very easy to read and understand. Twenty-one percent (11/52) reported the website as "somewhat easy" followed by only 12% (6/52) who found it "neither easy nor difficult." Only 1 parent (2%, 1/52) found the NKF website to be "somewhat difficult" to read and understand. Parents were also asked about their "favorite" part(s) of the NKF website and were allowed to give multiple responses (Table 1). Overwhelmingly, the NKF website was used to find more information about the 2 summer camps. Health information and Canadian content appealed to a large number of respondents. Supportive resources were reportedly also popular reasons to access the website. Please note percentages do not sum to 100% because of multiple responses.

Focus Group

Of the 4 parents in the focus group, all were mothers with a child who had undergone neurosurgery a minimum of 2 years ago. The mothers' ages ranged from 35 to 44 years, 2 had university or college degrees, and all had high school diplomas. Three self-reported their computer literacy as proficient and 1 described it as poor. All had familiarity with and used mobile phones and tablets regularly, and all of their children had attended Camp Everest. The focus group took place in a room with audiovisual equipment, and the NKF website was loaded and "surfed" throughout the session.

User Experience

Parents were asked to describe their experiences about where and how they began searching for information about their child's neurosurgical diagnosis. All 4 of the parents strongly responded that they were reluctant to search online for mainly 2 reasons: (1) the timing of their child's illness was a chaotic time and "when you're in the hospital, it's all very overwhelming" so searching online for information was not a priority. One parent reported not accessing it "until I was ready to go and do that," further illustrating the impact of timing. This sentiment was further supported by the other parents in the focus group (Table 2).

Table 1. Parents' favorite part(s) of the Neurosurgery Kids Fund website.

	Frequency n (%[a])
Camp Everest and L'il Everest Camp information	41 (78.8)
News and events	34 (65.4)
Hope Stones	26 (50.0)
Social support and resources	23 (44.2)
Ease of use	22 (42.3)
Health information	21 (40.4)
Canadian content	19 (36.5)
Attractiveness, design, and layout	17 (32.7)
Donation information	15 (28.8)
Join the Community page	13 (25.0)

[a]Percentages do not sum to 100% because of multiple responses.

Table 2. Concepts and examples of parental experience using, or not using, the Internet.

Concept	Parent	Experience
Timing at acute phase of illness	Parent 2	"We were thrown into it … so you don't have any time to do any research … so when that's all happening and you're bringing in a priest to give someone last rites, you're not really thinking about a computer, see, and I would never read … when you had that thing up about trauma and stuff, I've already lived that nightmare, so I wouldn't want to read that because I've already lived it, so I would never click that right now because I already know what it is (shaking her head, voice low and controlled, and pointing at the NKF screen)."
	Parent 3	"It was boom, boom, boom … everything happened at a very fast rate…. I remember [a nurse] saying going onto the NKF group, but I didn't go home immediately and do it. I mean it, it sat there for a bit until I was ready to go and do that (arms gesturing dramatically in the air)."
Timing at chronic phase of illness	Parent 1	"Because he was born so early … we [searched online] later, before you had this [NKF website] set up."
	Parent 2	"Because [our child] is pretty stable right at this moment."
	Parent 3	"[Now] we're okay; we're in that stage of our lives where, you know, there's nothing for us to do [like search online]. We have the support that we need."
	Parent 4	"I think for us, just because [our child] has been stable for so, so long that really I go on here mostly about camp…. I know we've been blessed so far that—touch wood—you know, we're not really going in for a lot of medical stuff."
Influence of medical staff	Parent 2	"[Physician B] was very adamant. Don't you dare touch that Internet, do not look at that—you listen to what I say, I'm the boss, and this is the way it's going to run (other parents nodding)."
	Parent 3	"Well, I remember both [Physician A and Physician B] saying don't Google it … we were directed by [a nurse]. And the doctors saying don't go really anywhere (all other parents nodding)."
	Parent 4	"When we did research, it was basically only [Physician C]."

The second reason reported in the focus group for how or when these parents searched online for health information was that 3 of the 4 parents were advised by a physician or nurse to avoid using the Internet. Two mothers explain:

> *So when that's all happening and you're bringing in a priest to give someone last rites, you're really not thinking about a computer. [Physician B] was very adamant, "Don't you dare touch that Internet, do not look at it, do not— you listen to what I say, I'm the boss, and this is the way it's going to run.*" [Parent 2]

> *I remember both [Physician A and Physician B] saying don't Google it. [So later when searching online], I remember typing it in and feeling guilty about it. I just wanted the definition … I just wanted to know what the words meant….* [Parent 3]

Despite receiving cautionary warnings from their health care professionals, most of the parents reported going online eventually when their child was in stable health. Parents reported that they typed in a keyword, such as "VP shunt," "cerebral palsy," or "third ventriculostomy" into a browser. One parent described also using a "big encyclopedia book of brain and thinking, well, it doesn't really have what I'm looking for." One

participant (with poor self-reported computer literacy skills) did not seek information on the Internet about her son's diagnosis because "I've already lived that nightmare."

All parents reported hearing about the NKF website by "word of mouth" from staff. All parents reported that the webpages were easy to navigate, "colorful, inviting, and joyful," and even the non-tech parent said, "I'm not a computer person … I can just click that right there on the front, and that's what I like." All reported accessing the NKF website on their mobile phones without any difficulties, but when they wanted to read or explore the website at length, they used their home computers. One parent made many positive references to using her mobile phone to follow the NKF's news and events via social media (eg, Twitter, Facebook). Difficulties on the website included the some technical errors (eg, not receiving a confirmation for registration into Camp Everest) and broken links (eg, brain tumor information page reported only an error message). Another parent agreed with the problem of broken links and also mentioned that some pages are not updated regularly. Parents described these 2 reasons for why the "medical conditions" pages were among the pages with the fewest page views. Findings from the Google Analytics data identified that the Community Resources page was infrequently viewed and used. Following up with parents on this identified some potential reasons for low page views and infrequent usage. Parents reported they did not know it existed, did not see the link, or had never visited the webpage. One parent questioned, "Is that the best name for it?" This led into discussion among the parents with a resolution that "Community Funding Support Resources" would more accurately describe the content.

Participants consistently used language of "safe" and "credible" when discussing the NKF website. The parents expressed feelings of "fear" and "mistrust" surrounding what they may find on the Internet and thus preferred to place their trust in their primary care providers (and the NKF website) to mediate the health information they received. This sense of legitimacy of the information on the NKF website is described by 2 parents:

> *This [NKF website] is a verifiable source … [said to be safe by other parents] … definitely … so they've kind of [sifted] out some of it so it isn't this flukey, you know, therapy or surgery or doctor. Yeah, I felt safer … and if the doctors are telling parents not to Google it, if they are able to say, "Yeah, this is a verifiable source," you know (other parents nodding in agreement).* [Parent 1]

> *[T]his is a safer place … definitely more … yeah, its' credible … I had just the right information.… Here, I felt like, again, it's been—someone's already, you know, looked at it and thought, "This is right, this is perfect for what our parents are going to hear or read or see," and I'd feel safer if it was through [the NKF website].* [Parent 3]

Parents also expressed fear surrounding accessing the Internet in search of health information and finding upsetting stories or poor outcomes:

> *I would never read … about trauma and stuff, I've already lived that nightmare, so I wouldn't want to read that because I've already lived it, so I would never click that right now because I already know what it is.* [Parent 2]

> *I try and stay clear of reading other people's stories or surgeries or mishaps or things like that or what went wrong, all that kind of things that you're going to find.* [Parent 3]

Join the Community Tab

The NKF website is enabled with its own password-protected social network webpage called "Join the Community," which is designed to function and serve as a forum or blog for parents, caregivers, and their children. By requiring them to register their minor children, parents give consent for their children to use it. Despite the Join the Community tab being on the home page, with one-click access, it was a seldom viewed and utilized feature of the NKF website. Parents were directed to the Join the Community tab for discussion and only 1 parent reported previously using it. The parent placed a message on the dashboard, never received a response, and thus abandoned it altogether. The parents cited reasons such as technical difficulties or unawareness as reasons for not using the Join the Community webpage.

Parents also described preferring to have an additional tab on the NKF homepage that is just for their children, "because I'd love for her to connect outside of camp with some of these kids." When informed that this was the intended purpose of the Join the Community page, parents collectively identified hesitance in using it (Table 3).

Table 3. Parental opinion about having a blog or forum as a source of support parent-to-parent or just for the children.

Source of Support	Parent	Opinion
Blog or forum as a source of support for parent-to-parent	Parent 3	"If somebody was going through a similar situation, you could offer that I've been there, and you give … so even though it may not pertain to you, because right now [your daughter] is doing well and you already lived with it, as somebody else new comes, too, you could pop in and say … where you need to connect with others and chat.… (looking at parent 4)"
	Parent 4	"Yeah. I'd be very happy to be able to say to somebody, 'Hey you can get through this.' In fact, I went and did a talk at the [hospital] and it felt good to do it, sort of give some hope back, I guess … I know when I was going through it, I was pretty much a wreck.…"
Blog or forum as a source of support just for the children	Parent 1	"If you had a tab for adults and a tab for kids, I think would be better you know … just letting them go into their own site. I just think … if a parent is asking a question about something that maybe a parent doesn't want their child to see, you know, like something went wrong … if the kids amongst themselves want to talk about, 'hey, this is what I did,' you know, that's different than coming out of our fear as parents.… [If the kids have their own site] … so they're not seeing the kind of … I think it would be better, you know?"
	Parent 3	"I think you have to get the kids involved with it, too. I showed him all of the pictures. I think the pictures really helped … but I was hoping that there could be a little bit more of that … because this is a safer place."
	Parent 4	"I think I wonder about whether you want the kids—like, I kind of think sometimes the kids should almost have a different area than the adults for some of that stuff."

The parents wanted a "safe" place to connect with other parents, or to ask a question, and they wanted their children, who are often too young or vulnerable to go online seeking peer support (eg, Facebook) to have a different tab to ensure a completely distinct and separate forum. One parent explains:

> *[My son] is absolutely terrified of needles, so if a parent is talking about "In this procedure you have to get this many needles" kind of thing … [my son is] not having to read that.… If the kids, amongst themselves, want to talk about, "hey, this is what I did," that's different than coming out of our fear as parents.* [Parent 1]

When prompted, the parents elaborated further:

> *If you had a tab for adults and a tab for kids … I think it would be better you know … just letting them go into their own site.… I just think—so the kids—if a parent is asking a question about something that maybe [another] parent doesn't want their child to see, you know, like something went wrong … so they're not seeing that kind of stuff.… I think would be better, you know?* [Parent 1]

> *I think you have to get the kids involved with it, too. I showed [my son] all of the pictures. I think the pictures really helped … but I was hoping that there could be a little bit more of that, because this is a safer place.* [Parent 3]

> *I think I wonder about whether you want the kids—like, I kind of think sometimes the kids should almost have a different area than the adults for some of that stuff.* [Parent 4]

Discussion

This study contributes to the literature demonstrating the legitimacy of using an online health website, Neurosurgery Kids Fund, for supporting parents seeking health information and fulfilling their social and resource needs. This study found that the health information found on the NKF website contributed and improved parents' understanding of their child's neurosurgical illness or condition. Themes not formally considered, such as how the timing during their child's illness trajectory, parents' fear of searching online, the context of what was being searched, and the influence of health care provider's advice against online surfing were illuminated. The NKF website also serves as a single portal for meeting children's and their parents' support and resource needs in an accessible, attractive, and user friendly method that is easy to read and comprehend. Several studies have found that the Internet is a popular and efficient mode for distributing health information and offering social support because it is interactive, user controlled, offers anonymity, and is available around the clock [2,4-6,8,25]. In 2010, 8 out of 10 Canadian households (79%) had access to the Internet, with the second highest rate being in Alberta at 83% [29]. Among those, 70% of Canadians reported searching for medical or health-related information online [29].

Parents' Approaches to Searching the Internet

In this study we found that parents are increasingly accessing the Internet, particularly health websites, in search of health information, support, and resources. Hand et al [30] found that 83.4% of parents reported going online in search of information regarding their child's health. DeLuca et al [2] and Kurup et al [31] found that parents are increasingly consulting other sources, mainly the Internet, even before visiting a health care professional. Parental usage of health websites for getting immediate answers; learning about the diagnosis, treatment options, and prognosis; adding to what the physician has explained; finding support groups; and sharing with others having similar experiences is well documented in the literature [2,5,11,13,25,30,32].

While the marrying of Web analytic, survey, and interview data created a picture of NKF website use, it can potentially lead to more confusion and questions. For example, both the Google Analytics and focus group data revealed that the Medical Conditions information pages (eg, hydrocephalus, achondroplasia) on the NKF website were less frequently visited compared to other pages (eg, Hope Stone, NKF News and Event

, Media Centre). In contrast, the survey results reported that almost 25% of the parents visited the NKF website in search of health information and 40% of the surveyed parents rated it as one of their favorite parts. Inconsistencies in the findings can be perceived as a strength using methodological triangulation because it provides an opportunity to capture an unexpected new concept or theme [27]. Careful collection and insightful interpretation guided the concepts of timing and sample as potential reasons for the inconsistency in this study's findings. The Google Analytics data was collected during the first 6 months after the website was launched and included data about anyone in the public accessing the site (eg, not parents with a sick child). For these visitors, digging deeper into the health information pages may not have held any relevance, and thus they avoided those pages. All the parents in the interview had children who had been diagnosed some time ago, described how they were more in the "chronic" phase in their child's illness trajectory, and thus their health information needs were already met. In addition, the sample size was small and therefore these parents' perspectives may not be representative of all NKF users. This example justifies why it is important to combine Google Analytics reports with other qualitative methods.

During the focus group, the parents explained not using the Internet to search for health information, primarily because their child's neurosurgical diagnosis came during the acute phase of the illness—a time when life-saving decisions are needed in a very stressful situation. The parents in the focus group further described being overwhelmed and fearful, not wanting to relive the "nightmare," and that the fear and uncertainty of their child's health outweighed their desire to go online. Similarly, DeLuca et al found that parents wanted to learn about the medical condition, but were too anxious to directly search the Internet because of fear, further fueling their anxieties, or the potential for obsessing over negative content [2]. In contrast, Tuffrey and Finlay's 2002 research involving parents of pediatric outpatients had a generally positive attitude toward the Internet and 88% felt that doctors should suggest suitable websites to parents [32]. Another study found that most people (72%) believe that all or most of the health information on the Internet is credible [33].

Is Internet Health Information Seeking Context Dependent?

Gage and Panagakis's 2012 study proposed that the type of health issue (eg, life-threatening condition versus routine health information) being confronted may be a critical dimension in understanding how, when, and why parents use the Internet as a source of health information [12]. A study involving patients before and after cardiac surgery, found that only 21% of the patients had used the Internet for health information [34]. Conversely, Chisolm found that health crises were consistent predictors of increased Internet use by patients for health information [35]. Knapp et al similarly stated that 76% of parents of children with life-threatening illness used the Internet for medical information [36]. Further, DeLuca et al found that nearly every parent acquired online information in the first hours and days after learning of the referral to a genetics specialist [2]. Despite the parents in our focus group describing cautious use of the Internet for neurosurgical information, 60% of the surveyed parents reported using websites for health information, which is comparable to the Canadian national average of 70% [29].

Influence of Health Care Providers on Parents' Health Information Seeking

Similar to the DeLuca et al 2012 study, some of the parents in this study were advised against seeking medical information on websites by their child's health care providers [2]. The literature is replete with reasons why health care providers may be cautious about referring their patients to the Internet as a health resource: it may be inaccurate, unreliable, possibly even dangerous, has not been critically appraised (ie, peer reviewed), or may even be threatening to the image of the primary care provider [12,37,38]. However, as Nichols and Oermann stated, caution may well be advised when using the health information received on the Internet because of the unregulated nature of the medium, potentially giving way to obsolete and inaccurate information [39].

This study found that 98% of parents with a sick child prefer to receive specific health information from a trusted health care provider rather than on the Internet, and other studies found similar findings [2,6,7,40]. Similarly, Gage and Panagakis cited that during the highly emotional period following a diagnosis, parents may not want to be empowered through the Internet, but prefer to transfer some of the burden of decision-making to a trusted health care professional [12]. Knapp et al found that parents were more likely to trust information from a health care provider versus the information they located from Internet sources [36]. AlSaadi found that 68% of parents used health care providers as their main source of health information, although 79% of these same parents also reported using the Internet to gain information on their child's health [8]. However, what is unique about the NKF website is that this information is created and provided by health care professionals.

Parents' Usage and Experiences Using the NKF Website

The results of this study showed that it is more common to seek health information on the NKF website among young to middle-aged Caucasian women who have higher levels of education and direct access to the Internet at home. Similar characteristics have been found in many other studies and have been dubbed the "digital divide" [6,7,31,41,42]. With the increasing ubiquity of mobile devices and tablets, this socioeconomic disparity may be negligible in the near future. Glynn et al dubbed the burgeoning use of mobile wireless communication devices as a subsection of eHealth called mHealth [6]. In this study, parents reported that being able to access the NKF website on their mobile devices or tablets (at their child's bedside) day or night was a vital source of information and support.

In this study, 40% of the parents reported using the NKF website for health information. Despite 60% of the parents in this study reporting that the NKF health information added to their knowledge, only 20% reported that it may influence their medical decision making. Similarly, Glynn et al found that 29.1% of parents felt that the health information found online would influence the treatment decisions for their child [6]. In

contrast, another study found that 68% of patients reported that the health information received online impacted their medical decision making [33]. However, 50% of the parents who received health information on the NKF website had discussed, or planned to discuss, their findings with their health care providers as compared to 34% of parents in another study [32]. Glynn et al similarly found that over half of the parents in their study had discussed, or intended to discuss, health information with their surgeon [6]. Only 6% of the parents in this study reported looking for health information elsewhere other than the NKF website. One of the parents in the focus group stated that the health information on the NKF website has been "verified" and is "just right for what our parents need." Other studies found that some of the information available on the Internet is too technical in nature and not easily understood by the layman [2,8].

Evaluating the NKF Website's Usability

MacCulloch et al stated that website quality and presentation are critical elements in order for a website to be used effectively [43]. The findings demonstrated that the NKF website's usability was evaluated to be: very easy to use, very easy to read and understand, informative, attractive, colorful and inviting, and easy to navigate. The parents reported the NKF website to have great "responsiveness," meaning the dimensions were able to "flex" to the device (eg, mobile phone, tablet) being used—despite the Google Analytics reports indicating a high bounce rate for mobile phone users. When examined further, it was found that when parents used their mobile phones, it was mostly for quick fact finding, such as an address or contact information, or they were "on the go" and didn't have time to graze on the NKF website.

Findings in this study suggest that the NKF website is congruent with the underpinning premise of TAM, which is that a website is more likely to be accepted and used by parents if they perceive it to be useful and easy to use [19,20]. However, some technical errors or broken links were identified by the parents; addressing these points and maintaining current updates can improve NKF usability and usage. Pew Internet and American Life found that 37% of users will leave a website if there are inadequate updates [33]. It is encouraging that 94% of the parents found what they were looking for on the NKF website, thus suggesting good usability. Ninety-two percent of parents plan to use the NKF website in the future, suggesting a good user experience.

Parents Use of the Internet and NKF Website for Social Support and Resources

One of the most prevalent themes to emerge out of the collected data was the use of the NKF website for social support, connecting with peer parents, and resources. Plantin and Daneback found that using the Internet to establish connections with others in similar situations is of particular importance for parents whose children have serious medical conditions [7]. Google Analytics revealed that 6 of the top 7 landing pages were "social-related" pages. MacCulloch et al found a strong endorsement from the parents in their study for an online peer-based support network [43]. Similarly, Holtslander et al found in their study involving parents with diabetic children, that when parents can share experiences, it may more rapidly enable parents to achieve "normalization" following a life-altering diagnosis [44]. Results in this study revealed that 67% of parents reported using the NKF website for socially-related information and support—accessing Camp Everest and L'il Everest Camp information and parents "staying on top of things" by tracking the NKF's News and Events (eg, fundraisers, parties, social gatherings)—and 70% arrived at the site via Facebook (another social gathering webpage).

Study Limitations

There was only 1 focus group and the sample size was small (eg, 4 particiapants), however, parents brought a range and depth of experiences about having a child with neurosurgical concerns and their health information, support, and resource needs. The findings from the combined data of the Google Analytics, online survey questionnaire, focus group, and field notes were similar, indicating the main issues were identified (eg, theoretical saturation was met). The sample was predominantly mothers and, therefore, the relevance to fathers may be inappropriate. In future studies, health information should be clearly defined because it may mean different things to different people. Strict adherence to criteria for ensuring qualitative research trustworthiness increased confidence in the findings. There is a small potential for a margin of error in the Google Analytics data because all crawlers were granted access to the NKF website. In the future, to refine exploring only parents' usage, a robot.txt file should be encrypted in the NKF website. The data were also collected over a relatively short period of time. Findings of website usage and experiences among parents of children undergoing neurosurgery may not be generalizable given the NKF website is targeted to the Edmonton, Alberta, region.

Conclusions

There is a lack of research about the specific health information, support, and resource needs of parents with children undergoing neurosurgery. There is even less known about when they seek health information online, what health websites they are visiting, how useful the information was or was not, how e-literate they are, and, especially, why they are visiting the health websites that they do [14]. This study aimed to assess and evaluate whether a custom-designed health website could be used to meet parents' health information, support, and resource needs. From this study, the majority of parents felt that the NKF website is credible, useful, and informative. Key findings that impacted whether parents sought online health information included the timing during the child's illness, the context of the information being sought, and the impact of cautionary advice from their health care providers. However, after visiting the NKF website, many parents reported that the health information improved their understanding of their child's condition, surgery, or illness. Other parents found the website to be a portal for joining the "NKF family" and for connecting with other parents for support and shared experiences.

Utilizing data and findings from this study, modifications to the NKF website will include expanding on specific health information and adding pictures related to neurosurgical diagnoses, equipment, treatment options, interventions, and prognoses provided by their own pediatric neurosurgeons,

pediatric nurse practitioners, and allied health care providers involved in the care of this pediatric neurosurgical population. Blogs, video posts, and messaging designed by the health care team at the Stollery Children's Hospital will be encouraged. These blogs, posts, and messages would reflect the 98% of parents who report relying on their direct health care providers for needed health information.

Additional modifications to the NKF website should be targeted at the support services and resources offered by the NKF including both L'il and Camp Everests, Hope Stones, and splitting the Join the Community pages between parents and children. These modifications would include more detailed explanation of the mission and purposes of the camps, eligibility, accommodations to the children's specific health care needs, and qualifications of the camp counselors. More attention to the Just for Kids page will be outlined on the homepage explaining its purpose, target audience, and its safety measures to protect identity and confidentiality to the end users. Over 40% of parents also accessed the NKF website to stay abreast of news and events; therefore, keeping information updated, accurate, and informative will be stressed. From a technical standpoint, the NKF website should be monitored more closely and regularly for correct linkages and active pages.

The method of health care delivery is being transformed by the ubiquity of the Internet and the newly empowered, computer-literate public is making a claim in becoming partners in managing their own health. Such changes have the potential to bring about positive outcomes, such as improved medical decision making, increased efficiency in the clinic or hospital appointment, and strengthening the relationship between primary health care providers and the patient's parents. The time is now for the health care profession to respond to the "Internet-informed" parent by guiding them to reliable health information websites, giving them a "health website prescription," and collaborating with them in obtaining and analyzing the information received.

Conflicts of Interest

None declared.

Multimedia Appendix 1

The NFK website was developed specifically for parents to address health information needs and to provide resources and support tools.

[PDF File (Adobe PDF File), 752KB - resprot_v5i2e55_app1.pdf]

Multimedia Appendix 2

Guiding Focus Group Interview Questions.

[PDF File (Adobe PDF File), 34KB - resprot_v5i2e55_app2.pdf]

References

1. Neurosurgery Kids Fund. URL: http://www.neurosurgerykids.com/ [accessed 2016-02-29] [WebCite Cache ID 6fiTWD9B9]
2. DeLuca JM, Kearney MH, Norton SA, Arnold GL. Internet use by parents of infants with positive newborn screens. J Inherit Metab Dis 2012 Sep;35(5):879-884. [doi: 10.1007/s10545-011-9449-7] [Medline: 22297410]
3. Peterson G, Aslani P, Williams KA. How do consumers search for and appraise information on medicines on the Internet? A qualitative study using focus groups. J Med Internet Res 2003 Dec 19;5(4):e33 [FREE Full text] [doi: 10.2196/jmir.5.4.e33] [Medline: 14713661]
4. Patel CO, Garg V, Khan SA. What do patients search for when seeking clinical trial information online? AMIA Annu Symp Proc 2010;2010:597-601 [FREE Full text] [Medline: 21347048]
5. Klemenc-Ketis Z, Kersnik J. Seeking health advice on the Internet in patients with health problems: a cross-sectional population study in Slovenia. Inform Health Soc Care 2013 Sep;38(3):280-290. [doi: 10.3109/17538157.2013.764306] [Medline: 23514043]
6. Glynn RW, O'Duffy F, O'Dwyer TP, Colreavy MP, Rowley HM. Patterns of Internet and smartphone use by parents of children attending a pediatric otolaryngology service. Int J Pediatr Otorhinolaryngol 2013 May;77(5):699-702. [doi: 10.1016/j.ijporl.2013.01.021] [Medline: 23434200]
7. Plantin L, Daneback K. Parenthood, information and support on the Internet. A literature review of research on parents and professionals online. BMC Fam Pract 2009;10:34 [FREE Full text] [doi: 10.1186/1471-2296-10-34] [Medline: 19450251]
8. AlSaadi MM. Evaluation of Internet use for health information by parents of asthmatic children attending pediatric clinics in Riyadh, Saudi Arabia. Ann Saudi Med 2012;32(6):630-636. [Medline: 23396028]
9. Bauer C, Scharl A. Quantitive evaluation of Web site content and structure. Internet Research 2000 Mar;10(1):31-44 [FREE Full text] [doi: 10.1108/10662240010312138]
10. Thomas D. A General Inductive Approach for Analyzing Qualitative Evaluation Data. American Journal of Evaluation 2006 Jun 01;27(2):237-246 [FREE Full text] [doi: 10.1177/1098214005283748]

11. Walsh AM, Hyde MK, Hamilton K, White KM. Predictive modelling: parents' decision making to use online child health information to increase their understanding and/or diagnose or treat their child's health. BMC Med Inform Decis Mak 2012;12:144 [FREE Full text] [doi: 10.1186/1472-6947-12-144] [Medline: 23228171]
12. Gage EA, Panagakis C. The devil you know: parents seeking information online for paediatric cancer. Sociol Health Illn 2012 Mar;34(3):444-458 [FREE Full text] [doi: 10.1111/j.1467-9566.2011.01386.x] [Medline: 21854400]
13. Roche MI, Skinner D. How parents search, interpret, and evaluate genetic information obtained from the Internet. J Genet Couns 2009 Apr;18(2):119-129 [FREE Full text] [doi: 10.1007/s10897-008-9198-4] [Medline: 18937062]
14. Lewis D, Gunawardena S, El Saadawi G. Caring connection: developing an Internet resource for family caregivers of children with cancer. Comput Inform Nurs 2005;23(5):265-274. [Medline: 16166829]
15. Google Analytics. URL: https://www.google.com/analytics/ [accessed 2016-02-27] [WebCite Cache ID 6fiTaOOeA]
16. Crutzen R, Roosjen JL, Poelman J. Using Google Analytics as a process evaluation method for Internet-delivered interventions: an example on sexual health. Health Promot Int 2013 Mar;28(1):36-42 [FREE Full text] [doi: 10.1093/heapro/das008] [Medline: 22377974]
17. Ledford J, Teixeira J, Tyler M. Google Analytics. 3rd Edition. Indianapolis, In: John Wiley and Sons; 2010.
18. Wilfert H. FreePint. 2008 Nov 30. Web analytics and information architecture [Web log post] URL: http://web.freepint.com/go/blog/3460 [accessed 2015-08-29] [WebCite Cache ID 6bIope8ja]
19. Davis FD. Perceived usefulness, perceived ease of use, and user acceptance of information technology. MIS Quarterly 1989 Sep;13(3):319-340. [doi: 10.2307/249008]
20. Chuttur MY. Overview of the technology acceptance model: origins, developments and future directions. Working Papers on Information Systems 2009 Sep;9(37):9-37.
21. van der Heijden H. Factors influencing the usage of websites: the case of a generic portal in The Netherlands. 2001 Presented at: 14th Bled Electronic Commerce Conference; 2001 Jun 25-26; Bled, Slovenia. [doi: 10.1016/S0378-7206(02)00079-4]
22. Vélez J, Pagán L. Usage statistics analysis of specialized libraries websites. 2015 Jul 11 Presented at: 77th IFLA General Conference and Assembly; 2011 Aug 13-18; San Juan, Puerto Rico URL: http://conference.ifla.org/past-wlic/2011/111-velez-es.pdf
23. Scott SD, Sharpe H, O'Leary K, Dehaeck U, Hindmarsh K, Moore JG, et al. Court reporters: a viable solution for the challenges of focus group data collection? Qual Health Res 2009 Jan;19(1):140-146. [doi: 10.1177/1049732308327883] [Medline: 19074635]
24. Onwuegbuzie AJ, Dickinson WB, Leech NL, Zoran AG. A qualitative framework for collecting and analyzing data in focus group research. International Journal of Qualitative Methods 2009;8(3):1-21 [FREE Full text] [doi: 10.1177/160940690900800301]
25. Shuyler KS, Knight KM. What are patients seeking when they turn to the Internet? Qualitative content analysis of questions asked by visitors to an orthopaedics Web site. J Med Internet Res 2003 Oct 10;5(4):e24 [FREE Full text] [doi: 10.2196/jmir.5.4.e24] [Medline: 14713652]
26. Krueger RA, Casey MA. Focus Groups: A Practical Guide for Applied Research. 4th edition. Thousand Oaks, CA: Sage Publications; 2008.
27. Duffy ME. Methodological triangulation: a vehicle for merging quantitative and qualitative research methods. Image J Nurs Sch 1987;19(3):130-133. [Medline: 3666768]
28. Streubert HJ, Carpenter DR. Qualitative Research in Nursing: Advancing the Humanistic Imperative. 4th edition. Philadelphia, PA: Lippincott Williams & Wilkins; 2007.
29. Statistics Canada. The Daily. 2010 May 10. Canadian Internet use survey URL: http://www.statcan.gc.ca/daily-quotidien/110525/dq110525b-eng.htm [accessed 2015-09-01] [WebCite Cache ID 6bIiULTKI]
30. Hand F, McDowell DT, Glynn RW, Rowley H, Mortell A. Patterns of Internet use by parents of children attending a pediatric surgical service. Pediatr Surg Int 2013 Jul;29(7):729-733. [doi: 10.1007/s00383-013-3317-5] [Medline: 23615872]
31. Kurup V. E-patients--revolutionizing the practice of medicine. Int Anesthesiol Clin 2010;48(3):123-129. [doi: 10.1097/AIA.0b013e3181e5c1c5] [Medline: 20616641]
32. Tuffrey C, Finlay F. Use of the Internet by parents of paediatric outpatients. Arch Dis Child 2002;87(6):534-536 [FREE Full text] [doi: 10.1136/adc.87.6.534]
33. Fox S, Raine L. Vital decisions: a Pew Internet health report. Washington, DC: Pew Internet & American Life Project; 2002 May 22. URL: http://www.pewinternet.org/2002/05/22/vital-decisions-a-pew-internet-health-report/ [accessed 2015-09-01] [WebCite Cache ID 6bIiZP6rl]
34. Murero M, D'Ancona G, Karamanoukian H. Use of the Internet by patients before and after cardiac surgery: telephone survey. J Med Internet Res 2001;3(3):E27 [FREE Full text] [doi: 10.2196/jmir.3.3.e27] [Medline: 11720969]
35. Chisolm DJ. Does online health information seeking act like a health behavior?: a test of the behavioral model. Telemed J E Health 2010 Mar;16(2):154-160. [doi: 10.1089/tmj.2009.0102] [Medline: 20156127]
36. Knapp C, Madden V, Marcu M, Wang H, Curtis C, Sloyer P, et al. Information seeking behaviors of parents whose children have life-threatening illnesses. Pediatr Blood Cancer 2011 May;56(5):805-811. [doi: 10.1002/pbc.22674] [Medline: 21370415]

37. Dornan BA, Oermann MH. Evaluation of breastfeeding Web sites for patient education. MCN Am J Matern Child Nurs 2006;31(1):18-23. [Medline: 16371821]
38. Jariwala AC, Paterson CR, Cochrane L, Abboud RJ, Wigderowitz CA. Prescribing a website. Scott Med J 2005 Nov;50(4):169-171. [Medline: 16374982]
39. Nichols C, Oermann MH. An evaluation of bariatric Web sites for patient education and guidance. Gastroenterol Nurs 2005;28(2):112-117. [Medline: 15832111]
40. Lowes L, Lyne P, Gregory JW. Childhood diabetes: parents' experience of home management and the first year following diagnosis. Diabet Med 2004 Jun;21(6):531-538. [doi: 10.1111/j.1464-5491.2004.01193.x] [Medline: 15154935]
41. Fox S. Health fact sheet. Washington, DC: Pew Internet Project URL: http://www.pewinternet.org/fact-sheets/health-fact-sheet/ [accessed 2016-02-26] [WebCite Cache ID 6fk8pCVr9]
42. Underhill C, McKeown L. Health Reports. Ottawa: Statistics Canada; 2008 Mar 01. Getting a second opinion: health information and the Internet URL: http://www.statcan.gc.ca/pub/82-003-x/2008001/article/10515-eng.htm/ [accessed 2016-02-29] [WebCite Cache ID 6bIid4fSp]
43. Macculloch R, Nyhof-Young J, Nicholas D, Donaldson S, Wright JG. Development of an online information and support resource for adolescent idiopathic scoliosis patients considering surgery: perspectives of health care providers. Scoliosis 2010;5:13 [FREE Full text] [doi: 10.1186/1748-7161-5-13] [Medline: 20587057]
44. Holtslander L, Kornder N, Letourneau N, Turner H, Paterson B. Finding straight answers: identifying the needs of parents and service providers of adolescents with type 1 diabetes to aid in the creation of an online support intervention. J Clin Nurs 2012 Sep;21(17-18):2419-2428. [doi: 10.1111/j.1365-2702.2012.04182.x] [Medline: 22889443]

Abbreviations

JMIR: Journal of Medical Internet Research
NKF: Neurosurgery Kids Fund
TAM: technology acceptance model

Edited by G Eysenbach; submitted 24.09.15; peer-reviewed by A Walsh, R Fournier; comments to author 22.10.15; revised version received 22.12.15; accepted 17.01.16; published 12.04.16.

Please cite as:
Vogel TK, Kleib M, Davidson SJ, Scott SD
Parental Evaluation of a Nurse Practitioner-Developed Pediatric Neurosurgery Website
JMIR Res Protoc 2016;5(2):e55
URL: http://www.researchprotocols.org/2016/2/e55/
doi:10.2196/resprot.5156
PMID:27072930

Original Paper

Development of a Self-Help Web-Based Intervention Targeting Young Cancer Patients With Sexual Problems and Fertility Distress in Collaboration With Patient Research Partners

Jeanette Winterling[1,2*], RN, PhD; Maria Wiklander[1,3*], Registered Psychologist, PhD; Claire Micaux Obol[1], RN, MScN; Claudia Lampic[1], Registered Psycholgist, PhD; Lars E Eriksson[4,5,6], RN, MSc, PhD; Britta Pelters[7], Certified Sexual Educator, PhD; Lena Wettergren[1], RN, PhD

[1]Division of Nursing, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Huddinge, Sweden

[2]Center of Haematology, Karolinska University Hospital, Stockholm, Sweden

[3]Stress Rehabilitation Research, Department of Clinical Sciences Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden

[4]Medical Management Center, Department of Learning, Informatics, Management and Ethics, Karolinska Institutet, Stockholm, Sweden

[5]Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden

[6]School of Health Sciences, City University London, London, United Kingdom

[7]School of Health and Welfare, Halmstad University, Halmstad, Sweden

[*]these authors contributed equally

Corresponding Author:
Maria Wiklander, Registered Psychologist, PhD
Division of Nursing
Department of Neurobiology, Care Sciences and Society
Karolinska Institutet
Karolinska Institutet 23 300
Huddinge, SE-141 83
Sweden
Phone: 46 8 524 839 01
Fax: 46 8 31 11 01
Email: maria.wiklander@ki.se

Abstract

Background: The Internet should be suitable for delivery of interventions targeting young cancer patients. Young people are familiar with the technologies, and this patient group is small and geographically dispersed. Still, only few psycho-educational Web-based interventions are designed for this group. Young cancer patients consider reproductive health, including sexuality, an area of great importance and approximately 50% report sexual problems and fertility-related concerns following cancer treatment. Therefore, we set out to develop a self-help Web-based intervention, Fex-Can, to alleviate such problems. To improve its quality, we decided to involve patients and significant others as research partners. The first 18 months of our collaboration are described in this paper. The intervention will subsequently be tested in a feasibility study followed by a randomized controlled trial.

Objective: The study aims to describe the development of a Web-based intervention in long-term collaboration with patient research partners (PRPs).

Methods: Ten former cancer patients and two significant others participated in building the Web-based intervention, using a participatory design. The development process is described according to the design step in the holistic framework presented by van Gemert-Pijnen et al and evaluates the PRPs' impact on the content, system, and service quality of the planned intervention.

Results: The collaboration between the research group and the PRPs mainly took place in the form of 1-day meetings to develop the key components of the intervention: educational and behavior change content, multimedia (pictures, video vignettes, and audios), interactive online activities (eg, self-monitoring), and partial feedback support (discussion forum, tailored feedback from experts). The PRPs influenced the intervention's content quality in several ways. By repeated feedback on prototypes, the information became more comprehensive, relevant, and understandable. The PRPs gave suggestions concerning the number of exercises and pointed out texts and pictures needing revision (eg, experienced as normative or stereotypical) to increase the

persuasiveness of the program. The system quality was improved by PRPs' feedback on design, technical malfunctions, and navigation on the website. Based on feedback about availability of professional support (technical problems and program content), the organization for support was clarified, which increased service quality. The PRPs also influenced the research project on an overall level by suggesting modifications of inclusion criteria for the RCT and by questioning the implementation plan.

Conclusions: With suggestions and continuous feedback from PRPs, it was possible to develop a Web-based intervention with persuasive design, believed to be relevant and attractive for young persons with cancer who have sexual problems or fertility distress. In the next step, the intervention will be tested in a feasibility study, followed by an RCT to test the intervention's effectiveness in reducing sexual problems and fertility distress.

Trial Registration: International Standard Randomized Controlled Trial Number (ISRCTN): 36621459; http://www.isrctn.com/ISRCTN36621459 (Archived by WebCite at http://www.webcitation.org/6gFX40F6T)

(JMIR Res Protoc 2016;5(2):e60) doi:10.2196/resprot.5499

KEYWORDS

adolescent; clinical trial; Internet; neoplasms; online systems; patient participation; technology; telemedicine; young adult

Introduction

There is a need for psycho-educational interventions adapted for adolescents and young adults with cancer [1,2]. Web-based interventions are presumed to be a useful mode to deliver such interventions as young people are well accustomed to the technologies [1] and the patient group is relatively small and geographically dispersed. The Internet has proven to be effective for both delivery of information [3,4], support [5,6] and psychological treatment [7] for a wide range of health problems; such delivery is known as eHealth [8]. However, Internet interventions also face problems such as high dropout rates and non-usage during the test phase as well as after implementation [9,10]. Collaboration with patients in the development of Web-based interventions has been suggested to make the technology more attractive and user friendly, thereby improving uptake and impact of the intervention [10].

Patient and Public Involvement

Patient and public involvement in research [10] is regarded as an integral part of good scientific practice [11] and is increasingly requested from research funders. A recent systematic review showed that patient and public involvement has beneficial effects on all stages of the research process [12]. Different approaches to involvement exist. Consultation is when end users are asked for their views and these views are used to inform decision making. Collaboration involves active, ongoing partnership with end users where both collaborating parties share decisions about the research. In user-controlled research, the end users rather than the professionals have the power and the initiative to carry out the research. Long-term collaboration with end users has been proposed to increase the relevance, quality, and validity of eHealth interventions [13,14]. Still, patient and public involvement has, with few exceptions [9], been limited to the consultation level and involved end users only on single occasions [15-17]. Patient and public involvement has seldom been applied in the development of Internet interventions to be tested in randomized controlled trials (RCTs) [12]. In this study, a collaboration level of patient and public involvement was used, in preparation for a subsequent RCT.

The Fertility and Sexuality Following Cancer (Fex-Can) Project

Previous studies from our research group [18-20] and others [21] have shown that adolescents and young adults diagnosed with and treated for cancer have concerns about fertility and sexuality. It is also well known that sexual problems and reproductive issues often are neglected in clinical care [22,23] and that care providers lack training for such discussions [22,24]. Meta-analyses have found Web-based interventions to be effective in the areas of sexual [25] and reproductive health [26]. Based on the above findings, we set out to develop a self-help Web-based intervention, Fex-Can, to alleviate sexual problems and fertility-related distress in young people treated for cancer.

The effectiveness of the intervention will be evaluated in an RCT embedded in a nationwide cohort study directed towards individuals aged 16-40 in Sweden with selected cancer types, 1 year post-diagnosis. During 1 year, potential participants will be identified through national cancer registers and invited to participate in the cohort study. After consenting, participants will complete standardized questionnaires measuring sexual function and fertility distress (online or paper version). Those rating high levels of sexual dysfunction and/or fertility distress at baseline will be invited to participate in the RCT (closed user group trial) with two arms, testing the Fex-Can intervention versus control group. The Regional Ethical Review Board in Stockholm has approved the study. In Sweden, health care is mainly tax-funded and all Swedish citizens receive health care at limited costs [27]. The project, including development of the intervention followed by a feasibility study and an RCT, is financed by research grants. If the intervention is shown to be effective, it is planned to be implemented in regular care.

The Holistic Framework for Development of eHealth Technologies

This study is based on the holistic framework for developing eHealth technologies by van Gemert-Pijnen et al [10] and focuses primarily on the design step of the model, that is, the co-creative participatory process of building the Web-based intervention. An essential principle in this framework is end users' involvement throughout the development process. End users in this study were represented by former cancer patients

and significant others, hereafter referred to as patient research partners (PRPs), who participated in repeated evaluation cycles of the eHealth technology. According to theory, the quality of an eHealth intervention can be evaluated on three different levels: content, system, and service quality [10,28]. Content quality includes creating information that is understandable, meaningful, and persuasive. System quality means that the technology is safe, user-friendly, and easy to manage. Service quality entails providing an e-service that is adequate and reliable, that is, providing prompt and empathetic support to participants regarding technical and general issues.

The study aims to describe the development of a Web-based intervention in long-term collaboration with PRPs.

Methods

Recruitment of Patient Research Partners

The PRPs were recruited from a previous study investigating sexuality and fertility among childhood cancer survivors [18], and through cancer nurse navigators at a university hospital. The research group set out to recruit women and men, aged 16-40, who had undergone cancer treatment for any of the cancer types selected for the planned RCT. In addition, we wanted to recruit a few significant others (partners or parents of young patients). In total, 13 PRPs were recruited—11 individuals previously diagnosed with cancer (2-9 years earlier) and 2 mothers of teenagers who had undergone cancer treatment agreed to participate in a 5-year long collaboration. The PRPs were all born in Sweden but lived in different parts of the country. All were fulltime working or studying with a majority having a university degree. The former patients were 7 women and 4 men, aged 20-41, and included singles as well as partnered individuals of whom 2 had children and 1 became a parent during our collaboration. The following cancer diagnoses were represented: Hodgkin lymphoma (n=5), tumors of the central nervous system (n=2), breast cancer (n=2), testicular cancer (n=2), cervical cancer (n=1), and Ewing sarcoma (n=1). One PRP (former patient) decided to leave the collaboration after attending one meeting, while the other 12 PRPs remained in the group.

The PRPs had a status of research partners rather than research participants and were paid for their participation in project meetings and time working with assignments. Additionally, PRPs were reimbursed for travel expenses and if needed, accommodation, as some traveled to meetings from distant places in Sweden.

Project Management

The research group included researchers, health care providers, and a project coordinator with academic backgrounds in medicine, psychology, psychiatry, sociology, nursing, and arts. Their clinical backgrounds included primary care, psychotherapy, and counseling in cancer care and sexually transmissible infections, respectively. The composition of the research group altered during the 18-month period described, with an average of 6-7 researchers present at each meeting with the PRPs. The researchers had weekly project management meetings and regular contact with a network of professional collaborators including physicians and nurse practitioners in cancer and reproductive care, and sexual therapists. The research group was responsible for managing the collaboration with the PRPs, including strategic and logistic planning of meetings with PRPs. The researchers were also responsible for documenting and implementing PRPs' ideas and for decisions regarding the scientific process.

A software company was contracted to build the Fex-Can Internet portal. Additionally, we collaborated with a Web designer, an illustrator, and a photographer. One of the research group members was responsible for contacts with the software company, and another team member acted as main contact person for the PRPs throughout the process.

Forms for Collaboration

The collaboration mainly took place in the form of 1-day meetings. Efforts were made to establish a trustful collaboration between the researchers and the PRPs. All meetings included a joint lunch for all involved PRPs and researchers at the expense of the project.

During the first meeting, the forms for collaboration between researchers and PRPs were agreed upon. Different forms of collaboration were discussed, for example, Web-based discussion forums for different age groups, video conferences, or physical meetings. The PRPs preferred to have meetings in person on a regular basis as 1-day get-togethers during weekends (PRP meetings), while communication between these meetings was to be carried out by email. The 1-day meetings included plenary (see Figure 1) and small group discussions as well as individual assignments. At subsequent meetings, the forms for collaboration were revisited and PRPs were asked if they wanted to continue to work in the same way. This procedure generated four additional PRP meetings within the design step; PRPs attended a median of four of the total five PRP meetings.

Figure 1. Plenary discussion at PRP meeting.

Documentation

The results in this article are based on several sources of data. First, notes were taken by 2 members of the research team during each 1-day meeting with the PRPs. These notes covered all topics discussed and all opinions raised by the PRPs. The notes were compiled and presented at research group meetings when the notes were adjusted according to the impressions of all research group members. Minutes from all meetings, together with notes from contacts with PRPs between meetings were continuously compiled into a log book. Second, all researchers met directly after each 1-day meeting with the PRPs and reflected upon their impressions throughout the day. These reflections were added to the log of the collaboration with the PRPs. Third, the notes from previous meetings were also discussed with the PRPs to check that their opinions had been correctly understood. Fourth, the PRPs gave confidential feedback on content, layout, and functionality on some of the modules of the intervention directly into the Fex-Can portal.

The results in this article are based on this documentation and will be presented according to the quality criteria suggested by the holistic framework by Gemert-Pijnen et al [10]: content, system, and service quality. Furthermore, the process of building the intervention will be described, as well as the PRPs' impact on the overall research project.

Predefined Components of the Web-Based Intervention

Some features were planned to be included in the intervention, prior to the recruitment of patient research partners. According to key components for Internet interventions defined by Barak [29], these features were educational and behavior change content, multimedia (eg, pictures, video vignettes, and audios), interactive online activities (eg, self-monitoring), and partial feedback support (eg, discussion forum, tailored feedback from experts). The behavior change content was intended to convey a balance between problem solving (change) and acceptance strategies, including mindfulness. An aim was to affect participants' autonomy (sense of control over one's life), competence (perceived efficacy), and relatedness ("I am not alone with these problems") [30]. However, details of the intervention were not planned and an objective for the collaboration was to let the PRPs have an impact on the composition of the content and structure of the intervention, to make it more relevant and attractive for users.

Results

Building the Intervention

In the first meeting, PRPs received information about the aims and framework of the planned study, and basic ethical principles in research. We also spent time on getting to know each other; the PRPs and the researchers introduced themselves and the PRPs shared their "cancer story." For the second meeting, a mock-up of the Fex-Can Internet portal was created, based on existing knowledge regarding Web-based interventions, and presented to the PRPs. The mock-up suggested content divided into different modules and other functions such as expert and discussion forums. After discussing the planned set-up of the intervention, a prototype was produced for the following meeting. The researchers refined the Fex-Can intervention

several times and the revised versions were discussed at meetings so that the PRPs were able to contribute to the process. Working materials, such as topic-relevant websites, suggested contents of specific modules, and access to different preliminary versions of a module, were mailed to the PRPs to be read before scheduled meetings. The Fex-Can intervention came to include several features organized in subsequent modules and divided in two streams: fertility and sexuality. Examples of two module overview webpages are presented in Figures 2 and 3. The following paragraphs describe how the PRPs had an impact on the intervention's content quality, system quality, service quality, and overall project.

Figure 2. Example of module in the fertility stream of the intervention.

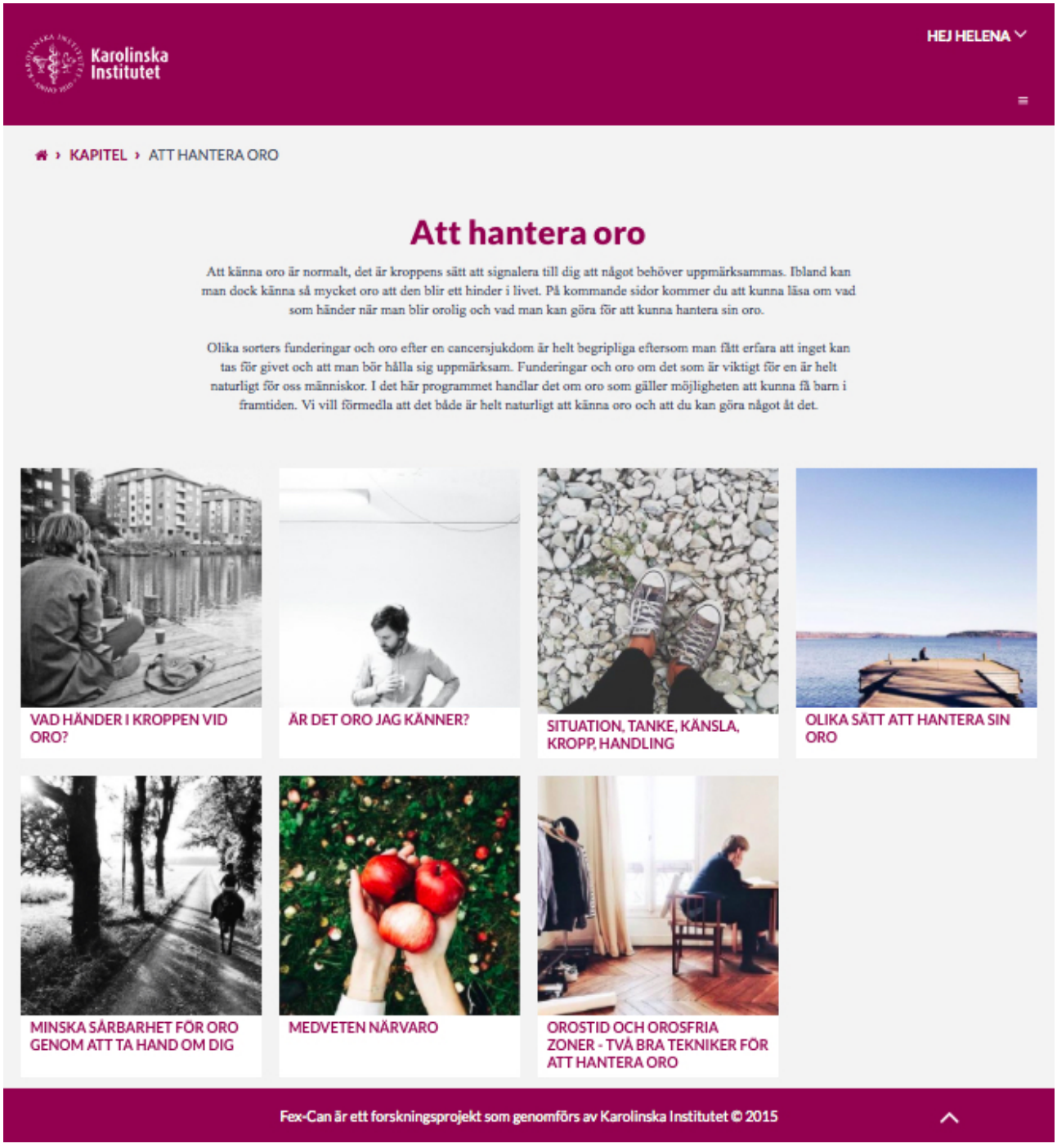
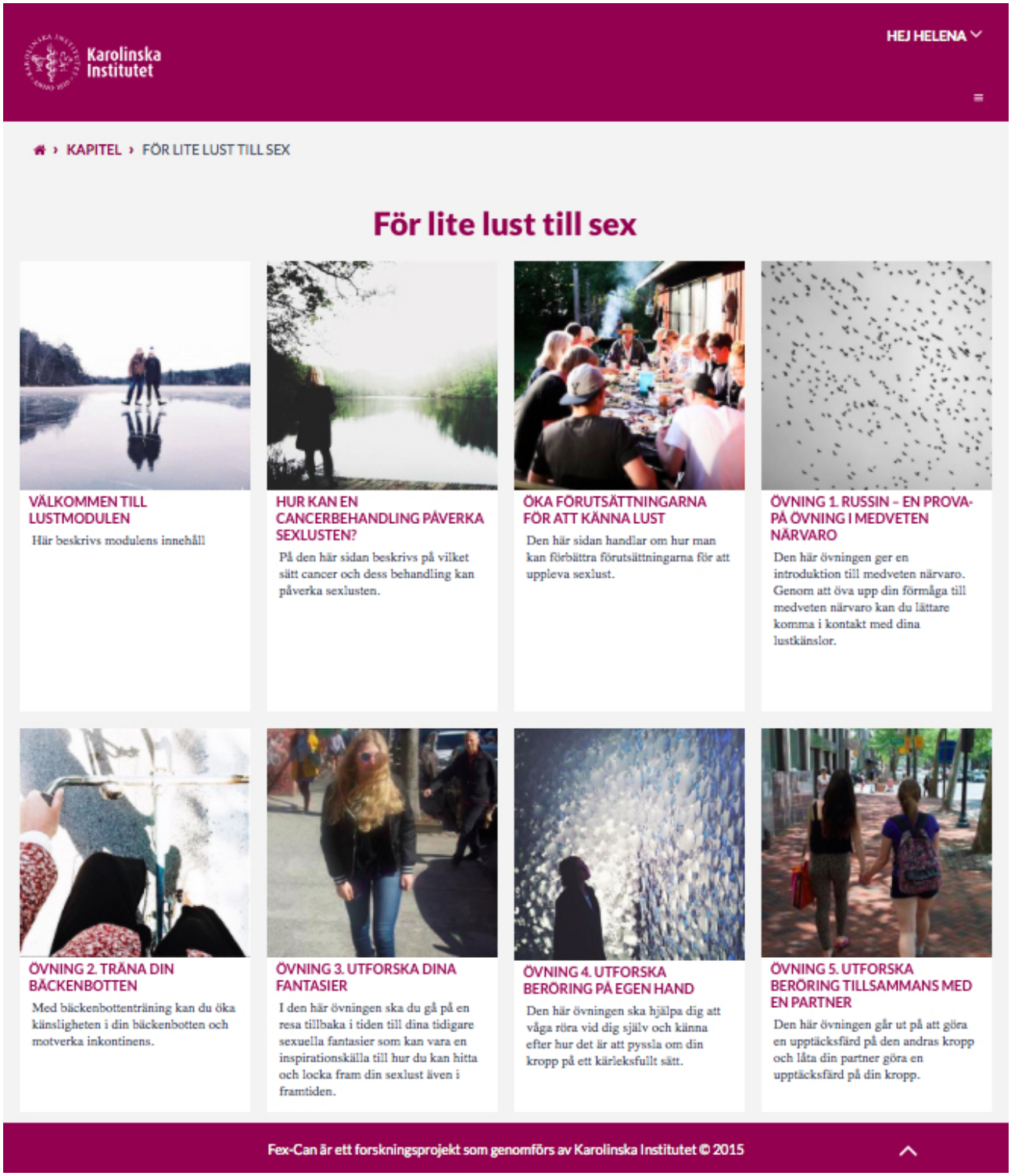


Figure 3. Example of module in the sexuality stream of the intervention.



Patient Research Partners' Impact on Content Quality

During the first meetings, the PRPs expressed an overall concern that information on the website could cause emotional distress, especially in relation to information on risks of infertility and relapse of disease. At the same time, the importance of offering accurate and evidence-based detailed information was underscored. The views of what kind of information might be perceived as distressing differed within the group of PRPs. Following further discussion, we agreed that the Fex-Can intervention would convey a hopeful and encouraging attitude and present examples and strategies for dealing with problems, that its, it would be empowering. The PRPs wanted information on the website to be tailored to meet participants' diverse needs regarding the amount of information, which made us organize the information on several levels, where participants have the option to read extended text.

The PRPs wished for the intervention to include more facts on sexuality and fertility related to side effects of specific cancer treatments as well as information about what side effects or symptoms were to be expected. All of this was added.

Furthermore, the PRPs stressed the importance of including content related to bodily changes or body image in the sexual stream of the Fex-Can, which resulted in the addition of a separate module focusing on this aspect.

The PRPs shared their opinions about what types of exercises they thought should be included and how much time participants would be willing to spend on an exercise. They thought there were too many exercises and recommended us to carefully select a reduced number to be included and present all of them as optional. In particular, the included mindfulness exercises were debated since some PRPs were skeptical and questioned if the technique was evidence-based. After being presented with facts about the effects of such exercises followed by thorough discussions, the PRPs were supportive of including mindfulness in the Fex-Can intervention. Furthermore, PRPs appreciated that some misconceptions about mindfulness were disentangled on the website. In later versions of the intervention, the PRPs expressed that the included exercises appeared useful and reliable.

Another issue stressed by the PRPs was the importance of using an inclusive, easily comprehensible language matching a broad group of end users, including individuals with cognitive difficulties (common when diagnosed with brain tumors). A challenge was to use language without jargon, neither too colloquial, nor too formal. The PRPs stressed this necessity during earlier stages of working with the texts and expressed their satisfaction with the comprehensibility of the texts in the later versions of the website, indicating that a well-balanced language level had been established.

The PRPs emphasized that the content of the program should communicate an awareness of participants' cancer experience. One part of this was the PRPs' wish that the program should include other cancer patients' stories to increase relatedness to others, for example, "I'm not the only one having these problems." The researchers asked if the PRPs were willing to share their own stories (in text or as videos), which 5 agreed to do. The importance of choosing appropriate photos for the website was also emphasized by the PRPs. The photos should be representative also for participants who were still under treatment and troubled by side effects, for example, include persons with visible signs of cancer treatment such as hair loss, overweight/underweight, and scars.

In order to persuade participants in the intervention to stay in the program, the researchers suggested that a new module would be introduced every 2 weeks for participants in the intervention. This was supported by the PRPs who thought participants would be curious to see the next module. The PRPs also supported the idea that participants would receive feedback on what they had done so far in the program. Based on this, a timeline was included on the opening page of the intervention to visualize the progression of time during the 12-week program. Following suggestions made by PRPs to increase active participation in the intervention, weekly email reminders were also added as a feature in the program. Another topic discussed was the possibility of including quizzes in the program since they are interactive and have the potential to increase a sense of progressing. However, since some of the PRPs perceived such quizzes as stressfully competitive, quizzes were not included in the program.

A way to increase social dynamics in the program was to incorporate a discussion forum in the intervention as well as a counseling feature in the sexuality stream of the intervention, which also was supported by the PRPs. The feasibility of having a discussion forum with participants in such a wide age span as 16-40 years was thoroughly discussed, since persons of different ages might think differently about fertility and sexuality. After reflecting on advantages and disadvantages of dividing the forum into age groups, it was decided to keep one discussion forum but to create discussion threads for different age groups.

The PRPs emphasized that text and pictures included in Fex-Can should not be overly normative when relating to sexual problems and fertility distress. This includes addressing a diversity of sexualities, ethnicities, relationships, and ways of building a family instead of exclusively presenting white heterosexuals in monogamous relationships having biological children of their own. Initially, PRPs expressed that the intervention focused too much on couples and did not give enough attention to the potential problem of finding a partner. Therefore, the intervention was developed to better reflect the situation of singles, and a module on "How to meet a partner" was included in the sexual stream of the intervention.

Patient Research Partners' Impact on System Quality

The layout of the website was frequently discussed with the PRPs. They stressed that young people have high expectations on a website and that a design that is perceived as unprofessional would risk increasing participant dropout of the RCT. Researchers and PRPs agreed on the idea that the website should have a responsive design, that is, it should adapt its layout to various devices such as computers, smartphones, or tablets. PRPs also considered the Web address/domain to be an important factor that should communicate a rigorous and valid source, preferably university-based. The PRPs recommended using a more professional design than the first mock-up and suggested using a light background color, black text with classic font, and header in Karolinska Institutet's promotional color. Furthermore, they wanted pictures to be included only if they had a function related to the text and not merely for esthetic purposes. A Web designer was consulted to make a neater layout with a uniform style and a better structure throughout the intervention, since the PRPs repeatedly stressed that the website was difficult to navigate. During the entire development process, the website had several technical malfunctions, which were pointed out by the PRPs. These problems were continuously adjusted in collaboration between the project coordinator and the software developer.

Patient Research Partners' Impact on Service Quality

The PRPs repeatedly stressed that technical malfunctions on the website were very frustrating. This increased the researchers' awareness of the importance of almost instant support when intervention participants experienced technical problems. A plan for implementation of technical support within the intervention was added.

PRPs had objections to the suggested rules for the planned discussion forum. The PRPs expressed concerns regarding our plan to check all postings before they were published to prevent inappropriate texts and topics. This was believed to negatively affect the communication in the discussion forum because participants would lose interest if postings were delayed. Therefore, we decided that postings would be instantly visible in the forum but the researchers would be responsible for continuously checking for (and deleting) potentially inappropriate postings (or comments) within every 24 hours. Further, the PRPs stressed that replies to postings in the feature "ask an expert" should not take too long. Therefore, it was decided that the researchers would be responsible for the contact with external experts to make sure postings were replied to within 3 workdays. Likewise, it would be problematic if other website functions would not work properly. A Web-based support (e-service) was added within the program, where participants could ask researchers any type of questions (technical, content, and/or how to use the partial feedback support) via mail and get a fast reply. This e-service was planned to be given by someone from the research group who would understand and know all parts of the intervention and would be able to give this e-service in an emphatic way. Furthermore, a telephone support run by research group members was planned to be available for the website.

Patient Research Partners' Overall Impact on the Research Project

Naming the Project

After thoroughly discussing the purpose of the intervention, most of the PRPs did not appreciate the initial name of the project ("Life Interrupted"). They thought that the program should focus on moving forward in life rather than on the interruption in life that a cancer diagnosis might constitute. Several suggestions were discussed between the researchers and the PRPs, resulting in the more neutral name "Fex-Can, Fertility and sexuality following cancer".

Plan for Evaluation and Implementation

In the beginning of the collaboration, the PRPs emphasized the need for the program to improve the care of cancer patients. They expressed that they would have appreciated access to such a program during and after their own cancer treatment, whether they had problems or not. Therefore, they thought the program should be available for anyone with a cancer experience, and not offered only to those with sexual problems and fertility distress. The reasons for conducting an RCT before making the intervention available to unselected patient groups were explained (by the researchers) and accepted. Furthermore, we explained that if the intervention showed to be effective in reducing sexual problems and fertility-related distress, the goal was to collaborate with health care services to implement the program into regular care. Regarding the RCT testing, PRPs questioned why the Fex-Can intervention would be available only for study participants at baseline (1 year after diagnosis). They argued that problems could occur later during the planned follow-up period and suggested that the intervention should be made available to those with sexual problems or fertility distress in connection to late follow-ups (3 and 5 years after diagnosis). This promising suggestion will be taken into consideration in the RCT phase of the project. Other issues of value for implementation were identified, and it may be possible to address them throughout the development process (eg, ways to avoid dropout).

Input on Outcome Measures

The questionnaire measuring fertility distress, Reproductive Concerns After Cancer [31], which was one of the primary outcomes of the Fex-Can program, was discussed with the PRPs. Several items raised concern among the significant others about the risk of evoking worries, especially among participants in young ages (16-17 years). Based on this, we conducted additional cognitive interviews with 4 adolescents who had been treated for cancer to verify the acceptability of the measure among the youngest respondents.

Discussion

Principal Results

This study aimed to describe a co-creative process in the development of a self-help Web-based intervention to alleviate sexual problems and fertility-related distress in young cancer patients. The ultimate goal for patient and public involvement in research is to get another perspective on research projects by taking the PRPs' lived experience into account [11] and getting new insights [32], which will result in more relevant interventions. We believe that our collaboration with 12 PRPs accomplished this goal and that both the demands of the PRPs and the needs of the study have been met in the development of the intervention, as stressed by van Gemert-Pijnen et al [10]. The input from the PRPs contributed to making the content of the Fex-Can intervention meaningful, relevant, and understandable. Furthermore, PRPs addressed the importance of an inclusive, diverse imagery and of creating a professional layout and persuasive design, and to improve support systems included in the intervention. The PRPs also affected the research project on an overall level by participating in naming the project, suggesting changes in the follow-up, and by questioning the implementation plan.

The co-creative process comprises bringing together researchers and stakeholders, exchanging ideas, and interacting to improve research [11]. This project is unusual as it from the start aimed to establish a long-term collaboration over 5 years, with a PRP group of considerable size in contrast to the more common set-up with multiple participants at a single event [15,16] or one or two participants on multiple occasions [9].The recruitment procedure [13,33] proved to be successful, with high attendance at meetings and only one person dropping out from the collaboration. The PRPs themselves described that their main motive for commitment in the project was a wish to help others in a situation similar to the ones they had experienced themselves when diagnosed with cancer. They also expressed that they appreciated sharing their experiences with people in the same age group, as described in other studies of young cancer patients [34].

We believe that our careful preparation and set-up of the collaboration created beneficial circumstances for PRPs to have

a real impact on the project [12,32] for four main reasons. First, we allocated one person in the research group for all contacts with the PRPs and invested time getting to know each other. This procedure contributed to an environment that facilitated a positive and committed collaboration that may be especially important for younger PRPs, who otherwise might be too shy to express their opinion in a group [13]. Second, the involved researchers early on reflected on and discussed their expectations and perceptions regarding the roles of the PRPs in the project. We expected that a successful collaboration would require commitment, openness, and flexibility in the research group, where the PRPs were seen as experts on the patient perspective. However, this did not imply the incorporation of all PRP ideas. In cases when there was disagreement between researchers and PRPs, the researchers argued their points and clarified their view in order to achieve a common standpoint. Third, we compensated the PRPs for their time and expenses and also served food and drinks, which has been reported to increase PRPs' feelings of being important for the project [33]. Fourth, in contrast to the common procedure when researchers are solely responsible for decisions on forms of collaboration [10], researchers and PRPs reached a common agreement on how meetings were to be organized in the Fex-Can study, even though the researchers decided on the agendas.

One of the main advantages of the long-term co-creative process was the possibility to, in an iterative way, fine-tune the Internet intervention through the PRPs' repeated feedback on aspects that had been adapted following their earlier suggestions. The collaboration with PRPs was also timesaving for the researchers. Prompt confirmation of ideas and solutions that were well functioning enabled further development of these without delay, and weaker solutions could likewise be adjusted or discarded promptly. This made the researchers more confident in their work, and fewer parallel versions of layouts and contents had to be produced when existing versions were approved by the PRPs. Furthermore, when the PRPs saw that their feedback was incorporated in the program, they expressed satisfaction that their impact was valued, which further increased their motivation to participate. Another advantage of such a long-term collaboration was that the PRPs were able to contribute more as their understanding of the intervention's intention grew. In addition, the researchers and the PRPs became more equal partners over time, and the researchers relied more on the PRPs who became indispensable in the project.

Limitations

This study is novel in many ways and some methodological limitations should be mentioned. A problem with a long-term collaboration might be, as has been discussed elsewhere [35,36], that the PRPs become "professional" patients, who incorporate the researchers' views and alienate themselves from the target group. As the relationship between researchers and patients is asymmetrical [35], patients' experiential knowledge and input might also be unintentionally overruled [37]. However, the PRPs were encouraged to express their opinions during the meetings and all PRPs did so, including expressing divergent opinions and questioning ideas from the researchers. The PRPs often referred to how they would have reacted 1 year after their cancer, clearly identifying themselves with future users of the intervention. The meetings were held 2-3 times per year and the PRPs outnumbered the researchers in all discussions, limiting the risk that PRPs became "professional" patients. An opposite problem might be that researchers let the PRPs' ideas and suggestions run the project without being critical. However, we strived to create a balance between new ideas and methods known to be effective.

Further, the PRPs were not recruited based on their level of problems in the areas targeted in the intervention (ie, sexual problems and fertility distress). Therefore, it was not known if individuals with high levels of problems/distress were adequately represented, thus possibly limiting representativeness. We are also aware of the lack of heterogeneity in the PRP group, as most of them were well educated and there seemingly was a lack of diversity in ethnicity and sexual orientation. The characteristics of the PRPs may therefore have contributed to less variety in expressed opinions. However, the perspectives of different groups of future users were often brought up by the PRPs, who argued that the intervention must suit users with, for example, different sexual orientations. Furthermore, the research team's composition was mixed regarding country of birth and sexual orientation, which may to some degree have broadened the perspectives represented. In other aspects the PRP group was heterogeneous in that it included men and women of different ages, both singles and those living with a partner, from different parts of the country. An important limitation is, however, that this study is based on the researchers' views of the co-creative process, with only indirect reports from the PRPs and no independent assessment of the collaboration process.

When individual PRPs expressed conflicting viewpoints the researchers sometimes found it difficult to know whom they should listen to. There is a risk that those who talk loudly or eloquently receive more attention or that researchers pay attention to comments that are close to their own opinions. We tried to avoid this in several ways, for example, by letting PRPs give feedback on the mock-up and early versions of the website confidentially by writing comments online and by discussing topics in small groups to facilitate expression of opinions. Another way of equalizing power relations between the collaborating parties was to strive for researchers to be in the minority in all discussions. Finally, several of the researchers had training in counseling and were used to encouraging other persons, which we believe contributed to a sensitive and constructive discussion climate at collaboration meetings.

Conclusion

A long-term collaboration between researchers and a committed group of patient research partners contributed substantially to the development of a self-help Web-based intervention. With suggestions and continuous feedback from PRPs, it was possible to develop a Web-based intervention believed to be relevant and attractive for young persons with cancer having sexual problems or fertility distress. The collaboration with PRPs will continue in the following steps of testing the Fex-Can intervention. The intervention will first be tested in a feasibility study with cancer patients, where PRPs will participate in the interpretation of results. The effectiveness of the intervention

will thereafter be tested in an RCT targeting a nationwide cohort of adolescents and young adults with problems and distress related to sexuality and fertility after cancer.

Acknowledgments

The study was supported by grants from the Swedish Childhood Cancer Foundation, the Doctoral School in Health Care Sciences at Karolinska Institutet, the Cancer Research Foundations of Radiumhemmet (121242), the Swedish Cancer Society (2010/877), the Vårdal Foundation, and the Swedish Research Council for Health, Working Life and Welfare.

Conflicts of Interest

None declared.

References

1. Phillips CR, Davis LL. Psychosocial Interventions for Adolescents and Young Adults with Cancer. Semin Oncol Nurs 2015 Aug;31(3):242-250. [doi: 10.1016/j.soncn.2015.05.004] [Medline: 26210202]
2. Richter D, Koehler M, Friedrich M, Hilgendorf I, Mehnert A, Weißflog G. Psychosocial interventions for adolescents and young adult cancer patients: A systematic review and meta-analysis. Crit Rev Oncol Hematol 2015 Sep;95(3):370-386. [doi: 10.1016/j.critrevonc.2015.04.003] [Medline: 25922217]
3. van de Poll-Franse Lonneke V, van Eenbergen Mies C H J. Internet use by cancer survivors: current use and future wishes. Support Care Cancer 2008 Oct;16(10):1189-1195. [doi: 10.1007/s00520-008-0419-z] [Medline: 18293014]
4. Nagler RH, Romantan A, Kelly BJ, Stevens RS, Gray SW, Hull SJ, et al. How do cancer patients navigate the public information environment? Understanding patterns and motivations for movement among information sources. J Cancer Educ 2010 Sep;25(3):360-370 [FREE Full text] [doi: 10.1007/s13187-010-0054-5] [Medline: 20204573]
5. Davies EB, Morriss R, Glazebrook C. Computer-delivered and web-based interventions to improve depression, anxiety, and psychological well-being of university students: a systematic review and meta-analysis. J Med Internet Res 2014;16(5):e130 [FREE Full text] [doi: 10.2196/jmir.3142] [Medline: 24836465]
6. Liebl P, Seilacher E, Koester M, Stellamanns J, Zell J, Hübner J. What cancer patients find in the internet: the visibility of evidence-based patient information - analysis of information on German websites. Oncol Res Treat 2015;38(5):212-218. [doi: 10.1159/000381739] [Medline: 25966768]
7. Barak A, Hen L, Boniel-Nissim M, Shapira N. A Comprehensive Review and a Meta-Analysis of the Effectiveness of Internet-Based Psychotherapeutic Interventions. Journal of Technology in Human Services 2008 Jul 03;26(2-4):109-160. [doi: 10.1080/15228830802094429]
8. Eysenbach G, CONSORT- E. CONSORT-EHEALTH: improving and standardizing evaluation reports of Web-based and mobile health interventions. J Med Internet Res 2011;13(4):e126 [FREE Full text] [doi: 10.2196/jmir.1923] [Medline: 22209829]
9. van Bruinessen IR, van Weel-Baumgarten EM, Snippe HW, Gouw H, Zijlstra JM, van DS. Active patient participation in the development of an online intervention. JMIR Res Protoc 2014;3(4):e59 [FREE Full text] [doi: 10.2196/resprot.3695] [Medline: 25379679]
10. van Gemert-Pijnen J, Nijland N, van LM, Ossebaard HC, Kelders SM, Eysenbach G, et al. A holistic framework to improve the uptake and impact of eHealth technologies. J Med Internet Res 2011;13(4):e111 [FREE Full text] [doi: 10.2196/jmir.1672] [Medline: 22155738]
11. Oliver S, Liabo K, Stewart R, Rees R. Public involvement in research: making sense of the diversity. J Health Serv Res Policy 2015 Jan;20(1):45-51. [doi: 10.1177/1355819614551848] [Medline: 25228453]
12. Brett J, Staniszewska S, Mockford C, Herron-Marx S, Hughes J, Tysall C, et al. Mapping the impact of patient and public involvement on health and social care research: a systematic review. Health Expect 2014 Oct;17(5):637-650. [doi: 10.1111/j.1369-7625.2012.00795.x] [Medline: 22809132]
13. de Wit MPT, Berlo SE, Aanerud GJ, Aletaha D, Bijlsma JW, Croucher L, et al. European League Against Rheumatism recommendations for the inclusion of patient representatives in scientific projects. Ann Rheum Dis 2011 May;70(5):722-726. [doi: 10.1136/ard.2010.135129] [Medline: 21257615]
14. McLaughlin H. Involving Young Service Users as Co-Researchers: Possibilities, Benefits and Costs. British Journal of Social Work 2005 Nov 18;36(8):1395-1410. [doi: 10.1093/bjsw/bch420]
15. Deady M, Kay-Lambkin F, Teesson M, Mills K. Developing an integrated, Internet-based self-help programme for young people with depression and alcohol use problems. Internet Interventions 2014 Jul;1(3):118-131. [doi: 10.1016/j.invent.2014.06.004]
16. Fledderus M, Schreurs KM, Bohlmeijer ET, Vollenbroek-Hutten MM. Development and Pilot Evaluation of an Online Relapse-Prevention Program Based on Acceptance and Commitment Therapy for Chronic Pain Patients. JMIR Human Factors 2015 Jan 05;2(1):e1. [doi: 10.2196/humanfactors.3302]

17. Orlowski SK, Lawn S, Venning A, Winsall M, Jones GM, Wyld K, et al. Participatory Research as One Piece of the Puzzle: A Systematic Review of Consumer Involvement in Design of Technology-Based Youth Mental Health and Well-Being Interventions. JMIR Human Factors 2015 Jul 09;2(2):e12. [doi: 10.2196/humanfactors.4361]
18. Nilsson J, Jervaeus A, Lampic C, Eriksson LE, Widmark C, Armuand GM, et al. 'Will I be able to have a baby?' Results from online focus group discussions with childhood cancer survivors in Sweden. Hum Reprod 2014 Dec;29(12):2704-2711 [FREE Full text] [doi: 10.1093/humrep/deu280] [Medline: 25344069]
19. Jervaeus A, Nilsson J, Eriksson LE, Lampic C, Widmark C, Wettergren L. Exploring childhood cancer survivors' views about sex and sexual experiences -findings from online focus group discussions. Eur J Oncol Nurs 2016 Feb;20:165-172 [FREE Full text] [doi: 10.1016/j.ejon.2015.07.009] [Medline: 26251362]
20. Armuand GM, Wettergren L, Rodriguez-Wallberg KA, Lampic C. Women more vulnerable than men when facing risk for treatment-induced infertility: a qualitative study of young adults newly diagnosed with cancer. Acta Oncol 2015 Feb;54(2):243-252. [doi: 10.3109/0284186X.2014.948573] [Medline: 25140859]
21. Penrose R, Beatty L, Mattiske J, Koczwara B. Fertility and cancer--a qualitative study of Australian cancer survivors. Support Care Cancer 2012 Jun;20(6):1259-1265. [doi: 10.1007/s00520-011-1212-y] [Medline: 21660668]
22. Flynn KE, Reese JB, Jeffery DD, Abernethy AP, Lin L, Shelby RA, et al. Patient experiences with communication about sex during and after treatment for cancer. Psychooncology 2012 Jun;21(6):594-601 [FREE Full text] [doi: 10.1002/pon.1947] [Medline: 21394821]
23. Armuand GM, Rodriguez-Wallberg KA, Wettergren L, Ahlgren J, Enblad G, Höglund M, et al. Sex differences in fertility-related information received by young adult cancer survivors. J Clin Oncol 2012 Jun 10;30(17):2147-2153 [FREE Full text] [doi: 10.1200/JCO.2011.40.6470] [Medline: 22585695]
24. Ussher JM, Cummings J, Dryden A, Perz J. Talking about fertility in the context of cancer: health care professional perspectives. Eur J Cancer Care (Engl) 2016 Jan;25(1):99-111. [doi: 10.1111/ecc.12379] [Medline: 26361092]
25. Bailey JV, Murray E, Rait G, Mercer CH, Morris RW, Peacock R, et al. Computer-based interventions for sexual health promotion: systematic review and meta-analyses. Int J STD AIDS 2012 Jun;23(6):408-413. [doi: 10.1258/ijsa.2011.011221] [Medline: 22807534]
26. Aarts J W JWM, van den Haak P, Nelen WLDM, Tuil WS, Faber MJ, Kremer JAM. Patient-focused internet interventions in reproductive medicine: a scoping review. Hum Reprod Update 2012;18(2):211-227 [FREE Full text] [doi: 10.1093/humupd/dmr045] [Medline: 22108381]
27. Anell A, Glenngård AH, Merkur S. Sweden health system review. Health Syst Transit 2012;14(5):1-159 [FREE Full text] [Medline: 22894859]
28. DeLone W, McLean E. The DeLone and McLean Model of Information Systems Success: A Ten-Year Update. J Manage Inform Syst 2003;19(4):9-30 ISSN:0742-1222. [doi: 10.1080/07421222.2003.11045748]
29. Barak A, Klein B, Proudfoot JG. Defining internet-supported therapeutic interventions. Ann Behav Med 2009 Aug;38(1):4-17. [doi: 10.1007/s12160-009-9130-7] [Medline: 19787305]
30. Pingree S, Hawkins R, Baker T, duBenske L, Roberts LJ, Gustafson DH. The value of theory for enhancing and understanding e-health interventions. Am J Prev Med 2010 Jan;38(1):103-109 [FREE Full text] [doi: 10.1016/j.amepre.2009.09.035] [Medline: 20117565]
31. Gorman JR, Su HI, Pierce JP, Roberts SC, Dominick SA, Malcarne VL. A multidimensional scale to measure the reproductive concerns of young adult female cancer survivors. J Cancer Surviv 2014 Jun;8(2):218-228 [FREE Full text] [doi: 10.1007/s11764-013-0333-3] [Medline: 24352870]
32. Brett J, Staniszewska S, Mockford C, Herron-Marx S, Hughes J, Tysall C, et al. A systematic review of the impact of patient and public involvement on service users, researchers and communities. Patient 2014;7(4):387-395. [doi: 10.1007/s40271-014-0065-0] [Medline: 25034612]
33. Blackburn H, Hanley B, Staley K. Turning the pyramid upside down: examples of public involvement in social care research. Eastleigh: INVOLVE; 2010.
34. Rabin C, Simpson N, Morrow K, Pinto B. Behavioral and psychosocial program needs of young adult cancer survivors. Qual Health Res 2011 Jun;21(6):796-806. [doi: 10.1177/1049732310380060] [Medline: 20705863]
35. de Wit MPT, Berlo SE, Aanerud GJ, Aletaha D, Bijlsma JW, Croucher L, et al. European League Against Rheumatism recommendations for the inclusion of patient representatives in scientific projects. Ann Rheum Dis 2011 May;70(5):722-726. [doi: 10.1136/ard.2010.135129] [Medline: 21257615]
36. Abma TA, Molewijk B, Widdershoven GAM. Good care in ongoing dialogue. Improving the quality of care through moral deliberation and responsive evaluation. Health Care Anal 2009 Sep;17(3):217-235 [FREE Full text] [doi: 10.1007/s10728-008-0102-z] [Medline: 19139992]
37. Kirwan JR, Ahlmén M, de WM, Heiberg T, Hehir M, Hewlett S, et al. Progress since OMERACT 6 on including patient perspective in rheumatoid arthritis outcome assessment. J Rheumatol 2005 Nov;32(11):2246-2249. [Medline: 16265711]

Abbreviations

Fex-Can: fertility and sexuality following cancer

PRP: patient research partner
RCT: randomized controlled trial

Edited by G Eysenbach; submitted 26.01.16; peer-reviewed by J Lundgren, IR Bruinessen; comments to author 16.02.16; revised version received 26.02.16; accepted 26.02.16; published 12.04.16.

Please cite as:
Winterling J, Wiklander M, Obol CM, Lampic C, Eriksson LE, Pelters B, Wettergren L
Development of a Self-Help Web-Based Intervention Targeting Young Cancer Patients With Sexual Problems and Fertility Distress in Collaboration With Patient Research Partners
JMIR Res Protoc 2016;5(2):e60
URL: http://www.researchprotocols.org/2016/2/e60/
doi:10.2196/resprot.5499
PMID:27073057

Original Paper

Feasibility of PRIME: A Cognitive Neuroscience-Informed Mobile App Intervention to Enhance Motivated Behavior and Improve Quality of Life in Recent Onset Schizophrenia

Danielle Schlosser[1], PhD; Timothy Campellone[2], MA; Daniel Kim[1], BA; Brandy Truong[1], BA; Silvia Vergani[3], MA; Charlie Ward[1], MA; Sophia Vinogradov[1,4], MD

[1]University of California, San Francisco, Department of Psychiatry, San Francisco, CA, United States

[2]University of California, Berekeley, Berkeley, CA, United States

[3]IDEO, Palo Alto, CA, United States

[4]San Francisco Veterans Affairs Medical Center, San Francisco, CA, United States

Corresponding Author:
Danielle Schlosser, PhD
University of California, San Francisco
Department of Psychiatry
401 Parnassus Ave
San Francisco, CA, 94134
United States
Phone: 1 415 476 8721
Fax: 1 415 476 7320
Email: danielle.schlosser@ucsf.edu

Abstract

Background: Despite improvements in treating psychosis, schizophrenia remains a chronic and debilitating disorder that affects approximately 1% of the US population and costs society more than depression, dementia, and other medical illnesses across most of the lifespan. Improving functioning early in the course of illness could have significant implications for long-term outcome of individuals with schizophrenia. Yet, current gold-standard treatments do not lead to clinically meaningful improvements in outcome, partly due to the inherent challenges of treating a population with significant cognitive and motivational impairments. The rise of technology presents an opportunity to develop novel treatments that may circumvent the motivational and cognitive challenges observed in schizophrenia.

Objective: The purpose of this study was two-fold: (1) to evaluate the feasibility and acceptability of implementing a Personalized Real-Time Intervention for Motivation Enhancement (PRIME), a mobile app intervention designed to target reward-processing impairments, enhance motivation, and thereby improve quality of life in recent onset schizophrenia, and (2) evaluate the empirical benefits of using an iterative, user-centered design (UCD) process.

Methods: We conducted two design workshops with 15 key stakeholders, followed by a series of in-depth interviews in collaboration with IDEO, a design and innovation firm. The UCD approach ultimately resulted in the first iteration of PRIME, which was evaluated by 10 RO participants. Results from the Stage 1 participants were then used to guide the next iteration that is currently being evaluated in an ongoing RCT. Participants in both phases were encouraged to use the app daily with a minimum frequency of 1/week over a 12-week period.

Results: The UCD process resulted in the following feature set: (1) delivery of text message (short message service, SMS)-based motivational coaching from trained therapists, (2) individualized goal setting in prognostically important psychosocial domains, (3) social networking via direct peer-to-peer messaging, and (4) community “moments feed” to capture and reinforce rewarding experiences and goal achievements. Users preferred an experience that highlighted several of the principles of self-determination theory, including the desire for more control of their future (autonomy and competence) and an approach that helps them improve existing relationships (relatedness). IDEO, also recommended an approach that was casual, friendly, and nonstigmatizing, which is in line with the recovery model of psychosis. After 12-weeks of using PRIME, participants used the app, on average, every other day, were actively engaged with its various features each time they logged in and retention and satisfaction was high (20/20, 100% retention, high satisfaction ratings). The iterative design process lead to a 2- to 3-fold increase in engagement from Stage 1 to Stage 2 in almost each aspect of the platform.

Conclusions: These results indicate that the neuroscience-informed mobile app, PRIME, is a feasible and acceptable intervention for young people with schizophrenia**.**

(JMIR Res Protoc 2016;5(2):e77) doi:10.2196/resprot.5450

KEYWORDS

schizophrenia; mobile app; smartphone; motivation; technology-based intervention; social networking; coaching; negative symptoms; quality of life

Introduction

Schizophrenia is associated with significant psychosocial impairments, which lead to poor quality of life [1,2]. Recent data suggest that negative symptoms, and amotivation in particular, are the single most important factor affecting functional disability in schizophrenia [3,4]. Recent cognitive neuroscience research demonstrates that motivational deficits in schizophrenia are characterized by impairments in reward prediction, maintenance of rewarding experiences to guide future behavior, and a reduction in higher effort allocation to obtain rewarding experiences [5-8]. The likelihood to anticipate experiences to be less rewarding and more effortful leads to significant functional impairments. Yet, some aspects of reward processing for individuals with schizophrenia may be preserved, such the degree to which reward experiences are perceived as pleasurable in the moment. Findings suggest that individuals with schizophrenia demonstrate intact hedonic experiences, as evidenced by subjective reports of in-the-moment positive emotion [6,9,10], self-reported arousal similar to healthy comparison subjects [11], and intact hedonic experiences in social contexts [11]. While it appears that the ability to experience pleasure from rewarding experiences is intact, individuals with schizophrenia are more likely to be alone and endorse a preference to be alone while in the company of others, relative to healthy subjects [11], which suggests that the in-the-moment experience of pleasure may not be motivating future social interactions. Given the progress we have made in understanding the complexity of reward processing deficits in schizophrenia and how they might influence motivated behavior, it is time to translate these findings into enhancements of traditional treatments and/or developing novel approaches.

Current gold-standard treatments for individuals with schizophrenia include atypical antipsychotic medication and psychotherapy, with cognitive behavioral therapy (CBT) as one of the most effective behavioral treatments. These approaches are particularly effective at treating the positive, psychotic symptoms, but they do not adequately treat the negative symptoms [12,13]. While some of this may be due to problems with engagement and/or cognitive deficits, which limit the degree to which the skills may be used in real-world settings, the evidence suggests that the current gold-standard treatments do not lead to clinically meaningful improvements in motivated behavior, negative symptom severity, functioning, and quality of life [12,13]. Negative symptoms in schizophrenia, including social withdrawal, limited affective expression, and decreased drive to engage in motivated behavior, pose significant challenges to traditional treatment approaches that require patients to attend in person sessions and make use of the treatment in real-world contexts [14]. As such, it is not surprising that treatments that use compensatory strategies, such as environmental supports and reinforcement in simulated contexts (cues, reminders, and reinforcement), may be more effective in treating negative symptoms and improving psychosocial functioning, than traditional approaches [15-19]. What this suggests is that treatments that target negative symptoms, may benefit from using strategies that bypass cognitive impairments and deliver environmental supports in real-world contexts that directly motivate individuals with schizophrenia to engage in more rewarding experiences.

The rise of digital health technology presents an opportunity to develop novel treatments that may circumvent the motivational and cognitive challenges observed in schizophrenia. Further, a mobile approach delivered in real-time and in real-world settings, may support the retention, reinforcement, and transfer of intact in-the-moment hedonic experiences to future behavior. Mobile interventions may be accessed with greater frequency than traditional psychotherapy approaches and briefer therapeutic interactions might require less effort and have a greater therapeutic benefit. Indeed, several research groups are taking advantage of technology to deliver behavioral treatments to individuals with schizophrenia [20,21].

These considerations led us to harness digital technology and translate current knowledge on reward processing deficits in schizophrenia into an intervention to improve motivated behavior in the early phases of the illness. We thus designed and developed a Personalized Real-time Intervention for Motivational Enhancement (PRIME), a mobile app treatment that delivers text message (short message service, SMS)-based motivational coaching from trained therapists; individualized goal setting in prognostically important psychosocial domains; and social networking via direct peer-to-peer messaging as well as a community “moments feed” to capture and reinforce rewarding experiences and goal achievements. PRIME was designed with a systematic user-centered design process that included the involvement of individuals with schizophrenia, family members, treatment providers, and research experts. The purpose of this report is two-fold: (1) to evaluate the initial feasibility and acceptability of implementing the PRIME intervention to individuals who were recently diagnosed with schizophrenia, and (2) to evaluate the empirical benefits of using an iterative, user-centered design (UCD) process to develop a digital intervention for individuals with schizophrenia.

Methods

User-Centered Design Process

UCD, also referred to as human-centered design, is a process for gaining insight into the needs of end-users, creating novel approaches to meet those needs, and delivering solutions that are optimized for specific contexts [22,23]. Our team worked in collaboration with IDEO, a design and innovation firm, to develop our design strategy and implement the UCD process. Over a 4-week period, we conducted two design workshops with 15 key stakeholders (young individuals with a schizophrenia-spectrum disorder, family members, treatment providers, and research experts), and conducted a series of in-depth, 1:1 in-person interviews with six young people with schizophrenia-spectrum disorders.

The 1:1 interviews included several exercises focused on gaining a better understanding of the values that drive participants to improve their lives. During the initial design workshop, key stakeholders generated 12 potential values that would improve quality of life, including: (1) feel part of a group, (2) be a role model, (3) deepen my relationships with family and friends, (4) have a partner/boyfriend/girlfriend, (5) feel energized, (6) feel appreciated when I achieve a goal, (7) feel a sense of progress, (8) feel productive, (9) remember positive moments, (10) feel happy, (11) feel "normal"/not like I am ill, and (12) feel a sense of control over my future. During the 1:1 interviews, participants discussed whether those values were personally relevant and ranked them in order of importance. While most of the values were important to participants, the top two priorities for participants were to feel a sense of control over my future and deepen my relationships with family and friends. This is in line with self-determination theory (SDT) [24], which emphasizes relatedness, autonomy, and competence as essential values that drive intrinsically motivated behavior. The SDT framework has been used to understand motivated behavior in schizophrenia, such as supporting the motivating role of relatedness [25], the importance of autonomous choices in engaging in health-promoting behaviors [26], and competence in driving reward learning [25,27]. We therefore explicitly integrated principles of SDT into the overall design structure of the app.

Another objective of the interviews was to evaluate each feature of the app. For instance, we used experiential strategies such as prototyping specific features and presenting potential paper mockups of the app. An example of a prototyping exercise was to invite participants to use their mobile phones to take photos of positive moments in their life. Our team was interested in developing a feature that prompted participants to capture rewarding experiences and share those experiences among peers and coaches. When participants came in for their interviews, we reviewed their photos and evaluated the subjective experience of engaging in this type of activity. Notably, in addition to participants reporting that they enjoyed the process of taking the photos, they also became much more affectively expressive, talkative, and overall more engaged during this portion of the interview, suggesting that this feature would be well received and that participants enjoyed the opportunity to communicate nonverbally through pictures.

Lastly, we presented paper mockups of the app, which enabled our team to evaluate the design, flow, and functionality of particular features. An example of how this significantly influenced the final design of the app was observed during the evaluation of the goal-setting feature. Participants were shown two options of how a user might navigate the goal-setting feature. In one case, participants were shown a "daily challenge" option that was highly customizable and in the other case, the feature was prepopulated with personalized content and a simplified interface. While we expected that our participants would prefer a more customizable option, the degree of complexity and effort required to navigate a customizable experience was undesirable, as almost all the users preferred simplicity to customization. This subtle, yet highly important preference significantly influenced the design of this feature.

The UCD approach ultimately resulted in the first iteration of PRIME, a mobile app intervention aimed at improving motivation and functioning in people with recent-onset schizophrenia-spectrum disorders. With PRIME, participants join a supportive online environment where they can select and document progress on small, self-determined goals in four key domains that have been shown to be significantly associated with better quality of life: (1) health/wellness [28,29], (2) social relationships [30], (3) creativity [31], and (4) productivity [32]. PRIME provides users with motivation coaches: Masters-level clinicians who use evidence-based "microinterventions" drawn from CBT, mindfulness, and psychoeducation to help participants overcome the daily obstacles that hinder goal progress and PRIME engagement. Additionally, the PRIME community provides a platform for users to interact with one another. Users may send messages directly to each other and can also capture and share positive moments in their daily life with the community. Importantly, the PRIME app also includes a unique tone. Our participants noted during the design process that existing mental health apps and treatment approaches overly emphasize illness, and as such, IDEO suggested an approach that focused on a more casual, friendly, nonstigmatizing tone. Examples include the overall "look" of the app, which feels like a mainstream social media app, rather than a clinical tool, and the language used in the automated responses to completed challenges (ie, "You're basically amazing. Way to rock that challenge!"). This approach is in line with the recovery model of psychosis, which emphasizes a collaborative, reinforcing and strengths-based approach [32,33]. The final design and screenshots of the PRIME app are shown in Figure 1.

Figure 1. Screenshots of the three primary features of PRIME (from left to right): Goals (goal-setting), Community (Text-based motivational coaching), and Moments (social networking and community feed).

Procedures: Using an Iterative Design Process to Improve PRIME Feasibility and Acceptability

Importantly, and unlike what occurs in traditional psychotherapy randomized control trials (RCTs), the PRIME development and evaluation process was iterative and consisted of two stages. In Stage 1, our first iteration, we enrolled 10 participants to evaluate initial feasibility and acceptability. The results from the first 10 participants were then used in Stage 2 to inform the next iteration of PRIME to be tested in a RCT, during which participants were randomized to either receive PRIME or a wait-list/treatment as usual control condition. Participants in both stages were encouraged to use the app daily with a minimum frequency of 1/week over a 12-week period. The same assessment schedule was used for both stages and included clinical evaluations at baseline, 12-weeks, and a 3-month follow-up assessment. Outcome evaluators in the RCT are blind to condition. The RCT is ongoing and as such, we only report the feasibility results of the Stage 1 participants and the first 10 randomized participants from Stage 2. Participants were compensated for their time to complete study-related assessments (US$20/hour), but were not paid for their participation in the intervention.

PRIME Protocol

Once participants completed their baseline assessments, participants were either provided with an Apple iPhone 5C with PRIME already installed or a study coordinator installed PRIME on their own personal iPhone. Participants initially met with an assigned "motivation coach" for a "set-up session." The purpose of the set up session is to orient participants to the app and to discuss goals the participant would like to achieve by using PRIME. The first time participants sign in to the app, they are guided through a process of creating a user profile. Participants create a user name, upload a profile picture, select their interests, goals, symptoms, and write a short bio. Goals and interests are categorized in the domains of health/wellness, social, productivity, and creativity. Participants are given the option to make their profile "private" or "public" to the PRIME community. If users select private, their peers will not be able to see their profile or posts to the community feed. However, coaches will be able to view their profile and posts in a Web-based "backoffice." Participants are informed of the privacy practices in the app and encouraged to be respectful of their peers' privacy.

Once the user is set up with his/her profile, the participant may select from prepopulated, personally tailored "daily challenges," associated with a participant's stated goals. For instance, if a participant endorsed "working out" as an interest and a goal of "feeling healthier," the participant will be shown a daily challenge of "Spend X number of minutes working out today." The participant may select the amount of time spent engaging in that daily challenge and set an alert to remind him/her to work on that particular daily challenge. Once a participant has completed their challenge, they have the option to post the goal achievement to the community or to their own private feed (also viewable to coaches in the backoffice). Participants are also encouraged to post spontaneous, positive moments in their life to encourage reinforcement of rewarding experiences. The daily challenge and spontaneous moments are displayed on the PRIME community feed and the participants' "My PRIME"

feed. Assigned coaches explain their role and immediately engage the user in a text-based chat about the participant's goals. For the Stage 1 participants, the coaches explained to their participants that they would reach out to them 1/week, but that the participants could message them at any time they would like help working on a goal or anything that might interfere with goal achievement. Based on use patterns and feedback from participants (reported below) the protocol was changed and coaches now explain that they will reach out to the user on "most days" (on average 4 days per week), but will modify the frequency depending on the user's preference, clinical issues, and degree of overall progress toward goal achievement. Participants are also shown the option to view their peers' profiles and shown how to message with them directly. Other opportunities for social interaction include "liking" or commenting on moments posted to the PRIME community feed.

PRIME Coach Training

The coaching staff currently consists of six Master's level clinicians who are experienced delivering CBT to patients in community practice settings. Coaches are trained over a 2-hour session using the PRIME treatment manual, which orients coaches to the clinical population, evidence-based approaches to managing symptoms, including CBT, psychoeducation, and mindfulness techniques, and suggested tone/approach to match the overall tone of the app. Due to the text-based modality of coaching, the manual discusses suggested adaptations, such as emphasizing more behavioral strategies during asynchronous interactions, delivering Web-based resources, such as short videos or websites providing psychoeducation about schizophrenia or other distressing symptoms, cognitive strategies, activity planning, and other behavioral suggestions. After an initial training, coaches "round" on their participants during a weekly meeting with the principal investigator and coaching team to review cases and troubleshoot potential challenges.

Participants

A total of twenty people (10 in the Stage 1 group and 10 in the Stage 2 group) met Diagnostic and Statistical Manual-IV-TR (American Psychiatric Association, 2000) criteria for a schizophrenia spectrum disorder: schizophrenia (n=13), schizophreniform (n=2), or schizoaffective disorder (n=5). Participants were recruited from the Early Psychosis Clinic at University of California, San Francisco as well as other community-based treatment providers in the San Francisco Bay Area. In addition to local recruitment, several participants (n=3) living outside of California were remotely enrolled from Texas, Maryland, and North Carolina. Participants were between the ages of 16 and 30 and in their early course of illness, defined as being within the first 5 years of formal diagnosis. In addition, participants had no history of neurological disorders or serious head trauma, were fluent in English, had an estimated intelligence quotient (IQ) > 70, and did not meet criteria for a substance dependence disorder within the past 6 months. Demographic information, such as age, years of education, as well as use of treatment resources (eg, therapy, psychiatric services) can be found in Table 1.

Table 1. Demographic and clinical characteristics.

	Stage 1 (n=10) Mean (SD)	Stage 2 (n=10) Mean (SD)	*t* or x^2 (*P*)
Age (years)	23.40 (2.6)	23.30 (3.7)	.95
n, (%) Male	8/10 (80%)	9/10 (90%)	.63
Education (years)	14.40 (1.6)	14.00 (1.9)	.62
Duration of Illness (months)	46.40 (20.3)	27.80 (16.5)	.04
Racial Background, n (%)			
Caucasian	3 (30%)	3 (30%)	.61
Asian	4 (40%)	2 (20%)	
African American	2 (20%)	2 (20%)	
Other	1 (10%)	3 (30%)	
n, % seeing therapist	6 (60%)	6 (60%)	.83
n, % seeing psychiatrist	4 (40%)	8 (80%)	.06
WTAR[a] FSIQ	106.90 (8.7)	108.90 (6.6)	.57
PANSS[b]			
Positive total	6.00 (2.8)	6.70 (4.3)	.75
Negative total	11.60 (6.6)	12.80 (6.6)	.67
Overall total	53.60 (12.9)	55.60 (12.2)	.69
RFS[c]			
Work Productivity	5.50 (1.5)	4.30 (1.7)	.11
Independent Living	6.00 (1.2)	5.20 (0.9)	.10
Social Networks	5.30 (1.9)	4.70 (1.6)	.46
Family	6.30 (.94)	6.250 (.53)	.57
QOL-A[d]	38.60 (11.2)	33.10 (9.1)	.25

[a]Wechsler Test of Adult Reading.

[b]Positive and Negative Syndrome Scale.

[c]Role Functioning Scale.

[d]Quality of Life Scale-Abbreviated.

Clinical and Interview-Based Assessment

Trained interviewers confirmed diagnoses using the Structured Clinical Interview for the Diagnostic and Statistical Manual-IV [34]. We assessed positive and negative symptoms using the positive and negative syndrome scale (PANSS) [35]. Functioning in the areas of work, self-care, family, and social was assessed with the role functioning scale (RFS) [36]. Quality of Life was assessed with the quality of life scale - abbreviated (QOL-A) [37]. See Table 1 for symptom, functioning, and quality of life characteristics. We estimated full-scale IQ with the Wechsler Test of Adult Reading (WTAR). For remote participants, the clinical and interview-based assessment was conducted via FaceTime or Skype.

Assessing PRIME Acceptability

We assessed PRIME acceptability during an exit interview where participants rated their satisfaction with the specific features of PRIME, such as the ability to interact with peers and the different goal categories, on a 1 (not at all) to 10 (very much) scale. We also assessed retention in the trial as a measure of acceptability.

Assessing PRIME Feasibility

To evaluate feasibility, we assessed the following: login frequency (average number of days logging in per week), average number of challenges completed (both overall and by individual challenge category), challenge completion percentage, and the average number of peer and coach interactions. Interactions included direct messaging on PRIME as well as commenting on and liking content posted to the community moments feed. To further understand how participants were engaging with the PRIME platform, we evaluated user metrics, such as active use (ie, while logged in, any type of interaction with coaches and/or peers, posting spontaneous or goal achievement moments) versus passive use (logging in, but not

engaging with peers or coaches or posting content onto the moments feed), the degree of social reciprocity (ie, initiating interactions and the ratio of initiated interactions to responsive interactions) from peer-to-peer and coach-to-peer interactions.

Data Analysis Plan

We examined whether any demographic variables were related to symptoms or functioning in the overall sample, and whether any demographic variables, symptoms, or functioning were related to PRIME use by conducting zero-order correlations. We also investigated any group differences (Stage 1 vs Stage 2) in demographic variables, symptoms, and functioning by conducting independent samples *t*-tests for continuous variables and chi-square tests for categorical variables. To examine initial acceptability of PRIME, we compared the average ratings for each group from the PRIME exit interview for overall satisfaction as well as the most and least popular PRIME features using independent samples *t*-tests. Furthermore, we also reviewed qualitative feedback from the PRIME exit interview.

To investigate initial feasibility of PRIME, we examined descriptive statistics for the following PRIME metrics: login frequency, challenges completed, peer and coach interactions, and active use rate. To understand participants use of PRIME on a daily basis, we computed a variable that represented how often participant's actively used PRIME, which we called the active use rate. To do this, we added together the average number of challenges completed, peer, and coach interactions and divided this total by the number of weeks the participant had access to PRIME. Thus, a value of 2.3 would mean that a participant was active on PRIME 2.3 times/week. Passive use was defined as logging into the app, but not posting a moment, completing a challenge or interacting with peers or coaches. Thus, a participant may login to the app 4 days/week, but actively engage with the features of the app 2 days/week.

In addition to examining the total number of coach and peer interactions, we also calculated the degree to which participants initiated interactions, relative to received interactions as an indicator of engagement. For instance, a ratio of 3:1 for peer-to-peer interactions would mean that for every three times a user sent a message, the peer received one message, which suggests that the user is more proactively engaging in interactions. For both PRIME acceptability and feasibility, we tested the effectiveness of our iterative design process by comparing the Stage 1 and Stage 2 participants using independent samples *t*-tests, correcting for multiple comparisons.

Results

Participant demographics are reported in Table 1. Participants in the Stage 1 group had a significantly longer duration of illness than the Stage 2 group. However, neither this nor any other demographic variable was related to symptoms or functioning in either group, nor were symptoms and functioning related to PRIME use in the two groups.

We also assessed participant digital health use (eg, health-related mobile app usage) over the past month. In terms of digital health resource usage, 75% (15/20) reported owning a smartphone. We then asked participants whether they used digital health apps in their daily lives. Overall, participants reported low levels of digital health use, with the most used applications falling in the categories of increasing exercise and fitness (5/20, 25%), improving relaxation (3/20, 15%), and improving mood (2/20, 10%). Only one of the 20 participants reported using digital health resources for managing weight or alcohol use. In comparison, 95% (19/20), reported using a social media platform (e.g. Facebook, Twitter), with 50% (10/20) also using social media for sharing photos and music. Participants in Stage 1 reported using social media apps daily and participants in Stage 2 reported social media use "more days than not."

PRIME Acceptability

To date, all of the participants were retained in the trial. Mean overall satisfaction with PRIME for the entire sample, as rated during the exit interview administered at the 12-week post-assessment, was 8.00 (standard deviation (SD): 2.0). The difference between the two groups was not significant (Stage 1: mean: 7.25, SD: 2.3; Stage 2: mean: 8.86, SD: 1.2). Some of the comments made by participants when asked about how PRIME influenced their lives included:

> *There's nothing like it out there*
>
> *It was a good chance to be more social, meet other people, and see what they're like.*
>
> *Definitely getting to do more, not chores, but be more active. Motivation to do more stuff, achieve more goals, and be more social.*

The most popular PRIME features for both groups were the ability to comment on other user's posts (mean: 8.53, SD: 1.9) and the least popular PRIME feature was the ability to view coach profiles (mean: 7.33, SD: 2.7).

PRIME Feasibility

PRIME use data (login frequency, challenge completion, and interactions) for the participants in both stages are shown in Table 2. Overall, participants logged into PRIME approximately every other day, with the Stage 2 sample logging in at a slightly higher frequency. Over a 12-week period, participants were highly engaged in the platform, with 177 direct messages sent from participants to coaches in the Stage 1 sample and 955 sent from participants to coaches in the Stage 2 sample (P=.04; d=1.02). In terms of peer-to-peer interactions, participants initiated interactions with each other 97 times in the Stage 1 sample and 151 times in the Stage 2 sample (P=.49, d=.23).

Table 2. PRIME usage data for the overall sample as well as both the Stage 1 and Stage 2 groups.

	Stage 1	Stage 2	
	Mean (SD)	Mean (SD)	*p*, *d* [95% CI]
Login frequency (average logins per week)	3.51 (1.8)	4.69 (1.4)	.13, .73 [-.20. to 1.60]
Challenge completion rate (%)	84.48 (18.4)	85.35 (15.3)	.91, .05 [-.83 to .93]
Average number of user-initiated peer interactions			
Comments	7.70 (6.4)	9.50 (10.1)	.68, .21 [-.67 to 1.08]
Likes	11.80 (11.9)	24.00 (20.6)	.12, .73 [-.21 to 1.60]
Messages	9.70 (8.8)	15.10 (22.5)	.49, .32 [-.58 to 1.18]
Total	29.20 (21.1)	48.60 (44.3)	.23, .56 [-.36 to 1.43]
Average number of user-initiated coach interactions			
Comments	7.80 (7.0)	12.90 (14.5)	.33, .45 [-.46 to 1.32]
Likes	4.40 (4.9)	10.00 (12.3)	.20, .60 [-.06 to 1.47]
Messages	17.70 (22.9)	95.50 (105.8)	**.04**[a], 1.02 [.05 to 1.90]
Total	29.90 (31.6)	118.40 (105.9)	**.02**, 1.13 [.15 to 2.02]
Challenges completed			
Overall	18.40 (14.5)	20.40 (18.2)	.79, .12 [-.76 to .99]
Health/wellness	6.80 (5.7)	7.80 (9.1)	.77, .10 [-1.47 to .49]
Social	3.20 (1.8)	4.40 (3.9)	.39, .40 [-.51 to 1.26]
Creativity	4.50 (4.7)	4.40 (3.7)	.96, -.02 [-.85 to .90]
Productivity	3.90 (5.7)	3.80 (3.6)	.95, -.02 [-.86 to .90]
Active engagement rate (average times active per week)	3.87 (2.7)	11.17 (9.4)	**.03**, 1.06 [.08 to 1.94]

[a]Bold Values indicate statistically significant results.

Participants in both groups completed an average of approximately 1.5 challenges per week, with the Stage 1 sample completing slightly more than the Stage 2 sample. For both groups, health/wellness challenges were the most popular at approximately one challenge completed per week, followed by creativity challenges, social challenges, and productivity challenges of which participants completed approximately 1 every 2 weeks. Challenge completion percentage was high for both groups (>16/20, 80%), suggesting that participants had little difficulty completing the challenges that they set. Participants had approximately two interactions with coaches and two interactions with peers each week. Participants in the Stage 2 sample tended to have more interactions with coaches and peers than those in the pilot group. The Stage 1 group, on average, was active on PRIME approximately 4 times/week. This rate almost tripled for the Stage 2 group at a little over 11 times/week (see Table 2). The degree to which participants reciprocated interactions initiated by a peer or coach user is shown in Table 3. The ratios reflect a higher degree of reciprocity in peer interactions than coach interactions. Yet, the Stage 2 participants were much more responsive to coach interactions than the Stage 1 participants (see below for a description of the change in the coaching strategy). Real examples of peer to peer and coach to peer interactions are shown in Textboxes 1 and .

Textbox 1. Examples of peer to peer interactions.

John: Hey the doctors said I should connect with you because you have some good insights about the diagnosis. What do you think about it?

David: Hey bud, sorry about the delayed response. Thanks for reaching out. I think this disease is definitely a huge challenge that we all sort of have to face. But I think its a type of challenge that can be overcome. When I first got the diagnosis, I was a wreck. Depression as well as an onslaught of negative symptoms... I think it's important to slowly get ur life back together step by step. As u progress, u will realize things really are not all that bad and that this disease is just one of the bumps in life that u will have to overcome.

John: I agree, it's just another challenge. How do you deal with your negative symptoms?

David: It takes time. Therapy helped. Also a goal orientated attitude is important. Gotta realize that u r no different than someone without the disorder after proper medical treatment.

Textbox 2. Examples of and coach to peer interactions.

Coach: Hey [participant's name]! I noticed you haven't completed any challenges or posted any moments recently. What have you been up to?

Participant: Playing video games. I haven't been up to it lately. Is there a way I can fight through this? Laziness or whatever it's called? How do you complete your goals in life? I feel stagnant more depressed and less motivated. I feel like this because I have low self esteem. So I play video games to distract myself and get lost. Doing much seems unrealistic.

Coach: I'm sorry to hear that you haven't been feeling great recently. Feeling blue happens to us all from time to time, and luckily there are some ways to combat feeling this way. One thing that might help is trying to be active. I know it's hard when you feel this way, but even something as simple as going for a walk can help. When you feel this way, do you notice that you are having negative thoughts as well?

Participant: Yeah ok Coach thank you. I love being active, working out, cleaning, walking my dogs, doing hw, cooking. These things help me focus.

Coach: Do you notice feeling different? Sometimes it helps to take a strep back and realize all that you have accomplished. You have worked very hard over the past 2 months and have made good progress. I am proud of you and hope that you feel proud as well.

Participant: Thank you so much you are right I have!!! I feel like I'm not going to be so harsh on my self and I feel like being more active!

Coach: Self-compassion is important as being too hard on yourself can make you feel down. Next time you think you are being hard on yourself, try writing down some things you recently accomplished. Or, you can write down evidence for and against the thoughts you are having. I have used both approaches and they both work!

Participant: Okay thank you so much. I'm going to try and write down some recent accomplishments and find evidence against being too hard on myself.

Coach: Great to hear! Let me know how it works. Maybe you can complete a challenge this weekend.

Iterative Design Process Results: Shifting the Coaching Strategy and Tone

The feasibility and acceptability results from the Stage 1 participants, reported above, for the most part demonstrated that the intervention was well tolerated, yet feedback from individual participants coupled with an examination of their use patterns suggested we should modify our approach to motivation coaching. For instance, one participant felt that it seemed that the coaches were working "off of a script," which made it hard for her to connect with her coach, stating:

> *It felt like every time [my coach] posted something, she was fitting me inside this box. Instead of having a normal conversation like "Hey what's up, how are midterms", they followed a script.*

Still, others found the coaching to be very helpful, with one participant stating:

> *It was great! I think the coaches were very, very, very supportive and they did as much as they could to help me participate and be active in the community. They helped me manage my stress and take on everyday life and they did a good job.*

Another key observation during the first iteration was the low response rate to coach initiated interactions (Table 3), with less than half of the messages sent by coaches receiving a response from participants. The ratio of coach to participant responses was 12:1 for the pilot participants. This led to the following changes in Stage 2: (1) we increased the frequency of the interactions initiated by motivation coaches from once a week to an initial 5 days/week followed by a decreased frequency over time, based on the preference of the participant and their clinical needs, (2) decreased the amount of content in each message, and (3) personalized the messages and adopted a more casual tone that reflected the tone recommendations by IDEO. For example, instead of sending a lengthy, once per week message, coaches would instead send a brief message most days per week, checking in with their participant (eg, "Hi there! I'd love to see you work on your goal to exercise more. How about going for a walk today?"). By initiating almost daily contact, we sought to increase overall engagement with PRIME and to facilitate more frequent interactions with coaches and among peers. By decreasing the amount of content in each message, we aimed to reduce the cognitive load for participants and make it easier to respond to messages. The data suggest that this change may have led to increased engagement as evidenced by a 2- to 3-fold increase in the following usage patterns between Stage 1 and Stage 2: number of logins (3.51 days/week to 4.69 days/week), overall peer and coach interactions (peers: from 29.20-48.60 (P=.23, d=.56); coaches: from 29.90-118.40 (P=.02; d=1.13)), active use rate (~4 times/week to ~11 times/week; see Table 2), and the degree of coaching interaction reciprocity (Table 3).

Table 3. Initiated to received coaching and peer interaction rate for Stage 1 and Stage 2 groups.

	Stage 1 Mean	Stage 2 Mean	*P*, *d* [95% CI]
Coach interaction (ratio of interactions initiated by coaches to received)			
Comments	10.88:1	8.16:1	44, -.37 [-1.24 to.53]
Like	44.40:1	24.17:1	.19, .-.65 [-1.52 to .27]
Messages	5.17:1	1.87:1	.07, -.87 [-1.75 to .08]
Overall	12.23:1	3.37:1	.01[a], -1.35 [-2.26 to -.33]
Peer interaction (ratio of interactions initiated by peers to received)			
Comments	1.68 : 1	1.89 : 1	.81, .12 [-.77 to .99]
Like	2.06 : 1	0.98 : 1	.42, -.41 [-1.28 to .49]
Messages	1.10 : 1	1.03 : 1	.65, -.20 [-1.07 to .69]
Overall	1.17 : 1	1.25 : 1	.84, .10 [-.78 to .97]

[a]Statistically significant result.

Discussion

Principal Findings

The results from this study demonstrated that the cognitive neuroscience-informed mobile app, PRIME, is a feasible and acceptable intervention for young people with schizophrenia**.** Over 70% (14/20) of our participants reported owning a smartphone and 95% (19/20) reported using social media, suggesting that using a smartphone-based, social networking platform to deliver an intervention would be an acceptable treatment modality for this population. The overall satisfaction with PRIME was relatively high, as reflected in the satisfaction ratings endorsed in the exit interview as well as the current 100% (20/20) study retention rate. The PRIME use data demonstrated a high degree of engagement with this digital treatment platform. Participants used the app, on average, every other day, and were actively engaged with its various features each time they logged in. Qualitative feedback from participants was overall positive, and the critiques of the platform during Stage 1 were used to guide refinements for Stage 2 (ie, the coaching strategy). A common theme in the feedback from participants was the positive experience of social support from coaches and their peers. This was also reflected in the total number and frequency of interactions and degree of reciprocity the participants exhibited with their coaches and peers. The quality of the interactions, as reflected in the provided examples, was also impressive given the entirely text-based messaging format.

The increase in various metrics of engagement between Stage 1 and Stage 2 participants, suggests that the integration of user feedback to influence the refinement of the intervention was successful. The changes we made in response to this user-centered, iterative approach led to a 2- to 3-fold increase from Stage 1 to Stage 2 in use of the app (ie, logins), greater active use (engagement with features), a significantly greater number of social interactions with peers and coaches and improved ratios of reciprocal interactions with coaching. While the changes we made were focused on the text-based coaching, these simple changes appeared to generalize to greater engagement in almost every aspect of the platform. Taken together, this suggests that the development of mobile digital interventions should continuously incorporate user feedback and adopt refinements to meet the needs of the population. This is in line with conclusions from the Agency for Healthcare Quality Improvement, which recently highlighted that the success of new technology-based interventions hinges on incorporating user feedback in design and implementation [38].

Limitations

This study has several limitations. First, our sample size is relatively small, which limits the generalizability of the results. However, the tradeoff for using a small sample size in Stage 1 was that we were able to very quickly evaluate the feasibility of the app and refine the platform for use in Stage 2. Another limitation of this feasibility study is that our participants were all in the early phase of schizophrenia and therefore the results of the study are likely not representative of the larger population of those with persistent schizophrenia. We decided to focus on designing the intervention to treat young patients early in their course of illness based on numerous findings promoting the benefits of early intervention [39,40]. By designing an intervention specifically for use with this population we are aiming to significantly improve the course of illness by improving functional outcome during a critical period.

Conclusions

With the proliferation of digital technology-based interventions to address mental health issues, it is encouraging to learn that a mobile app-based treatment is feasible, tolerable, and acceptable to young people with schizophrenia. Indeed, several other research groups have developed novel digital technologies to improve outcome for individuals with schizophrenia, often emphasizing CBT approaches for positive symptoms and focusing on people with persistent illness [29,41]. In addition, the existing digital treatment tools have not been developed with an explicit cognitive neuroscience rationale, have not focused on the needs of recent onset individuals, and have not included a social network with peers or mental health coaches

[21]. The results of our feasibility study seem to suggest that the delivery of a smartphone mobile app intervention that includes several opportunities for social engagement and to share goal achievements within a recovery-oriented framework is a desired treatment modality for young people with schizophrenia. The goal of our ongoing RCT will be to explicitly examine the degree to which the focus on targeting reward processing impairments and enhancing motivated behavior will lead to improved functional outcome in this population.

Conflicts of Interest

None declared.

References

1. Harvey PD. Validating the measurement of real-world functional outcomes: phase I results of the VALERO study. Am J Psychiatry 2011:1195-1201. [doi: 10.1176/appi.ajp.2011.10121723]
2. Saarni SI, Viertiö S, Perälä J, Koskinen S, Lönnqvist J, Suvisaari J. Quality of life of people with schizophrenia, bipolar disorder and other psychotic disorders. Br J Psychiatry 2010;197:386-394 [FREE Full text] [doi: 10.1192/bjp.bp.109.076489] [Medline: 21037216]
3. Fervaha G, Foussias G, Agid O, Remington G. Motivational deficits in early schizophrenia: prevalent, persistent, and key determinants of functional outcome. Schizophr Res 2015 Aug;166:9-16. [doi: 10.1016/j.schres.2015.04.040] [Medline: 25982811]
4. Foussias G, Remington G. Negative symptoms in schizophrenia: avolition and Occam's razor. Schizophr Bull 2010;36:359-369 [FREE Full text] [doi: 10.1093/schbul/sbn094] [Medline: 18644851]
5. Barch D, Dowd EC. Goal representations and motivational drive in schizophrenia: the role of prefrontal-striatal interactions. Schizophr Bull 2010;36:919-934 [FREE Full text] [doi: 10.1093/schbul/sbq068] [Medline: 20566491]
6. Barch D, Treadway MT, Schoen N. Effort, anhedonia, and function in schizophrenia: reduced effort allocation predicts amotivation and functional impairment. J Abnorm Psychol 2014;123:387-397 [FREE Full text] [doi: 10.1037/a0036299] [Medline: 24886012]
7. Gold J, Waltz JA, Matveeva TM, Kasanova Z, Strauss GP, Herbener ES, et al. Negative symptoms and the failure to represent the expected reward value of actions: behavioral and computational modeling evidence. Arch Gen Psychiatry 2012;69:129-138 [FREE Full text] [doi: 10.1001/archgenpsychiatry.2011.1269] [Medline: 22310503]
8. Gold J, Waltz JA, Prentice KJ, Morris SE, Heerey EA. Reward processing in schizophrenia: a deficit in the representation of value. Schizophr Bull 2008;34:835-847 [FREE Full text] [doi: 10.1093/schbul/sbn068] [Medline: 18591195]
9. Cohen A, Minor KS. Emotional experience in patients with schizophrenia revisited: meta-analysis of laboratory studies. Schizophr Bull 2010;36:143-150 [FREE Full text] [doi: 10.1093/schbul/sbn061] [Medline: 18562345]
10. Kring A, Barch DM. The motivation and pleasure dimension of negative symptoms: neural substrates and behavioral outputs. Eur Neuropsychopharmacol 2014;24:725-736 [FREE Full text] [doi: 10.1016/j.euroneuro.2013.06.007] [Medline: 24461724]
11. Oorschot M, Lataster T, Thewissen V, Lardinois M, Wichers M, van OJ, et al. Emotional experience in negative symptoms of schizophrenia--no evidence for a generalized hedonic deficit. Schizophr Bull 2013;39:217-225 [FREE Full text] [doi: 10.1093/schbul/sbr137] [Medline: 22021660]
12. Velthorst E, Koeter M, van der Gaag M, Nieman DH, Fett AJ, Smit F, et al. Adapted cognitive-behavioural therapy required for targeting negative symptoms in schizophrenia: meta-analysis and meta-regression. Psychol Med 2015;45:453-465. [doi: 10.1017/S0033291714001147] [Medline: 24993642]
13. Wykes T, Steel C, Everitt B, Tarrier N. Cognitive behavior therapy for schizophrenia: effect sizes, clinical models, and methodological rigor. Schizophr Bull 2008;34:523-537 [FREE Full text] [doi: 10.1093/schbul/sbm114] [Medline: 17962231]
14. Sarkar S, Hillner K, Velligan DI. Conceptualization and treatment of negative symptoms in schizophrenia. World J Psychiatry 2015;5:352-361 [FREE Full text] [doi: 10.5498/wjp.v5.i4.352] [Medline: 26740926]
15. Draper M, Stutes DS, Maples NJ, Velligan DI. Cognitive adaptation training for outpatients with schizophrenia. J Clin Psychol 2009;65:842-853. [doi: 10.1002/jclp.20612] [Medline: 19521972]
16. Velligan D, Diamond PM, Maples NJ, Mintz J, Li X, Glahn DC, et al. Comparing the efficacy of interventions that use environmental supports to improve outcomes in patients with schizophrenia. Schizophr Res 2008;102:312-319 [FREE Full text] [doi: 10.1016/j.schres.2008.02.005] [Medline: 18374542]
17. Velligan D, Diamond PM, Mintz J, Maples N, Li X, Zeber J, et al. The use of individually tailored environmental supports to improve medication adherence and outcomes in schizophrenia. Schizophr Bull 2008;34:483-493 [FREE Full text] [doi: 10.1093/schbul/sbm111] [Medline: 17932089]
18. Velligan D, Roberts D, Mintz J, Maples N, Li X, Medellin E, et al. A randomized pilot study of MOtiVation and Enhancement (MOVE) Training for negative symptoms in schizophrenia. Schizophr Res 2015;165:175-180. [doi: 10.1016/j.schres.2015.04.008] [Medline: 25937461]

19. Velligan D, Bow-Thomas CC, Huntzinger C, Ritch J, Ledbetter N, Prihoda TJ, et al. Randomized controlled trial of the use of compensatory strategies to enhance adaptive functioning in outpatients with schizophrenia. Am J Psychiatry 2000;157:1317-1323. [doi: 10.1176/appi.ajp.157.8.1317] [Medline: 10910797]
20. Ben-Zeev D, Brenner CJ, Begale M, Duffecy J, Mohr DC, Mueser KT. Feasibility, acceptability, and preliminary efficacy of a smartphone intervention for schizophrenia. Schizophr Bull 2014;40:1244-1253 [FREE Full text] [doi: 10.1093/schbul/sbu033] [Medline: 24609454]
21. Firth J, Torous J. Smartphone apps for schizophrenia: a systematic review. JMIR Mhealth Uhealth 2015;3:e102 [FREE Full text] [doi: 10.2196/mhealth.4930] [Medline: 26546039]
22. De Vito Dabbs A, Myers BA, Mc Curry KR, Dunbar-Jacob J, Hawkins RP, Begey A, et al. User-centered design and interactive health technologies for patients. Comput Inform Nurs 2009;27:175-183 [FREE Full text] [doi: 10.1097/NCN.0b013e31819f7c7c] [Medline: 19411947]
23. McCurdie T, Taneva S, Casselman M, Yeung M, McDaniel C, Ho W, et al. mHealth consumer apps: the case for user-centered design. Biomed Instrum Technol 2012;Suppl:49-56. [doi: 10.2345/0899-8205-46.s2.49] [Medline: 23039777]
24. Deci E, Ryan R. Intrinsic Motivation and Self-Determination in Human Behavior. New York: Plenum; 1985.
25. Gard D, Sanchez AH, Starr J, Cooper S, Fisher M, Rowlands A, et al. Using self-determination theory to understand motivation deficits in schizophrenia: the 'why' of motivated behavior. Schizophr Res 2014;156:217-222 [FREE Full text] [doi: 10.1016/j.schres.2014.04.027] [Medline: 24853060]
26. Vancampfort D, De Hert M, Vansteenkiste M, De Herdt A, Scheewe TW, Soundy A, et al. The importance of self-determined motivation towards physical activity in patients with schizophrenia. Psychiatry Res 2013;210:812-818. [doi: 10.1016/j.psychres.2013.10.004] [Medline: 24182688]
27. Wellner LJ, Kirks DR, Merten DF, Armstrong BE. Large opaque hemithorax due to cardiomegaly and atelectasis. South Med J 1985;78:805-809. [Medline: 3160119]
28. Dauwan M, Begemann MJH, Heringa SM, Sommer IE. Exercise improves clinical symptoms, quality of life, global functioning, and depression in schizophrenia: a systematic review and meta-analysis. Schizophr Bull 2015. [doi: 10.1093/schbul/sbv164] [Medline: 26547223]
29. Rosenbaum S, Tiedemann A, Sherrington C, Curtis J, Ward PB. Physical activity interventions for people with mental illness: a systematic review and meta-analysis. J Clin Psychiatry 2014;75:964-974. [doi: 10.4088/JCP.13r08765] [Medline: 24813261]
30. Siegrist K, Millier A, Amri I, Aballéa S, Toumi M. Association between social contact frequency and negative symptoms, psychosocial functioning and quality of life in patients with schizophrenia. Psychiatry Res 2015;230:860-866 [FREE Full text] [doi: 10.1016/j.psychres.2015.11.039] [Medline: 26626950]
31. Flaherty AW. Brain illness and creativity: mechanisms and treatment risks. Can J Psychiatry 2011;56:132-143. [Medline: 21443820]
32. Charzynska K, Kucharska K, Mortimer A. Does employment promote the process of recovery from schizophrenia? A review of the existing evidence. Int J Occup Med Environ Health 2015;28:407-418 [FREE Full text] [doi: 10.13075/ijomeh.1896.00341] [Medline: 26190722]
33. Frese F, Knight EL, Saks E. Recovery from schizophrenia: with views of psychiatrists, psychologists, and others diagnosed with this disorder. Schizophr Bull 2009;35:370-380 [FREE Full text] [doi: 10.1093/schbul/sbn175] [Medline: 19304812]
34. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV-TR Axis 1 Disorders, Research Version, Patient Edition. (SCID-I/P). New York State Psychiatric Institute: Biometrics Research; 2002.
35. Kay S, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261-276 [FREE Full text] [Medline: 3616518]
36. McPheeters HL. Statewide mental health outcome evaluation: a perspective of two southern states. Community Ment Health J 1984;20:44-55. [Medline: 6723258]
37. Bilker W, Brensinger C, Kurtz MM, Kohler C, Gur RC, Siegel SJ, et al. Development of an abbreviated schizophrenia quality of life scale using a new method. Neuropsychopharmacology 2003;28:773-777 [FREE Full text] [doi: 10.1038/sj.npp.1300093] [Medline: 12655324]
38. Agarwal R, Anderson C, Crowley K, Kannan P. HHSA. 0023. Understanding Development Methods From Other Industries to Improve the Design of Consumer Health IT: Background Report. (Prepared by Westat, under Contract No URL: https://healthit.ahrq.gov/sites/default/files/docs/citation/background_report_final.pdf [accessed 2016-04-12] [WebCite Cache ID 6gkUeVSJd]
39. Nordentoft M, Jeppesen P, Petersen L, Bertelsen M, Thorup A. The rationale for early intervention in schizophrenia and related disorders. Early Interv Psychiatry 2009;3 Suppl 1:S3-S7. [doi: 10.1111/j.1751-7893.2009.00123.x] [Medline: 21352194]
40. Bertolote J, McGorry P. Early intervention and recovery for young people with early psychosis: consensus statement. Br J Psychiatry Suppl 2005;48:S116-S119. [doi: 10.1192/bjp.187.48.s116] [Medline: 16055800]
41. Rotondi AJ, Anderson CM, Haas GL, Eack SM, Spring MB, Ganguli R, et al. Web-based psychoeducational intervention for persons with schizophrenia and their supporters: one-year outcomes. Psychiatr Serv 2010;61:1099-1105. [doi: 10.1176/ps.2010.61.11.1099] [Medline: 21041348]

Abbreviations

CBT: cognitive behavioral therapy
IQ: intelligence quotient
PANSS: positive and negative syndrome scale
PRIME: personalized real-time intervention for motivation enhancement
QOL-A: quality of life scale – abbreviated
RCT: randomized control trials
RFS: role functioning scale
SD: standard deviation
SDT: self-determination theory
SMS: short message service
UCD: user-centered design
WTAR: Wechsler test of adult reading

Edited by G Eysenbach; submitted 16.12.15; peer-reviewed by K Woodberry, D Ben-Zeev; comments to author 31.12.15; revised version received 26.02.16; accepted 18.03.16; published 28.04.16.

Please cite as:
Schlosser D, Campellone T, Kim D, Truong B, Vergani S, Ward C, Vinogradov S
Feasibility of PRIME: A Cognitive Neuroscience-Informed Mobile App Intervention to Enhance Motivated Behavior and Improve Quality of Life in Recent Onset Schizophrenia
JMIR Res Protoc 2016;5(2):e77
URL: http://www.researchprotocols.org/2016/2/e77/
doi:10.2196/resprot.5450
PMID:27125771

Original Paper

Development of 'Twazon': An Arabic App for Weight Loss

Aroub Alnasser[1], MSc; Arjuna Sathiaseelan[2], PhD; Abdulrahman Al-Khalifa[3], Prof; Debbi Marais[4], PhD

[1]Food Science and Nutrition, King Saud University, SA, Applied Health Sciences, University of Aberdeen,, Food Science and Nutrition, Applied Health Sciences,, King Saud University, University of Aberdeen., Riyadh, Saudi Arabia

[2]The Computer Laboratory, University of Cambridge, Cambridge, United Kingdom

[3]King Saud University, Riyadh, Saudi Arabia

[4]Applied Health Sciences, University of Aberdeen, Applied Health Sciences,, University of Aberdeen, Aberdeen, United Kingdom

Corresponding Author:
Aroub Alnasser, MSc
Food Science and Nutrition, King Saud University, SA, Applied Health Sciences, University of Aberdeen,
King Saud University, University of Aberdeen
P.O. Box 86683
Riyadh, 11632
Saudi Arabia
Phone: 966 118056476
Fax: 966 114678394
Email: aroub@ksu.edu.sa

Abstract

Background: Weight gain and its related illnesses have become a major public health issue across the world, with Saudi Arabia and other Gulf countries seeing dramatic increases in obesity and overweight, and yet there is very little information on how to intervene with this demographic due to cultural and linguistic barriers. As the use of smartphones and apps has also increased in the region, information communication technologies could be a cost-effective means of facilitating the delivery of behavior-modification interventions directly to the target population. Although there are existing apps that offer lifestyle-modification tools, they do not give consideration to the evidence-based practices for weight management. This offers an opportunity to create an Arabic language weight loss app that offers localized content and adheres to evidence-informed practices that are needed for effective weight loss.

Objective: This paper describes the process of developing an Arabic weight loss app designed to facilitate the modification of key nutritional and physical activity behaviors among Saudi adults, while taking into consideration cultural norms.

Methods: The development of the Twazon app involved: (1) reviewing all available Arabic weight loss apps and compared with evidence-based practices for weight loss, (2) conducting a qualitative study with overweight and obese Saudi women to ascertain their preferences, (3) selecting which behavioral change strategies and guidelines to be used in the app, (4) creating the Saudi Food Database, (5) deciding on graphic design for both iPhone operating system and Android platforms, including user interface, relational database, and programming code, and (6) testing the beta version of the app with health professionals and potential users.

Results: The Twazon app took 23 months to develop and included the compilation of an original Saudi Food database. Eight subjects gave feedback regarding the content validity and usability of the app and its features during a pilot study. The predominant issue among the group was the lack of information explaining how to use the app. This has since been resolved through the implementation of a tutorial. No other changes were required to be made.

Conclusions: Information communication technologies, such as smartphone apps, may be an effective tool for facilitating the modification of unhealthy lifestyle habits in Saudi; however, consideration must be given to the target population, cultural norms, and changing trends in the global market. The effectiveness of the app will be better determined during a 6-month intervention with 200 overweight and obese Saudi women.

(JMIR Res Protoc 2016;5(2):e76) doi:10.2196/resprot.5497

KEYWORDS

weight loss; smartphone; mobile apps; Arabic; obesity

Introduction

Obesity and overweight in the Saudi adult population has increased dramatically for both men and women, respectively; however, due to the cultural limitations and inaccessibility to physical activity, there is a predominant effect on the female population. Recent studies show that the rate of obesity and overweight in women has increased from 26.6% in the mid-1990's to 33.3% in a national survey conducted in 2013 [1,2]. This is supported by the World Health Organization's report published in 2014, which indicates that obesity has increased worldwide by more than 50% since 1980. This worldwide increase, paired with the statistical increase in Gulf countries, makes the prevalence of obesity a major public health issue in Saudi Arabia [3,4].

Certain local issues have contributed to the current and projected increase in the prevalence of overweight and obesity. These include aspects such as climate making it substantially harder to be physically fit [5], and the growing popularity of western fast foods resulting in a change in diet [6]. Additionally, the lack of nutritional and proportional information for regional dishes makes it difficult for locals to identify caloric content of meals [7]. Furthermore, cultural aspects relating to the status of women may also contribute to the higher prevalence of overweight and obesity in women specifically. These include high birth rate, and cultural restrictions that require women to stay inside the home, be accompanied by a male to go outside, and seek permission from family members to engage in physical activity [8]. Currently, the most popular method to lose weight among Saudi is gastric and bariatric surgery, as it is considered to be the fastest and most effortless method regardless of the risks associated with it [9].

Smartphone and app usage has shown exponential growth in Saudi Arabia in recent years ranking it third in smartphone usage in the world [10], with a penetration rate of 73% as of 2014 [11]. Saudi Arabia also has the highest-ranking Twitter usage in the world [12]. Cultural restrictions make it easier, for women especially, to express themselves socially and publically in a virtual environment through the use of smartphone technology. There is evidence that women are using websites and apps such as Instagram, Facebook, and Twitter to initiate home-based businesses [13] and participate in social solidarity [14].

The increasing ubiquity of these technologies therefore created an opportunity for the development of an Arabic app to be used as an appropriate tool to treat and prevent obesity in this population. To inform this development, two important aspects were investigated. First, Saudi Arabian women were consulted about their use and needs for a weight loss app [15]. Although women in Saudi Arabia reported using weight loss apps, they highlighted language barriers and cultural insensitivity, making recommendations for the development of a culturally sensitive Arabic weight loss app [15]. Second, it was important to ascertain whether there were any effective weight loss apps already available, specifically Arabic apps as recommended by the Saudi women. Although there was evidence available that English apps [16,17] fail to comply with evidence-informed practices for weight management, there was a paucity of evidence for Arabic apps. Screening of Arabic weight loss apps confirmed that they also did not comply with evidence-informed practices for weight management [18]. The development of an Arabic weight loss app including evidence-informed practices for weight management was therefore justified.

This article sets out to elaborate on the steps taken in the development of the Twazon app and tools included, the challenges that were faced, and the insights gleaned from the process.

Methods

Description of 'Twazon'

The Arabic name, Twazon, means balance, which refers to the balance of dietary intake compared with energy expended through physical activity. The name and logo were developed through consultation with the community, including participants from the initial focus group discussions.

The use of the app begins with membership and social networking features. The user is required to complete a "5-step" registration process that allows them to use their email, Facebook, or Twitter accounts when signing in or out of their Twazon account. The process begins with the input of basic, required information such as name/nickname, gender, age, height, current weight, waist circumference, current health status, pre-existing diseases, and physical activity status. After submitting this information, the app provides the user with their ideal weight goal and the date by which this weight can be achieved by reducing the user's daily caloric intake by 600 [19]. An optional tutorial presents the user with instructions on how to use the app.

There are many different theories that guide health promotion interventions. The social cognitive theory [20] forms the theoretical base of this application as it considers the importance of the social system in relation to the behavior of the individual, as well at the value of self-efficacy and self-regulation. It is considered a dynamic interaction between personal factors, behavior, and environment and confirms the importance of observational learning, which is based on observing others' experience or results [20].

The Twazon app includes various tools to address evidence-informed practices for weight loss interventions as identified and used for screening of Arabic apps [16] (Table 1), and based on recommendations provided during the focus group discussions with overweight and obese Saudi women [15].

Table 1. Tools in Twazon addressing evidence-informed weight loss practices.

Practice	App Information
Weight assessment and goal setting	Assesses weight by calculating body mass index and waist circumference
	Allows users to set their ideal weight, and sets a target date for achieving the weight loss goal
	Calculates the number of calories needed daily based on their target weight
	Recommends a decrease of at least 600 calories consumed per day in order to achieve weight loss goal
Healthy diet	Recommends daily servings/portions of all foods and beverages, including 6 cups of water per day
	Recommendations given according to healthy lifestyle self-assessment score
	Provides a customized healthy food palm based on the user's intake report
	Recommends the reading of labels and describes how to properly read labels
	Offers some suggestions for healthy food options in place of unhealthy food items.
	Allows users to correct a poor meal/diet as an education tool for menu planning
	Tips will be sent if the intake/activity ratio is off-balance according to healthy lifestyle self-assessment score
Physical activity	Recommends a minimum of 30 minutes of physical activity three times a week and allows users to assess their physical activity every 2 weeks
	Tips will be sent if the amount of physical activity is low
	Recommends taking at least 10,000 steps and provides a pedometer that tracks the daily number of steps
Self-monitoring	Allows users to track their daily food (calories) and water intake, and number of servings per food group, every 2 weeks
	Allows users to self-assess their physical activity, every 2 weeks
	Provides a weight loss tracker that informs user of current weight loss toward their goal weight (kg)
Social support	Provides an app-specific message board allowing users to privately share experiences, weight loss goals achieved, and photos with other users
	Allows users access to social networking services such as Twitter

Evidence-Informed Weight Loss Practices

Weight Assessment and Goal Setting

Users will be able to assess their current weight goals by providing physical and lifestyle information. The app calculates the current body mass index and ideal body weight based on the formula from Lemmens et al [21]. The app will provide a realistic goals setting feature with a target weight loss of 0.5 to 1 kg (1-2 lb) a week [19] and will encourage modest loss of initial weight (5%-10%) as it is significantly correlated with meaningful changes in chronic disease risk [22]. The app will calculate the duration (days) required for the weight loss, enabling users to set appropriate and realistic goals. The app will also provide a daily caloric intake goal by calculating the daily calories needed based on the ideal weight with a recommended daily decrease of 600 calories less than current consumption.

Healthy Diet

The app also includes a healthy lifestyle self-assessment score. Users will be prompted to complete the self-assessment every 2 weeks to track their level of achievement. As several studies have shown that there is a link between increasing consumption of a Mediterranean diet and lowering obesity rate [23,24], this self-assessment tool was developed using the Mediterranean diet assessment tool [25], however the alcohol question was excluded as alcohol intake is forbidden in the Saudi culture. Four additional questions were included based on the Saudi Healthy Food Palm guide [26] (Figure 1).

The additional questions cover aspects of dairy and whole grain consumption as well as daily physical activity. The healthy lifestyle self-assessment is therefore scored out of 17 and each question is linked to the relevant part of the Healthy Food Palm. Each question asks for the level of intake of a specific food/food group and this response is then used to calculate whether this is within the recommended levels or not (Textbox 1).

Textbox 1. Lifestyle self-assessment questions

Vegetables:

- Are ≥2 servings (of 200 g each) of vegetables eaten each day?
- Are pasta, vegetable, or rice dishes flavored with garlic, tomato, leek, or onion eaten ≥2 a week?

Fruits:

- Are ≥3 servings of fruit (of 80 g each) eaten each day?

Oils:

- Is olive oil the main culinary fat used?
- Are ≥4 tablespoons of olive oil used each day?
- Is <1 serving (12 g) of butter, margarine, or cream eaten each day?

Sugar:

- Is <1 serving (330 ml) of sweet or sugar sweetened carbonated beverages consumed each day?
- Is <3 servings of commercial sweets/pastries eaten each week?

Meat and beans:

- Is <1 serving (100-150 g) of red meat/hamburgers/other meat products eaten each day?
- Are ≥3 servings (of 150 g) of legumes consumed each week?
- Are ≥3 servings of fish (100-150 g) or seafood (200 g) eaten each week?
- Is ≥1 serving (of 30 g) of nuts consumed each week?
- Is chicken, turkey, or rabbit routinely eaten instead of veal, hamburger, or sausage?

In addition to the 14-Item Mediterranean Diet Assessment above, these questions were added to the current assessment:

Dairy:

- Are ≥2 servings of dairy products consumed each day? (One serving=one cup of milk or yogurt, three slices of processed cheese slices)
- Are low fat or skimmed milk products consumed instead of full fat?

Bread and cereal:

- Are whole wheat grains consumed instead of refined grains?

Physical activities:

- Do you do physical activity for 30 minutes or more three times a week or more?

The results of the assessment will be provided in a graphic format of the Healthy Food Palm guide and responses within recommended levels will turn the palm leaves green (Figure 2). For a full list of app prompts and feedback, see Supplementary Table 2.

A response below the recommended levels will prompt a notification to be sent to users with tailored tips based on the healthy food palm guidelines [26] as well as other international government health websites [27-29]. The app will recommend daily servings or portions of all foods and beverages, including six cups of water per day as well as describe how to properly read labels (Figure 3). The app will offer some suggestions for healthy food options in place of unhealthy food items and allows users to correct a poor meal/diet as an education tool for menu planning (Figure 4). Tips will be sent if the intake/activity ratio is off-balance according to the healthy lifestyle self-assessment score.

Figure 1. The Healthy Food Palm.

Figure 2. Graphic display of results of the healthy lifestyle self-assessment score.

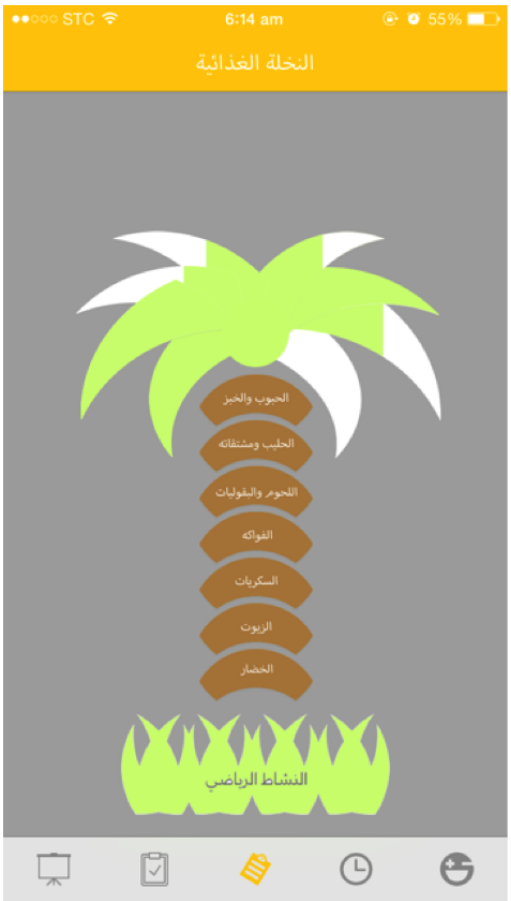


Figure 3. How to read food labels.

Figure 4. Education tool for menu planning.

Physical Activity

Energy expenditure is calculated using the Metabolic Equivalent of Task values based on The Compendium of Physical Activities, which provides a wide variety of sports and fitness activities as well as activities of daily living [30]. The Twazon app physical activity practice was created to ensure context validity to include only activities that Saudi women would be involved in (H. Al-Hazza, email communication, July 2014). Physical activities that are traditionally not available to most women such as tennis, running, or playing sport outdoors have been replaced with suggestions to do exercises at home or find support from others in order to find physical activities that are easily accessible by Saudi women. The app will recommend a minimum of 30 minutes of a physical activity selected from a provided list, at least three times a week. The app will also recommend taking at least 10,000 steps per day and will provide a pedometer that tracks the daily number of steps. It will also allow users to assess their physical activity every 2 weeks, sending tips if the amount of physical activity is low.

Self-Monitoring

As there is a significant association between self-monitoring of both diet and physical activity and weight loss [31], the app will enable self-monitoring of daily energy (kCal) of food and drink consumed (in) and physical activity (out) as well as weight tracking. For the purposes of tracking the balance of calories (in vs out), the Twazon app includes customized databases for dietary intake (calories only) and physical activity. These databases will allow users to keep a daily food and physical activity diary. The home page, or dashboard, of the app will provide this information for easy access to tracking and goals (Figure 5).

The app will allow the users to monitor their weight progress including starting weight, current weight, and goal weight. The app allows the user to report the foods consumed daily and then calculates the equivalent amount of calories, providing the user with a number of calories remaining for the day. The dashboard will provide a system to track calories consumed, steps taken, water consumed, and physical activity. When a user exceeds

the number of calories required in a day for weight loss, consumes more servings of a particular food group, or does not practice the minimum amount of daily physical activity, they will receive a notification informing them to engage in more physical activity.

Figure 5. 'Twazon' home page indicating daily self-monitoring of dietary intake and physical activity and goal tracking.

Social Support

Twazon will encourage the user to connect to social networks to add social support, which has a positive effect on health behavior [32]. This allows participants to view other app users and their progress, post pictures, and share them on a variety of social networking services (eg, Instagram, Facebook, and Twitter) to facilitate real-time communication and peer support among participants. This was one of the major shortcomings identified in both English [16,17] and Arabic weight loss apps [18], and an aspect highly recommended for inclusion by overweight Saudi women during the focus group discussions [15].

Customized Saudi Food Database

A Saudi food composition database was developed to provide the caloric information of more than 400-food item servings. This database was developed specifically for the app and compiled using multiple data sources. These include the Saudi food composition tables [33], the food composition tables for the Kingdom of Bahrain [34], the Kuwait food composition tables [35], the US food composition tables (ESHA Food Processor, version 10.8, nutrient analysis software), and the UK food composition tables [36]. If the calorie value was not available in the Saudi food composition tables, the international food tables were consulted in a relevant order. In the event that there was a complete lack of food composition data for specific traditional dishes (eg, falafel sandwich, yogurt cucumber salad), common recipes taken from restaurants were added by calculating the nutrient values of ingredients using the ESHA food processor program. As the current Arabic food databases (Saudi, Bahrain, and Kuwait) measure food only in grams, average household measure portion sizes (cups, spoons) were calculated for each of the food items/dishes for which this information was not available. If a user consumes a product that is not found in the finished database, they are able to input the food item into a private database, which sends a notification to the administrator alerting them to update the database with the new product.

Behavior Change Techniques

All system requirements were based on proposed features for and ideal weight loss app by the target group [15] as well as trying to include all aspects for evidence informed practices. As most weight loss apps tend to lack behavior change techniques (BCT), these were incorporated into this app using Michie's taxonomy [37] to code the techniques (Supplementary table 2 in Table 2). A total of 29 BCTs were included, related to goals and planning (4 codes), feedback and monitoring (4 codes), social support (3 codes), shaping knowledge (1 code), natural consequences (1 codes), comparison of behavior (2 codes), associations (2 codes), comparison of outcome (1 code), repetition and substitution (3 codes), comparison of outcomes (1 code), rewards and threats (1 code), regulation (1 code), antecedents (3 codes), and identity (1 code). An overview of the system requirements, BCTs, and associated features in Twazon App is provided in Supplementary Table 2.

Results

Testing the App

The Twazon app was piloted as a preliminary evaluation by two groups made up of experts in the field and potential users. These groups were asked to use the app for 5 to 7 days and give feedback and suggestions.

Expert Testing

The group of Saudi health professionals included two physical activity specialists and three nutritionists/dietitians. They provided content validity by reading app info, tips, and goals set by the app, and so on, and verified that it was accurate based on their professional knowledge. They were given access to the app itself, as well as an attached document listing the app's content sent by email. Three professionals reviewed the app and reported that it met all necessary criteria and found the content to be valid and accurate. They approved the information given to potential users although they raised a few questions about the use of the palm tree as the food guide, using waist-to-hip ratio instead of waist circumference, the accuracy of the "energy-expenditure formula," and inquired about the relationship between the pedometer and the offline function.

Potential Users Testing

The group of potential users included 10 overweight Saudi women over the age of 18. They were asked to input their personal data into the app, and then follow the goals set by the app including any physical activity recommended. They checked for usability, design satisfaction, and any problems in the app's system. In order to facilitate fast response times, their feedback was sent by WhatsApp. Five women submitted feedback on what they liked and disliked about the app. The majority of the users liked that the app raised awareness, and encouraged commitment and self-monitoring.

> *...It made me realize that a lot of foods that I eat between meals, which I don't care about, have a great effect on increasing the calories.*"

They also liked that it assigned a weight goal and calculated daily caloric intake, water consumption, and effort exerted.

> *"What I liked in the application is that it calculates my steps, and water quantity, and how many calories I consumed; even the effort; it could calculate it.*"

The Healthy Food Palm Tree was also beneficial to the users by identifying current health status.

> *I liked the palm tree…I came to know my nutrition disorder through it unfortunately, and the need to adapt my eating and nutrition habits.*"

The app's design and simplicity was also well received and the users enjoyed being able to add specific dishes as "favorites" and reference them in the future.

Future Suggestions

Suggestions made included that they would like to be able to view the history of the previous day's food intake and activity, in addition to being able to "add forgotten meals" or activity. Moreover, the majority felt that the app needed to be even easier and should offer a detailed explanation on how to use the app. A couple of the women wanted notifications on meal times and one woman mentioned "the need for the caloric information for certain fruits and juices." The results show that the usability of the app varies between potential users and this might be attributed to the different learning styles or technological literacy of users.

Discussion

Principal Findings

To our knowledge the development of previous Arabic weight loss apps has not complied with sufficient evidence-informed practices for weight management. The Twazon app differs from previous commercial Arabic weight loss apps in the following key areas: (1) it has been designed in collaboration with final users, (2) it complies with evidence-informed weight loss practices, (3) it provides social-network access, and (4) it includes a caloric content of Saudi local food.

The Twazon app, developed under the Android and iPhone operating system platforms, is a user-friendly, interactive app designed to track daily physical activity and food intake, and then provides customized advice to losing weight. The app took 23 months to build primarily because of the lack of information regarding household measurements of local foods [7]. During the creation of the local food databases, we reviewed the content of Arabic weight control apps and explored overweight Saudi women's opinions in order to design a smartphone app to fit their needs.

The Twazon app was tested in collaboration with the local community and health professionals. Three health professionals determined content validity and five potential users (overweight Saudi females) evaluated the app for usability.

Overall, the app was reviewed to provide accurate information and was reported to have helped several of the potential users identify and understand their weight loss goals. The app was found to be aesthetically pleasing in design and many of the features were user-friendly.

In order to better explain the functions of the app and its features, a tutorial that includes pop-up messages will guide the user through the general use of the app, identifying the most important points and steps. The lack of nutritional data for certain foods will be solved by a detailed explanation of use in the aforementioned tutorial as well as a constantly updated crowd-sourced admin-reviewed food data bank. The users will be allowed to input their favorite daily foods, and an administrative team will review these foods to see if they should be added to the official data bank. Notifications of mealtimes and the ability to view and modify your "history" are features that are currently being worked on, and will be made available to users in the future.

Limitations

The Twazon app possesses some limitations such as: (1) it doesn't record the daily calories or activity into a history or backlog, (2) there is no meal planning available or recipes offered, (3) there is no professional support, (4) there is no

bar-code scanning feature available as of yet, (5) it cannot generate new tips 365 days a year, and (6) for clarification, the app cannot work offline. Finding solutions to these limitations and upgrading the app consistently will be necessary to encourage and maintain engagement.

Strengths

The Twazon app is different from other available weight loss applications in that it applies the information found in evidence informed practices and focus group findings, allowing for the specific needs of overweight Saudis to be met through a localized and tailored approach. The Twazon app is currently the only app to provide household measurements for local foods and dishes, making it easier for the user to manage their portion control. The app also offers recommended daily exercise that is culturally sensitive and suited to individual physical status. It also provides social networking features that allow users to connect and support each other. Based on the biweekly self-assessment, the users receive notifications that give tips about avoiding certain foods and increasing the intake of others.

The Way Ahead

The effect of the app on weight loss will be examined in a 6-month pre-post intervention study with 200 overweight and obese women from Riyadh, Saudi Arabia. The primary endpoint will be the proportion of the group who lose at least 5% body weight.

Acknowledgments

This research project was supported by a grant from the “Research Center of the Female Scientific and Medical Colleges”, Deanship of Scientific Research, King Saud University.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Supplementary Table 1.

[PDF File (Adobe PDF File), 153KB - resprot_v5i2e76_app1.pdf]

Multimedia Appendix 2

Supplementary Multimedia Appendix 2.

[PDF File (Adobe PDF File), 56KB - resprot_v5i2e76_app2.pdf]

References

1. Al-Quwaidhi AJ, Pearce MS, Critchley JA, Sobngwi E, O'Flaherty M. Trends and future projections of the prevalence of adult obesity in Saudi Arabia, 1992-2022. East Mediterr Health J 2014;20:589-595. [Medline: 25356689]
2. Daoud F, El BC, Tuffaha M, AlMazroa M, Al SM, Nooh R, Al Rabeeah Abdullah A, et al. The health status of Saudi women: findings from a national survey. J Public Health 2015. [doi: 10.1093/pubmed/fdv157] [Medline: 26518041]
3. World Health Organization. Global Status Report on Noncommunicable Diseases 2014: Attaining the Nine Global Noncommunicable Diseases Targets; A Shared Responsibility. Geneva; 2015. URL: http://apps.who.int/iris/bitstream/10665/148114/1/9789241564854_eng.pdf [accessed 2016-03-24] [WebCite Cache ID 6f03xxHuA]
4. ALNohair S. Obesity in gulf countries. Int J Health Sci (Qassim) 2014;8:79-83 [FREE Full text] [Medline: 24899882]
5. Albawardi NM, Jardi H, Al-Hazza H. Levels and determinants of physical activity and body mass index among Saudi women working in office jobs in Riyadh City. Occup Med Health Aff 2015;03. [doi: 10.4172/2329-6879.1000196]
6. Al-Otaibi HH, Basuny AM. Fast food consumption associated with obesity/overweight risk among University female student in Saudi Arabia. Pakistan J of Nutrition 2015;14:511-516. [doi: 10.3923/pjn.2015.511.516]
7. Al Moraie N. Dietary Patterns in Saudi Arabian Adults Residing in Different Geographical Locations in Saudi Arabia and in the UK In Relation to Heart Disease Risk [dissertation]. Australia: Newcastle University; 2014. URL: https://theses.ncl.ac.uk/dspace/handle/10443/2562 [accessed 2016-03-24] [WebCite Cache ID 6gEcMwWvl]
8. Alqout O, Reynolds F. Experiences of obesity among Saudi Arabian women contemplating bariatric surgery: an interpretative phenomenological analysis. J Health Psychol 2014;19:664-677. [doi: 10.1177/1359105313476977] [Medline: 23479306]
9. DeNicola E, Aburizaiza OS, Siddique A, Khwaja H, Carpenter DO. Obesity and public health in the Kingdom of Saudi Arabia. Rev Environ Health 2015;30:191-205. [doi: 10.1515/reveh-2015-0008] [Medline: 26351801]
10. Raben F, Snip E. The MENAP region is developing, but can it keep its promise? Research World 2014;2014:6-11. [doi: 10.1002/rwm3.20144]
11. Saleem S. Consumer Attitudes Toward Mobile Advertising in the Kingdom of Saudi Arabia [dissertation]. Saudi Arabia: Effat University; 2015. URL: http://library.effatuniversity.edu.sa/finalprojects/Business/

Consumer-attitudes-towards-mobile-advertising-in-the-Kingdom-of-Saudi-Arabia-2015.pdf [accessed 2016-03-24] [WebCite Cache ID 6gEcj7Mu4]
12. Dubai School of Government. Citizen Engagement and Public Services in the Arab World: The Potential of Social Media. 2014. URL: http://www.mbrsg.ae/getattachment/e9ea2ac8-13dd-4cd7-9104-b8f1f405cab3/Citizen-Engagement-and-Public-Services-in-the-Arab.aspx [accessed 2015-09-29] [WebCite Cache ID 6btBuS3QF]
13. Al Gamdi E, Reilly D. Social media based business in saudi arabia. 2013 Presented at: Ã‚Â Dalhousie Computer Science In-House Conference (DCSI); 2013; Dalhousie University p. 1-3.
14. Yuce S, Agarwal N, Wigand R, Lim M, Robinson R. Studying the evolution of online collective action: Saudi arabian Women's 'Oct26Driving'Twitter campaign. In: Salerno JJ, editor. Social Computing, Behavioral-Cultural Modeling and Prediction: 4th International Conference, SBP 2011, College Park, MD, USA, March 29-31, 2011... Applications, incl. Internet/Web, and HCI). New York: Springer; 2014:413-420.
15. Alnasser AA, Alkhalifa AS, Sathiaseelan A, Marais D. What overweight women want from a weight loss app: a qualitative study on arabic women. JMIR Mhealth Uhealth 2015;3:e41 [FREE Full text] [doi: 10.2196/mhealth.4409] [Medline: 25993907]
16. Breton ER, Fuemmeler BF, Abroms LC. Weight loss-there is an app for that! But does it adhere to evidence-informed practices? Transl Behav Med 2011;1:523-529 [FREE Full text] [doi: 10.1007/s13142-011-0076-5] [Medline: 24073074]
17. Pagoto S, Schneider K, Jojic M, DeBiasse M, Mann D. Evidence-based strategies in weight-loss mobile apps. Am J Prev Med 2013;45:576-582. [doi: 10.1016/j.amepre.2013.04.025] [Medline: 24139770]
18. Alnasser A, Amalraj R, Sathiaseelan A, Al-Khalifa A, Marais D. Do Arabic weight-loss apps adhere to evidence-informed practices? TBM 2015. [doi: 10.1007/s13142-015-0347-7]
19. Centre for Public Health Excellence at NICE (UK), National Collaborating Centre for Primary Care (UK). Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children. NICE 2006. [Medline: 22497033]
20. Bandura A. Health promotion from the perspective of social cognitive theory. Psychology & Health 1998;13:623-649. [doi: 10.1080/08870449808407422]
21. Lemmens Harry J M, Brodsky JB, Bernstein DP. Estimating ideal body weight--a new formula. Obes Surg 2005;15:1082-1083. [doi: 10.1381/0960892054621350] [Medline: 16105412]
22. Wing RR, Lang W, Wadden TA, Safford M, Knowler WC, Bertoni AG, Look AHEAD Research Group. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. Diabetes Care 2011;34:1481-1486 [FREE Full text] [doi: 10.2337/dc10-2415] [Medline: 21593294]
23. Mendez MA, Popkin BM, Jakszyn P, Berenguer A, Tormo MJ, Sanchéz MJ, et al. Adherence to a Mediterranean diet is associated with reduced 3-year incidence of obesity. J Nutr 2006;136:2934-2938 [FREE Full text] [Medline: 17056825]
24. Esposito K, Kastorini C, Panagiotakos DB, Giugliano D. Mediterranean diet and weight loss: meta-analysis of randomized controlled trials. Metab Syndr Relat Disord 2011;9:1-12. [doi: 10.1089/met.2010.0031] [Medline: 20973675]
25. Martínez-González MA, García-Arellano A, Toledo E, Salas-Salvadó J, Buil-Cosiales P, Corella D, et al. A 14-item Mediterranean diet assessment tool and obesity indexes among high-risk subjects: the PREDIMED trial. PLoS One 2012;7:e43134 [FREE Full text] [doi: 10.1371/journal.pone.0043134] [Medline: 22905215]
26. Ministry of Health (MOH). The healthy food palm. 2015. URL: http://www.moh.gov.sa/en/Ministry/MediaCenter/News/Pages/News-2013-01-13-001.aspx [accessed 2015-01-15] [WebCite Cache ID 6gEen9Owm]
27. U.S. Department of Agriculture. ChooseMyPlate. URL: http://www.choosemyplate.gov/ [accessed 2015-09-29] [WebCite Cache ID 6btSYw6OM]
28. Oldways. Traditional Healthy Mediterranean Food Pyramid Updated 2008. 2015. URL: http://oldwayspt.org/resources/heritage-pyramids/mediterranean-diet-pyramid [accessed 2015-09-29] [WebCite Cache ID 6btSm07L7]
29. Healthier takeaways. 2015. URL: http://www.nhs.uk/Livewell/men1839/Pages/Dodgytakeaways.aspx [accessed 2015-09-29] [WebCite Cache ID 6btSsjjzz]
30. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR, Tudor-Locke C, et al. 2011 Compendium of physical activities: a second update of codes and MET values. Med Sci Sports Exerc 2011;43:1575-1581. [doi: 10.1249/MSS.0b013e31821ece12] [Medline: 21681120]
31. Burke LE, Wang J, Sevick MA. Self-monitoring in weight loss: a systematic review of the literature. J Am Diet Assoc 2011;111:92-102 [FREE Full text] [doi: 10.1016/j.jada.2010.10.008] [Medline: 21185970]
32. Ahmadi A. Social support and women's health. Women's Health Bull 2015;3:189-210. [doi: 10.17795/whb-31083]
33. Musaiger A. Food Composition Tables for Arab Gulf Countries. Manamah, Bahrain: Arab Center for Nutrition; 2006.
34. Musaiger A. Food Composition Tables for Kingdom of Bahrain. Manama, Bahrain: Arab Center for Nutrition; 2011.
35. Dashti B, Al-Awadi F, Khalafawi M, Al-Zenki S, Sawaya W. Nutrient contents of some traditional Kuwaiti dishes. Food Chemistry 2001;74:169-175. [doi: 10.1016/S0308-8146(01)00111-X]
36. Food Standard Agency, Public Health England. McCance and Widdowson's the Composition of Foods. UK: Royal Society of Chemistry; 2014.

37. Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. Ann Behav Med 2013;46:81-95. [doi: 10.1007/s12160-013-9486-6] [Medline: 23512568]

Abbreviations

BCT: behavior change techniques

Edited by G Eysenbach; submitted 01.01.16; peer-reviewed by M McKinley; comments to author 22.01.16; revised version received 23.02.16; accepted 23.02.16; published 16.05.16.

Please cite as:
Alnasser A, Sathiaseelan A, Al-Khalifa A, Marais D
Development of 'Twazon': An Arabic App for Weight Loss
JMIR Res Protoc 2016;5(2):e76
URL: http://www.researchprotocols.org/2016/2/e76/
doi:10.2196/resprot.5497
PMID:27185568

Original Paper

Developing a Web-Based Version of An Exercise-Based Rehabilitation Program for People With Chronic Knee and Hip Pain: A Mixed Methods Study

Jennifer Pearson[1,2*], PhD; Nicola Walsh[2*], PhD; Desmond Carter[3*]; Sian Koskela[1*], MSc (Hons); Michael Hurley[1,4*], PhD

[1]School of Rehabilitation Sciences, Faculty of Health, Social Care and Education, St Georges University of London and Kingston University, London, United Kingdom

[2]Centre for Health and Clinical Research, Department of Allied Health Professions, University of the West of England, Bristol, United Kingdom

[3]Health Innovation Network, NHS, London, United Kingdom

[4]Health Innovation Network South London, NHS England, London, United Kingdom

[*]all authors contributed equally

Corresponding Author:
Michael Hurley, PhD
Health Innovation Network South London
NHS England
Minerva House
5 Montague Close
London, SE1 9BB
United Kingdom
Phone: 44 20 8725 4602
Fax: 44 20 8725 4602
Email: michael.hurley@sgul.kingston.ac.uk

Abstract

Background: Osteoarthritis is highly prevalent and has enormous personal and socioeconomic impact. Enabling Self-management and Coping with Arthritic Pain through Exercise (ESCAPE-pain) is an integrated rehabilitation program that helps people understand how exercise can improve physical and psychosocial well-being. Unfortunately, its availability is limited. A Web-based version of the program could increase access for more people. Many Web-based resources are developed without end-user input and result in over-complex, unwanted, ineffective products with limited uptake.

Objective: The objective of this study was to codesign a Web-based version of ESCAPE-pain that people with chronic joint pain find engaging, informative, and useful.

Methods: To establish older persons' Internet use we conducted a postal survey of 200 people. To establish their opinions, likes or dislikes, and requirements for a Web-based version of the ESCAPE-pain program, we conducted two focus groups with 11 people who had participated in a program based on ESCAPE-pain and two with 13 people who had not. Information from the postal survey and focus groups was used to develop an online prototype website. People's opinions of the prototype website were gauged from thematic analysis of eight semistructured “think aloud” interviews.

Results: The survey response rate was 42% (83/200), of whom 67% (56/83) were female and mean age was 67 years. Eighty-three percent of the people had used the Internet, 69% described themselves as either very confident or confident Internet users, and 77% had looked online for health information. With regard to participating online, 34% had read a commentary or watched a video of someone else’s experience of a health problem and 23% had tracked a health issue. Key qualitative themes emerged that included engagement, acceptability and usability, and structure and content of the program.

Conclusions: Older people use the Internet as a source of health information but have concerns about safe use and quality of information. Users require a credible website that provides personalized information, support, monitoring, and feedback.

(JMIR Res Protoc 2016;5(2):e67) doi:10.2196/resprot.5446

KEYWORDS

osteoarthritis; exercise; self-care; web-based program; behavioral change; qualitative research; quantitative research

Introduction

Chronic joint pain, often labeled osteoarthritis (OA), is one of the most prevalent health conditions [1,2]. It compromises mobility and physical activity, increases the risk of developing comorbidity [3], reduces quality of life, independence [4,5], and makes people feel anxious and depressed [6]. The socioeconomic cost is high and the consequences associated with chronic joint pain will increase as people live longer, become less physically active, and obesity rates increase [2,7].

Evidence-based guidelines recommend exercise/physical activity, simple analgesics, patient information and advice about self-management, pain coping strategies, and maintaining appropriate body weight [8-10]. Unfortunately, only a small minority of people receive these interventions [11-13], whereas most people are prescribed long-term analgesics despite concerns about safety [14,15], effectiveness, costs [16], and unpopularity [17,18]. Others receive an inappropriately early referral for surgery.

Enabling Self-management and Coping with Arthritic Pain through Exercise (ESCAPE-pain) is a rehabilitation program that integrates information, advice, and self-management and coping strategies with an exercise regimen. The program incorporates behavioral change techniques (BCTs) [19] that challenge people's erroneous health beliefs about the harmful effects of physical activity on joint pain. It helps them to appreciate that exercise is safe and has wide physical and psychosocial benefits, which results in changes to their behavior by increasing physical activity levels to reduce pain and improve physical function [17,20,21]. ESCAPE-pain is more clinically effective and cost-effective than usual care [22-25] and popular with participants who have pain associated with knee OA [17,18]. Unfortunately, limited clinical resources (such as time, space, and funding) mean that relatively few clinical departments run the program. Therefore, innovative ways are needed to reach the large and rapidly increasing number of people who could benefit from the intervention.

Digital technologies (telemedicine, Web-based programs, mobile phone apps, and so on) are increasingly popular ways of enabling many more people to access information [26-28]. Adapting ESCAPE-pain as a Web-based program would increase access. However, programs are rarely developed with input from end users [29-31] and little consideration is given to the human-technological interaction or context [32]. The resulting products are often unwanted, unusable, "high-tech, low-impact" Web-based programs that users regard as irrelevant and overly complex. These Web-based solutions have poor uptake, lack effectiveness and adherence, and are often unsuccessfully implemented [26-29,33-36]. Adopting a user-centered approach when designing the program might improve the "fit" between human needs and the technology, improving uptake, implementation, and effectiveness [37]. We used quantitative and qualitative research methods, the principles of persuasive technology, and human-centered design to discover what people considered important in the content and design of a Web-based version of the ESCAPE-pain program.

Methods

Survey

A postal survey was distributed to 200 people aged 50 years and older with chronic (>6 months' duration) knee, hip and/or back pain who had participated in a trial based on the ESCAPE-pain program in the West of England in the United Kingdom [38]. Of these trial participants, 100 were "experienced" (ie, had undertaken the ESCAPE-pain program, in order to understand what they found useful and necessary to be included in a Web-based program) and 100 people were "naïve" (ie, they had not participated in the program but had received a verbal description of the program's content and format) in order to understand the needs of a typical person taking part in the Web-based program. Demographic data and Internet use and experience of the participants were collected. The survey posed questions and invited comments about the format and content of the proposed Web-based resource and people's preferences [39] for features that may improve the effectiveness of Web-based interventions (text messaging, prompts, diaries, support forums, and so on) [37,40-42]. Descriptive analyses were used to describe the survey data.

Focus Groups and One-to-One Interviews

To gain a better understanding of people's (dis)likes, opinions, and preferences about the ESCAPE-pain program, how to engage people, and what the Web-based program needed to convey, four focus groups were conducted (n=24 participants in total). Table 1 provides further details of the participant characteristics. Two focus groups involved "experienced" people who had participated in the program (n=11), and two focus groups involved people "naïve" to the program (n=13). Participants were purposively selected from the survey based on characteristics of age, sex, duration and site of pain, and their use of and confidence in using the Internet. Focus groups comprised five to seven participants. The focus groups took place in university or hospital settings, facilitated by one of the authors (JP) using a topic guide (Multimedia Appendix 1), and lasted on average 94 minutes (range 84-105 minutes). Field notes were also taken.

The focus groups and interviews were recorded, transcribed, checked for accuracy, and anonymized, and emerging themes were identified using thematic analysis [43]. Transcripts from all focus groups were coded by JP. The first two focus group transcripts were independently coded by all the authors, who discussed the coding and initial emerging themes. The topic guide was amended to reflect the emerging themes, which was used in the following focus groups. The additional focus group transcripts were independently coded by DC.

Table 1. Focus group and interview participant characteristics.

Pseudonym	Sex	Age range (years)	Duration of pain (years)	Site of pain	Experienced or naïve to the ESCAPE-pain program	Confidence in using the Internet	One-to-one interview
John	Male	60-69	>10	Knee and back	Experienced	Very confident	No
Patricia	Female	60-69	>10	Hip and back	Experienced	Neither confident nor unconfident	Yes
Barbara	Female	60-69	1-5	Knee and back	Experienced	Very confident	No
Linda	Female	60-69	1-5	Hip and knee	Experienced	Very confident	No
James	Male	70-79	5-10	Knee	Experienced	Confident	Yes
Mary	Female	60-69	5-10	Multiple	Experienced	Confident	No
Carol	Female	60-69	>10	Multiple	Naïve	Confident	No
Richard	Male	60-69	5-10	Knee	Naïve	Confident	Yes
Betty	Female	70-79	>10	Back	Naïve	Neither confident nor unconfident	Yes
Edith	Female	70-79	>10	Multiple	Naïve	Neither confident nor unconfident	No
William	Male	70-79	5-10	Knee	Naïve	Neither confident nor unconfident	No
Charles	Male	70-79	<1	Knee	Naïve	Unconfident	No
Shirley	Female	70-79	>10	Knee	Experienced	Very confident	No
George	Male	50-59	1-5	Hands	Experienced	Very confident	No
Karen	Female	60-69	1-5	Knee	Experienced	Confident	Yes
Michael	Male	60-69	1-5	Knee	Experienced	Very confident	Yes
Susan	Female	70-79	5-10	Back	Experienced	Very confident	No
Gerald	Male	60-69	>10	Back	Naïve	Confident	No
Gary	Male	60-69	1-5	Knee	Naïve	Confident	Yes
Daniel	Male	60-69	5-10	Hip	Naïve	Confident	No
Donna	Female	60-69	5-10	Back	Naïve	Confident	Yes
Paul	Male	60-69	5-10	Knee	Naïve	Confident	No
Frank	Male	60-69	5-10	Back	Naïve	Very confident	No
Walter	Male	60-69	5-10	Knee and hip	Naïve	Very confident	No

Prototype Website

The results of the survey and emergent themes from the focus groups were used to design a prototype website (see Figure 1). This had limited online function and offline material and resources, consisting of four external pages and four internal pages. The external pages included the following:

- "Home" page gave a brief overview of the ESCAPE-pain program and a Web-based promotional video explained the concept of the program.
- "About ESCAPE" explained the history of the program and its potential benefits, provided information about the website's contents, videos of participant endorsements and testimonials, and information of partner organizations.
- "Frequently Asked Questions."
- "Contact Us" had a registration section and ways to contact the ESCAPE-pain team.

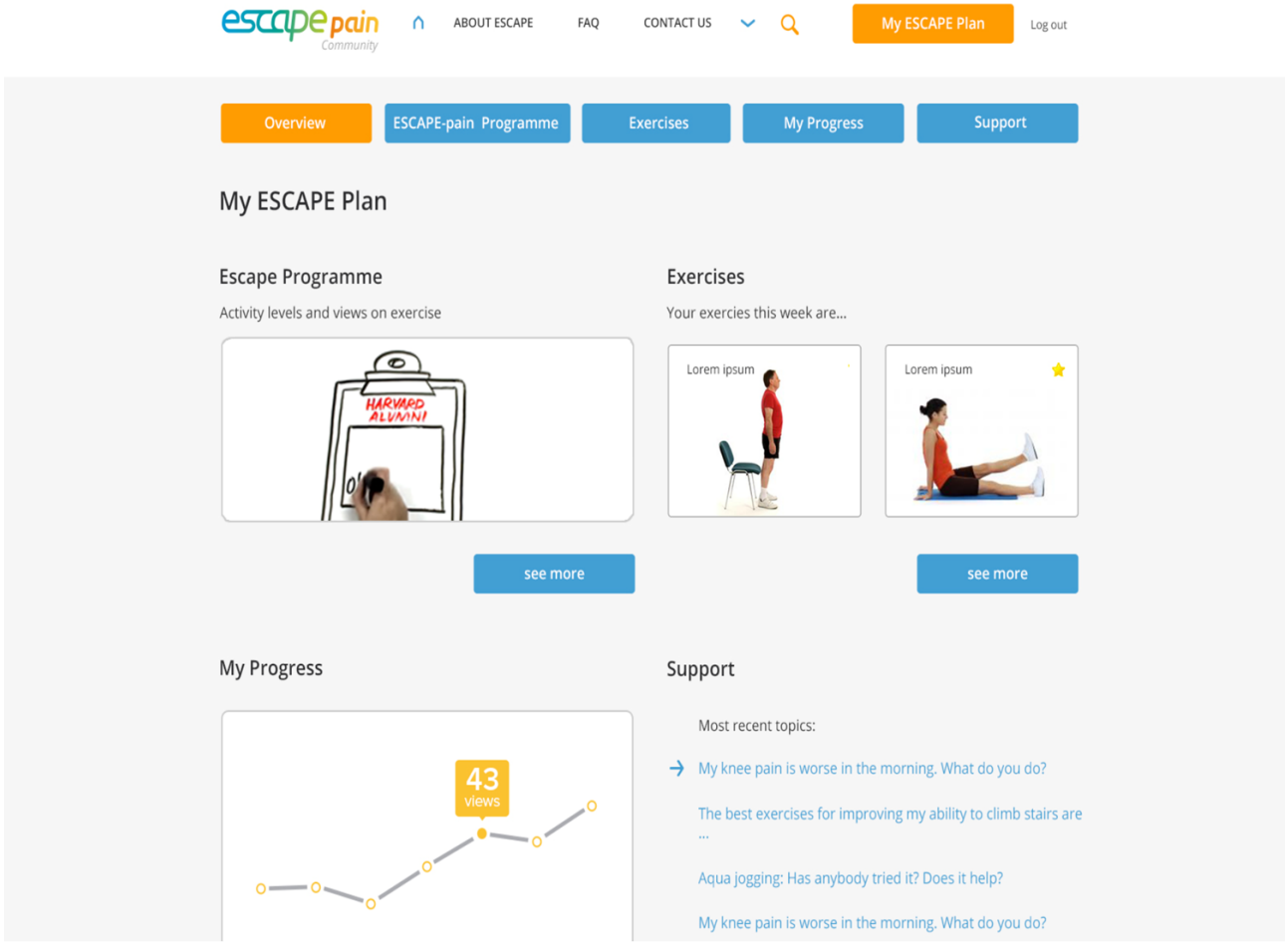
The internal pages consisted of the following:

- "My ESCAPE Plan" page provided an overview of the 12 modules that compose the program, such as physical activity, exercise, goal setting, action plans, pacing, drug management, diet, home exercises, understanding pain, pain management, and relaxation.
- "Exercise" consisted of a library of "easy," "medium," or "advanced" exercise videos suitable for people with joint pain, which they could watch and which provided instructions on how to perform the selected exercise.
- "My Progress" provided an example of how people could input data and view graphical feedback on the amount of

exercises they performed, as well as their activity levels, mood, and so on.

- "Support" provided an example of a forum where participants could join to discuss joint pain–related issues, with links to other Web-based resources.

Figure 1. A screenshot of the internal pages of the prototype ESCAPE-pain website.



"Think Aloud" Semistructured Interviews

The prototype website was then tested by eight participants using semistructured interviews and a modified "think-aloud" technique [44]. The participants were purposively selected based on the key characteristics of age, sex, duration, site of pain, and their confidence in using the Internet. JP conducted the interviews at participants' homes, which lasted on average 107 minutes (ranging between 78 minutes and 142 minutes). Participants were shown the prototype Web-based version of ESCAPE-pain and asked questions using a topic guide developed from themes emerging from the survey and focus groups and features of the prototype website (Multimedia Appendix 2). Table 1 indicates those participants who were involved in the "think aloud" interviews.

The interviews were analyzed using a thematic analysis [43]. JP coded all the interviews, the first two interview transcripts were independently coded a second time by MH, DC, and NW, then each member coded two additional transcripts so that each interview was coded independently by three authors. The final themes were then mapped to the behavioral change taxonomy [19]. The findings from the focus groups and interviews are presented together.

Ethics

Ethics approval was obtained from the National Research Ethics Service Committee South West-Central Bristol (Research Ethics Committee reference 11/SW/0053). All participants received information about the project and gave signed informed consent.

Results

Survey

The survey response rate was 42% (83/200). The demographics of the respondents reflect the demographics of people with OA, predominantly female (56/83, 67%), mean age was 67 years (range 53-84 years), over two thirds were retired and had pain in several joints for a prolonged time (Table 2).

Most respondents (71/83, 86%) had used the Internet, of whom 83% (59/71) used it daily and almost exclusively at home (99%). Most people felt confident or very confident using the Internet (49/71, 69%) with personal computers, tablets, laptops and/or mobile phones. Although more than three-fourths of the people used the Internet to search for information about health problems, few (14/71, 20%) had used this information to manage their condition (Table 3).

Table 2. Participant demographics.

Participant demographics		Survey (n=83), n (%)	Focus group (n=24)	Interviews (n=8)
Sex				
	Male	27 (33)	12	4
	Female	56 (67)	12	4
Age, years				
	50-59	10 (12)	1	-
	60-69	50 (60)	16	6
	≥70	23 (28)	7	2
Site of joint pain				
	Knee	17 (21)	5	3
	Hip	1 (1)	1	-
	Back	13 (16)	3	2
	Other	6 (7)	1	-
	Multiple	46 (55)	14	3
Duration of joint pain, years				
	<1	5 (6)	1	-
	1-5	27 (33)	6	3
	5-10	26 (31)	9	3
	>10	23 (28)	8	2
	Unknown	2 (2)	-	-
Trial group				
	Experienced	33 (40)	11	4
	Naïve	43 (50)	13	4
	Unknown	8 (10)	-	-

Table 3. Internet use and online activity.

Internet use and online activity		Survey (n=71), n (%)	Focus group (n=24)	Interviews (n=8)
All devices used (data represent use of multiple devices)				
	PC[a]	42 (59)	18	7
	Laptop	30 (42)	16	7
	Tablet	33 (46)	13	3
	Mobile phone	21 (30)	9	5
Confidence				
	Very confident/confident	49 (69)	18	6
	Not confident/unconfident	16 (22)	5	2
	Unconfident	4 (6)	1	-
	Unknown	2 (3)	-	-
Frequency of use				
	Daily	59 (83)	19	7
	Weekly	7 (10)	4	1
	Less often	5 (7)	1	-
Searched Internet for health information				
	Yes	55 (77)	18	6
	No	16 (23)	6	2
Watched/read someone's health-related experience				
	Yes	24 (34)	8	3
	No	47 (66)	16	5
Contributed to online discussion				
	Yes	3 (4)	2	1
	No	68 (96)	22	7
Tracked health-related symptoms				
	Yes	16 (23)	6	3
	No	55 (77)	18	5
Used an online resource to manage an existing health condition				
	Yes	14 (20)	9	3
	No	57 (80)	15	5

[a]PC: personal computer.

Focus Groups and Interviews

From the focus groups and “think aloud” interviews, three key themes emerged that influenced people's use of the proposed website (Table 4): (1) initial and sustained engagement with the website, (2) acceptability of a Web-based exercise-based self-management program, and (3) content/structure of the program.

Table 4. Features to encourage engagement with and improve effectiveness of a Web-based program mapped onto the behavioral change taxonomy [19].

Theme	Subtheme	Supporting quote	Taxonomy
Engagement	Credibility	"...you go to sources that you know are genuine...For medical information I would always go to the NHS website..." Mary	9 Comparisons of outcomes 9.1 Credible source
		"...it's got to be recommended to you by a professional..." Paul	
		"...I am very wary about the web and medical problems...but this is one that was recommended by the GP..." Daniel	
		"...[research information] adds weight to the thing...communicates integrity I think it's a serious piece of work..." Donna	
		"...not sponsored by drug companies..." Gerald	
	Patient testimonials	"...I think [patient testimonials] explained the purpose very well...it showed a good cross section of different people doing different exercises...I think I would be encouraged to pursue it further...Makes you realize that people can get good improvement. Yes that these are people who have been through the program and have found benefit and its much improved their quality of life...it makes you realize you are not alone..." Patricia	6 Comparison of behavior 6.1 Demonstration of the behavior 6.2 Social comparison 6.3 Information about others' approval
		"...I always skip over those sort of things..." John	
		"...I don't actually I like reading other people's experiences because it somehow makes it feel more real you know...this is really flippant but if it's a recipe I have looked up on line and you know a hundred people have said oh yeah that was absolutely brilliant I will give it five stars or something then you think well great I'll do that..." Mary	
	Social identification	"...this program is designed for later life people isn't it? So it should have them in it I think. Not young people who can do it easily and no pain, but people who are actually finding it hard..." James	
		"...I watched a little clip a couple of years ago because I had labyrinthitis and that was really awful and seeing this girl saying how she had experienced it and how she came through it and she was obviously ten time worse than mine..." Barbara	
Acceptability and usability	Aesthetics	"...something nice and bright that would attract you to the site, you know to attract you...very self-explanatory..." Betty	
		"...plying a very positive image..." Gerald	
		"...its plain and simple its not too fussy it tells you what you want to know..." Patricia	
		"...well I think simplicity is the best thing...it's got to be interesting..." George	
		"...big fonts, nice and clear, plain simple language, hasn't got thousands of links on it, asks intelligent questions and leads the user to the information you get to what you want within about 2 or 3 screens..." John	
		"...[not] loads and loads of advertisement..." Richard	
	Functionality	"...something simple you know so people can just click in and find out what they want..." Betty	
		"...easy to navigate through...navigation is the key..." Mary	
		"...I am not going to spend hours trawling through stuff but if there's a star or something like that that says this that and it you know captures the attention because there is a need then you can go into that and it opens up the bit that you need..." Karen	
		"...you don't want hundreds of links..." Richard	
		"...one of the problems with links as well is that you link to something and that gives you a link to something else and before you know where you are you can't remember how you got there..." Carol	

Theme	Subtheme	Supporting quote	Taxonomy
	Registration	"...oh not something you have to register for..." Barbara "...I hate that you have to put passwords in...and all that malarkey just get the flipping information..." Mary "...certainly not open an account because that always sounds like money to me..." James "...people ought to log on they should sign up I mean because I think it would help enormously the feeling of actually belonging to something..." Michael	
	Technical capability	"...my mother-in-law is 90 plus she has never switched a computer on she doesn't know how to use it...she will never use that website..." Gerald "...this problem of aged people and computers is going to drift away...maybe it's only a problem possibly for another 15 years..." Daniel	
Content and structure of program	Information and advice	"...[information] needs to be in a visual form rather than a written form...an executive summary of the sequence rather than the detail of the sequence so you would read the executive summary and then get into the detail..." James "...if I got them at my bedside cabinet or pinned up on the fridge, I will always remember to do them..." Shirley "...for someone that's coming in and using it for the first time it would be nice to if its presented sequentially if someone's going back to it they want to go directly to there..." John	4 Shaping knowledge 4.1 Instruction on how to perform a behavior 7 Associations 7.1 Cues/prompts
	Exercise	"...a nice little looped video wouldn't they, demonstrating the exercise..." John "...it's clear what the exercise is, and how it's going to benefit you, and what you might do wrong, and how that is going to affect you..." Linda "...how often should these exercises be done, and how many repetitions all the things that we had in the class that we went to..." Mary	4 Shaping knowledge 4.1 Instruction on how to perform a behavior 5 Natural consequences 5.1 Information about health consequences
	Personalized	"...need for the website to be an individual's website...they can have you know their own diary, they can have their own records..." Michael "...it has to be personalized to you otherwise you know why do you bother to turn it on...it shows you what you have done so that you can when you have done something you can actually tick it and you get something to show you have done something...this is the goal setting... right so you have got your goal setting you are achieving so and so there's your action plan have you done it and is there something along the line that shows you, you have done something..." Gary "...if I was going to start my activity and exercise with it I would want the goal setting..." Donna "...set your target and get a little bit better each time you do it, or each week you do it, sort of build yourself up..." Betty	1 Goal setting and planning 2 Feedback and monitoring 3 Social support

Theme	Subtheme	Supporting quote	Taxonomy
	Monitoring	"...if there was sort of a little personal diary where you could say, 'Tuesday did 10 of this and 15 of that,' then maybe some monitoring person says, 'well next week you should do 20 of those and 25...I would definitely want to monitor my progress..." Patricia "...you have got your exercises, you have got my progress. I like that because you can then monitor where you are and you have also got support...I can look at that and feel I have achieved...I like to see the chart because the progress bit like I did for my weight so I would like to see that you know because it would then tell me you know have you done them this week or haven't you done them...you can look to see well three months ago I could only do so and so ooh, look now I can do this so again its goal setting if you like, but I mean its yeah its moving forward all the time..." Gary "...I don't know whether I would monitor myself..." Betty	2 Feedback and monitoring 2.2 Feedback on behavior 2.3 Self-monitoring of behavior 2.4 Self-monitoring of outcome behavior
	Peer support	"...a members site you can have a blog....so you could actually contact then talk to people with similar problems..." Gerald "...it could be interesting to see how they are getting on and support each other you know if they have had a down day or something has gone wrong sort of be able to be a bit supportive...I would like to be in contact with other people...to see how other people do the exercises it gives you a good idea of whether you are doing it right...[has she used forums?] very rarely...it was too time consuming...I wasn't sure that it was being any help for me..." Patricia "...you get somebody else's feedback on what they do to get rid of their knee pain in the morning. I mean it might not suit you, you could try it and if it doesn't suit you perhaps you could look for something else that would help you, do you know what I mean?..." Betty	3 Social support 3.1 Unspecified 3.2 Practical 3.3 Emotional
	Professional support	"...you need some personal physio input to start with...you need to be doing that first set of exercises with a physio so you get direct feedback...eight weeks, or whatever it is, you can then go off and do it on the internet...not standing on its own as a substitute [for a face-to-face program]..." James "...I think I would want something personal...something more than just being told to go and look at a website...you want reassurances I guess so if you have been doing it for two months then nothing has happened then you actually want to know how long you should be doing the exercises..." Barbara "...I think it would be difficult to give people the confidence to accept [an Web-based program] as a sole treatment avenue..." John "...I would feel less confident about the information than if I had had some physical contact with doctor, physio something else beforehand and I think probably most people would think along those lines, you know, like your concerns about a replacement [for a face-to-face program] it doesn't feel that comfortable..." Linda "...websites that you can go on that there is literally somebody at the other end so you can type in a question and then you get an answer back..." Paul "...an email to say have you done your exercises this week..." Patricia "...I would need somebody who actually knew about pain and knew about exercise..." Michael	2 Feedback and monitoring 2.7 Feedback on outcomes of behavior 3 Social support 3.1 Unspecified 3.2 Practical 3.3 Emotional

Engagement

Finding a health-related website usually results from a purposeful search for information about a specific health issue, for example, joint pain. However, people are often skeptical and mistrustful of information they find online. In our study, people wanted to be directed to Web-based resources by a trusted "source" such as a health care professional [45] or

credible organization (ie, a statutory health body) [46-48]. They were mistrustful of commercial websites with advertisements, which they saw as promoting goods for financial gain with little regard to whether it will help the patient [46,47]. The website needed to capture people's attention visually, with content that was obviously relevant and created a positive association between the website and the health benefits it could bring [46,47]. Important determinants for engagement with the website were video testimonials of people discussing their experiences of participating in the program, with personal and social traits that potential users could identify with [46,47].

Acceptability and Usability

In general, people thought a Web-based ESCAPE-pain program could be an effective way to help them self-manage their condition. However, they thought there were limitations to how well they could do this and wanted to know when to seek advice from a health care professional, especially in regard to the exercise regimen. Some people were willing to accept the Web-based program as a replacement for face-to-face contact, while others saw it as an adjunct to the supervised face-to-face program that would help them sustain benefit and motivation after completing the program.

Acceptability partly depended on people's technical ability in using Web-based resources. Regular Internet users, familiar with technology and using Web-based resources to manage a health condition, were most accepting of the proposed website. Infrequent users, unconfident in their ability to use the Web-based resource correctly, thought they were less likely to use the website.

The website had to be aesthetically pleasing, which was defined as simple, bright, attractive, and interesting. However, people's aesthetic preferences (ie, color schemes, layout, icons, dropdown menus, scroll bars, and so on) varied greatly and were frequently mutually exclusive.

Navigation around the website had to be easy and intuitive so people could find what they wanted quickly, and information had to be easy to understand and free from jargon and acronyms. Internal and external links needed to be working, obvious, self-explanatory, and up to date. The website also needed to be optimized to work on different devices (ie, laptop, mobile phone, tablet), platforms (ie, Android, iOS), and Web browsers.

Content and Structure of a Web-Based ESCAPE-pain Program

People wanted information and advice tailored to their personal needs, which was easy to understand, was practicable, and brought tangible benefits [48]. To surmount the difficulties of individuals having different needs and preferences, they suggested each person could have “their own website” that stored personalized information and advice, allowed for creation and adjustment of personal goals, as well as monitoring and recording of progress and achievements. When it was suggested that people might need to register to use the website to its full potential (ie, monitor, record, and chart progress and enable provision of targeted personalized support) many people were uncomfortable [48]. Even if registration was free they thought it might be a barrier to some people using the website because they would be suspicious about the reasons for registration. People also expressed concerns about the difficulty of remembering usernames and passwords.

In general, people who had “experienced” ESCAPE-pain thought a Web-based version should replicate the program. People “naïve” to ESCAPE-pain asked for broader information to explain their joint pain and how to cope with its effects. For example, they wanted to know about the following: why they get pain at night; home adaptations or assistive devices that might help them cope; what the “placebo effect” was; and the association between alcohol and joint pain. People also wanted information about the effectiveness of diet and complimentary medicines (ie, fish oils, food supplements, acupuncture) in preventing or relieving joint pain. They thought this might be best presented as a brief summary of essential information, educational videos, supplemented with printable leaflets for reference and linked to reputable external sources for more in-depth information [39].

When delivered face-to-face in a clinical setting, the educational sessions of ESCAPE-pain are presented in a specific sequence. However, people thought that online this would be very restrictive and cumbersome; they wanted easy access to relevant information when it was most appropriate rather than having to navigate through “irrelevant” information. For example, people wanted to find information about dealing with an exacerbation of pain when they were in pain without going through sessions discussing weight control and diet.

Exercise

The ESCAPE-pain program focuses on the benefits that physical activity and exercise have on pain, mobility, and physical and psychosocial function. To achieve this, people undertake a progressive exercise regimen, starting off with simple exercises and gradually increasing both the number of repetitions and the quality of performance, while adding more challenging exercises as they improve. When delivered face-to-face, the exercises are supervised by an appropriately qualified professional. The Web-based program would necessitate participants to choose, perform, and progress their own exercise regimen. To achieve this, people thought they would need detailed information about exercises and exercising—how to choose appropriate exercises, how to perform them correctly, how many repetitions they should do, how often, what they should feel, and how they would know whether they were doing an exercise incorrectly or potentially causing harm. Videos showing people exercising with instructions on how to do them and how often were well received. Many people said they would be happy to try the exercise regimen, but some were concerned about performing the exercises without supervision and wanted to know when they should seek advice from a health care professional.

Monitoring

Many people wanted to document their progress to evaluate the usefulness of the program. Monitoring was also seen as a good way to engage people with the Web-based program. However, views on what should be monitored, how, and when varied. Most people thought online diaries documenting levels of pain and physical activity would be essential. Mood and medication

were also suggested but considered less important. People who were more engaged with self-managing their condition wanted to monitor symptoms frequently, whereas others thought they would only likely monitor themselves occasionally, when reminded, or if it was compulsory. In some cases, monitoring was considered an intrusive burden requiring time, effort, technical ability, and appropriate hardware.

Support

Another way of maintaining engagement and interaction with a website is by providing support. People were particularly keen to have some form of support from a health care professional (ie, physiotherapist, general practitioner) who could monitor progress, guide progression, reinforce health messages, and provide reassurance, motivation, and encouragement. Peer support through online communities (ie, forums, blogs) where people could share experiences to learn from and support other people with joint pain was seen as a positive feature, although users thought it would need to be moderated to prevent inaccurate and inappropriate postings.

Discussion

Using persuasive technology and human-centered design we investigated what features help people discover, engage with, and benefit from a Web-based program to manage chronic joint pain. If endorsed by credible organizations, some participants would be happy to accept a Web-based program as an alternative to a face-to-face program, although others did not believe it could adequately replace a face-to-face program aiming to change entrenched beliefs and behaviors. To be effective, information needs to be easy to understand and personalized for each user. People want to monitor their progress, receive feedback and guidance from a health care professional, and learn from others with similar problems. Feedback on what this might entail and the way it would be delivered varied considerably, and could be mutually exclusive, but overall it needed to be simple to minimize burden and technical requirements and, above all, protect people's privacy.

Increasingly, older people use the Internet as a source of health information [49] and accept it as part of their management [39], especially if it supplements—rather than replaces—personal care [50]. However, few utilize online information to fully self-manage their condition, often doubting the accuracy of the online information and the motives of commercially sponsored websites [46]. Approval and endorsement by health care professionals, coupled with testimonials by people that users could identify with, are very influential in encouraging people to visit a website and convincing them to engage with it and implement online advice [46,47,50].

Pain is a ubiquitous, multifaceted problem that evokes unique and varied personal experiences and consequences. It often induces health beliefs that result in harmful behavior. For example, people with chronic joint pain commonly experience pain during physical activity. They erroneously surmise activity-related pain is harmful and reduce or avoid activities to prevent causing pain and harm—"fear-avoidance behavior." Unfortunately, fear avoidance results in muscle weakness that can exacerbate pain, functional limitation, and disability [51,52]. Face-to-face behavioral change programs, such as ESCAPE-pain, incorporate BCTs to challenge these erroneous health beliefs and promote healthier behavior, namely, the role of physical activity in the management of chronic joint pain. Effective Web-based behavioral change programs need to incorporate the BCTs that make face-to-face programs effective [19,53-57].

Altering behavior involves several steps. First, people need to be convinced of the consequences of poor health behavior (inactivity) and good behavior (activity). They then need clear, unequivocal information and instructions about what (not) to do, demonstrations of how to perform specific exercises, how often, and what to expect. Knowing why and how to exercise helps form strong "implementation intentions" [58]. Unfortunately, good intentions are often not turned into action. Bridging this "intention-behavior gap" requires people to form "action plans" (which specify behaviors they want to perform, where, when, and how) and "coping plans," which raise awareness of their personal strengths, weaknesses, and situations that could undermine behavior and prepare a coping strategy to overcome these barriers [59-61]. Behavioral change is also facilitated if people self-monitor their behavior and compare it with what is expected of them (their level of physical activity compared with how physically active should they be) and this includes factors such as goal setting, feedback, and support of performance and progress [19,53,57]. Although information is usually provided in Web-based behavioral change programs, the incorporation of methods to help people construct intentions to change, such as goal setting, action plans, and interactive feedback and support, are more difficult and consequently do not often feature in many Web-based programs [56].

Our study highlights the importance of BCTs. Participants intuitively appreciated that they require in-depth, accessible information to explain and demonstrate why and how to exercise correctly. Additionally, users value self-monitoring and self-regulation, feedback, support, and encouragement, all of which can be personalized to each person's unique circumstances to make it effective and sustain engagement [55]. However, different people have varying preferences, which are often mutually exclusive. Achieving personalization is extremely difficult as it increases user time and effort burden, technical requirements, cost, and the need to register. These are features people identify as barriers to engaging with Web-based resources. Moreover, patient forums that are often advocated to facilitate health care professional and peer support [55] were rarely used by our survey respondents and the respondents in other studies [62,63].

Strengths of the Study

The survey response rate (83/200, 42%) was reasonable and allowed us to recruit focus groups and interviewees representative of people with chronic joint pain. Using participants who were "experienced" to an ESCAPE-pain based program enabled us to understand what they considered important to convey and how to convey it, while using people "naïve" to the program enabled us to understand what more

"typical" people with no prior experience of the program would need in order to apply it.

Limitations of the Study

Although participants were purposely sampled to reflect the wide opinions of people, only one person in the focus groups and none of the participants selected to test the website were unconfident about using the Internet. This means that Internet users lacking confidence were underrepresented. However, this did not have a significant impact on our findings because the prototype tested had limited functionality and was problematic even for experienced, confident Web users. Another limitation of the study was that the prototype website could only be displayed on a laptop or desktop computer, meaning it was difficult for users who are familiar with other devices, such as tablets, to feel as confident when testing the website and giving their opinions.

Conclusions

As more people live longer, and obesity and sedentary lifestyles increase, the prevalence of chronic joint pain will increase [1,2]. Web-based programs have the potential to reach the large number of people requiring help, but historically the uptake of, effectiveness of, and adherence to Web-based interventions are notoriously poor [64-66]. Persuasive technology and human-centered design and business modeling can inform the design and content of engaging, effective Web-based behavioral change programs.

Acknowledgments

The authors would like to acknowledge our patient research partner Edith Anderson, all study participants, and Salaso, who developed the prototype website. We also acknowledge Arthritis Research UK for funding the study.

Conflicts of Interest

NW is funded by Arthritis Research UK.

Multimedia Appendix 1

Focus group topic guide.

[PDF File (Adobe PDF File), 144KB - resprot_v5i2e67_app1.pdf]

Multimedia Appendix 2

Interview topic guide.

[PDF File (Adobe PDF File), 56KB - resprot_v5i2e67_app2.pdf]

References

1. Vos T, Barber R, Bell B, Bertozzi-Villa A, Biryukov S, Bolliger I, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet Aug 22 2015;386(9995):743-800.
2. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. Bull World Health Organ 2003;81(9):646-656 [FREE Full text] [Medline: 14710506]
3. Lee I, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT, Lancet Physical Activity Series Working Group. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet 2012 Jul 21;380(9838):219-229 [FREE Full text] [doi: 10.1016/S0140-6736(12)61031-9] [Medline: 22818936]
4. Dawson J, Linsell L, Zondervan K, Rose P, Carr A, Randall T, et al. Impact of persistent hip or knee pain on overall health status in elderly people: a longitudinal population study. Arthritis Rheum 2005 Jun 15;53(3):368-374. [doi: 10.1002/art.21180] [Medline: 15934104]
5. Dawson J, Linsell L, Zondervan K, Rose P, Randall T, Carr A, et al. Epidemiology of hip and knee pain and its impact on overall health status in older adults. Rheumatology (Oxford) 2004 Apr;43(4):497-504 [FREE Full text] [doi: 10.1093/rheumatology/keh086] [Medline: 14762225]
6. Losina E, Walensky RP, Reichmann WM, Holt HL, Gerlovin H, Solomon DH, et al. Impact of obesity and knee osteoarthritis on morbidity and mortality in older Americans. Ann Intern Med 2011 Feb 15;154(4):217-226 [FREE Full text] [doi: 10.7326/0003-4819-154-4-201102150-00001] [Medline: 21320937]
7. Underwood MR. Community management of knee pain in older people: is knee pain the new back pain? Rheumatology (Oxford) 2004 Jan;43(1):2-3 [FREE Full text] [doi: 10.1093/rheumatology/keg439] [Medline: 12923284]
8. National Institute for Health and Clinical Excellence. NICE Guide to the Methods of Technology Appraisal. PharmacoEconomics 2008 Sep;26(9):725-727.
9. Zhang W, Doherty M, Arden N, Bannwarth B, Bijlsma J, Gunther K, EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). EULAR evidence based recommendations for the management of hip

osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2005 May;64(5):669-681 [FREE Full text] [doi: 10.1136/ard.2004.028886] [Medline: 15471891]
10. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, American College of Rheumatology. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken) 2012 Apr;64(4):465-474. [Medline: 22563589]
11. Ganz DA, Chang JT, Roth CP, Guan M, Kamberg CJ, Niu F, et al. Quality of osteoarthritis care for community-dwelling older adults. Arthritis Rheum 2006 Apr 15;55(2):241-247. [doi: 10.1002/art.21844] [Medline: 16583414]
12. Cottrell E, Roddy E, Foster NE. The attitudes, beliefs and behaviours of GPs regarding exercise for chronic knee pain: a systematic review. BMC Fam Pract 2010;11:4 [FREE Full text] [doi: 10.1186/1471-2296-11-4] [Medline: 20082694]
13. Blakeman T, Macdonald W, Bower P, Gately C, Chew-Graham C. A qualitative study of GPs' attitudes to self-management of chronic disease. Br J Gen Pract 2006 Jun;56(527):407-414 [FREE Full text] [Medline: 16762121]
14. Hippisley-Cox J, Coupland C, Logan R. Risk of adverse gastrointestinal outcomes in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. BMJ 2005 Dec 3;331(7528):1310-1316 [FREE Full text] [doi: 10.1136/bmj.331.7528.1310] [Medline: 16322018]
15. Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger P, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 2011;342:c7086. [doi: 10.1136/bmj.c7086]
16. Solomon DH, Glynn RJ, Bohn R, Levin R, Avorn J. The hidden cost of nonselective nonsteroidal antiinflammatory drugs in older patients. J Rheumatol 2003 Apr;30(4):792-798. [Medline: 12672201]
17. Hurley MV, Walsh N, Bhavnani V, Britten N, Stevenson F. Health beliefs before and after participation on an exercised-based rehabilitation programme for chronic knee pain: doing is believing. BMC Musculoskelet Disord 2010;11:31 [FREE Full text] [doi: 10.1186/1471-2474-11-31] [Medline: 20149236]
18. Mitchell HL, Hurley MV. Management of chronic knee pain: a survey of patient preferences and treatment received. BMC Musculoskelet Disord 2008;9:123 [FREE Full text] [doi: 10.1186/1471-2474-9-123] [Medline: 18801169]
19. Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. Ann Behav Med 2013 Aug;46(1):81-95. [doi: 10.1007/s12160-013-9486-6] [Medline: 23512568]
20. Keefe FJ, Kashikar-Zuck S, Opiteck J, Hage E, Dalrymple L, Blumenthal JA. Pain in arthritis and musculoskeletal disorders: the role of coping skills training and exercise interventions. J Orthop Sports Phys Ther 1996 Oct;24(4):279-290. [doi: 10.2519/jospt.1996.24.4.279] [Medline: 8892142]
21. Penninx B, Rejeski W, Pandya J, Miller M, Di BM, Applegate W, et al. Exercise and depressive symptoms a comparison of aerobic and resistance exercise effects on emotional and physical function in older persons with high and low depressive symptomatology. The Journals of Gerontology Series B: Psychological Sciences and Social Sciences 2002;57(2):124-132.
22. Jessep SA, Walsh NE, Ratcliffe J, Hurley MV. Long-term clinical benefits and costs of an integrated rehabilitation programme compared with outpatient physiotherapy for chronic knee pain. Physiotherapy 2009 Jun;95(2):94-102. [doi: 10.1016/j.physio.2009.01.005] [Medline: 19627690]
23. Hurley MV, Walsh NE, Mitchell HL, Pimm TJ, Patel A, Williamson E, et al. Clinical effectiveness of a rehabilitation program integrating exercise, self-management, and active coping strategies for chronic knee pain: a cluster randomized trial. Arthritis Rheum 2007 Oct 15;57(7):1211-1219 [FREE Full text] [doi: 10.1002/art.22995] [Medline: 17907147]
24. Hurley MV, Walsh NE, Mitchell HL, Pimm TJ, Williamson E, Jones RH, et al. Economic evaluation of a rehabilitation program integrating exercise, self-management, and active coping strategies for chronic knee pain. Arthritis Rheum 2007 Oct 15;57(7):1220-1229 [FREE Full text] [doi: 10.1002/art.23011] [Medline: 17907207]
25. Hurley MV, Walsh NE, Mitchell H, Nicholas J, Patel A. Long-term outcomes and costs of an integrated rehabilitation program for chronic knee pain: a pragmatic, cluster randomized, controlled trial. Arthritis Care Res (Hoboken) 2012 Feb;64(2):238-247 [FREE Full text] [doi: 10.1002/acr.20642] [Medline: 21954131]
26. Griffiths F, Lindenmeyer A, Powell J, Lowe P, Thorogood M. Why are health care interventions delivered over the internet? A systematic review of the published literature. J Med Internet Res 2006;8(2):e10. [doi: 10.2196/jmir.8.2.e10] [Medline: 16867965]
27. Eysenbach G. What is e-health? J Med Internet Res 2001;3(2):e20. [doi: 10.2196/jmir.3.2.e20] [Medline: 11720962]
28. Tate DF, Finkelstein EA, Khavjou O, Gustafson A. Cost effectiveness of internet interventions: review and recommendations. Ann Behav Med 2009 Aug;38(1):40-45 [FREE Full text] [doi: 10.1007/s12160-009-9131-6] [Medline: 19834778]
29. van GJ, Nijland N, van LM, Ossebaard H, Kelders S, Eysenbach G, et al. A holistic framework to improve the uptake and impact of eHealth technologies. J Med Internet Res 2011;13(4):e111. [doi: 10.2196/jmir.1672]
30. Pagliari C. Design and evaluation in eHealth: challenges and implications for an interdisciplinary field. J Med Internet Res 2007;9(2):e15. [doi: 10.2196/jmir.9.2.e15] [Medline: 17537718]
31. Yusof MM, Papazafeiropoulou A, Paul RJ, Stergioulas LK. Investigating evaluation frameworks for health information systems. Int J Med Inform 2008 Jun;77(6):377-385. [doi: 10.1016/j.ijmedinf.2007.08.004] [Medline: 17904898]
32. Van't RJ, Crutzen R, De VH. Investigating predictors of visiting, using, and revisiting an online health-communication program: a longitudinal study. J Med Internet Res 2010;12(3):e37. [doi: 10.2196/jmir.1345] [Medline: 20813716]

33. Eysenbach G. The law of attrition. J Med Internet Res 2005;7(1):e11. [doi: 10.2196/jmir.7.1.e11] [Medline: 15829473]
34. Black A, Car J, Pagliari C, Anandan C, Cresswell K, Bokun T, et al. The impact of eHealth on the quality and safety of health care: a systematic overview. PLoS medicine Jan 18 2011;8(1):188.
35. Kelders S, Kok R, Ossebaard H, Van GJ. Persuasive system design does matter: a systematic review of adherence to web-based interventions. J Med Internet Res 2012;14(6):e152. [doi: 10.2196/jmir.2104] [Medline: 23151820]
36. Donkin L, Christensen H, Naismith S, Neal B, Hickie I, Glozier N. A systematic review of the impact of adherence on the effectiveness of e-therapies. J Med Internet Res 2011;13(3):e52. [doi: 10.2196/jmir.1772] [Medline: 21821503]
37. Murray E. Web-based interventions for behavior change and self-management: potential, pitfalls, and progress. Medicine 20 2012;1(2):e3. [doi: 10.2196/med20.1741]
38. Walsh N, Cramp F, Palmer S, Pollock J, Hampson L, Gooberman-Hill R, et al. Exercise and self-management for people with chronic knee, hip or lower back pain: a cluster randomised controlled trial of clinical and cost-effectiveness. Study protocol. Physiotherapy 2013 Dec;99(4):352-357. [doi: 10.1016/j.physio.2012.09.002] [Medline: 23200601]
39. Yardley L, Morrison LG, Andreou P, Joseph J, Little P. Understanding reactions to an internet-delivered health-care intervention: accommodating user preferences for information provision. BMC Med Inform Decis Mak 2010;10:52 [FREE Full text] [doi: 10.1186/1472-6947-10-52] [Medline: 20849599]
40. Fogg B. Using computers to change what we think and do. In: Persuasive Technology: Using Computers to Change What We Think and Do. San Francisco: Morgan Kaufmann; 2002:5.
41. Oinas-Kukkonen H, Harjumaa M. Persuasive systems design: Key issues, process model, and system features. Communications of the Association for Information Systems Mar 1 2009;24(1):28.
42. Morrison LG, Yardley L, Powell J, Michie S. What design features are used in effective e-health interventions? A review using techniques from Critical Interpretive Synthesis. Telemed J E Health 2012 Mar;18(2):137-144. [doi: 10.1089/tmj.2011.0062] [Medline: 22381060]
43. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative research in psychology 2006;3(2):77-101.
44. Ericsson K, Simon H. How to study thinking in everyday life: Contrasting think-aloud protocols with descriptions and explanations of thinking. Mind, Culture, and Activity 1998;5(3):178-186.
45. Cotten SR, Gupta SS. Characteristics of online and offline health information seekers and factors that discriminate between them. Soc Sci Med 2004 Nov;59(9):1795-1806. [doi: 10.1016/j.socscimed.2004.02.020] [Medline: 15312915]
46. Sillence E, Briggs P, Harris PR, Fishwick L. How do patients evaluate and make use of online health information? Soc Sci Med 2007 May;64(9):1853-1862. [doi: 10.1016/j.socscimed.2007.01.012] [Medline: 17328998]
47. Sillence E, Briggs P, Harris P, Fishwick L. Going online for health advice: changes in usage and trust practices over the last five years. Interacting with computers 2007;19(3):397-406.
48. Sillence E, Briggs P, Harris P, Fishwick L. A framework for understanding trust factors in web-based health advice. International Journal of Human-Computer Studies 2006;64(8):697-713.
49. United Kingdom Office for National Statistics. Office for National Statistics. 2012. Internet Access Quarterly Update, Q4 2012 URL: http://webarchive.nationalarchives.gov.uk/20160105160709/http://ons.gov.uk/ons/rel/rdit2/internet-access-quarterly-update/2012-q4/stb-ia-2012-q4.html [accessed 2016-03-29] [WebCite Cache ID 6gMjvM7Vs]
50. Currie M, Philip LJ, Roberts A. Attitudes towards the use and acceptance of eHealth technologies: a case study of older adults living with chronic pain and implications for rural healthcare. BMC Health Serv Res 2015;15:162 [FREE Full text] [doi: 10.1186/s12913-015-0825-0] [Medline: 25888988]
51. Leeuw M, Goossens Mariëlle E J B, Linton SJ, Crombez G, Boersma K, Vlaeyen Johan W S. The fear-avoidance model of musculoskeletal pain: current state of scientific evidence. J Behav Med 2007 Feb;30(1):77-94. [doi: 10.1007/s10865-006-9085-0] [Medline: 17180640]
52. Hurley MV. The role of muscle weakness in the pathogenesis of osteoarthritis. Rheum Dis Clin North Am 1999 May;25(2):283-98, vi. [Medline: 10356418]
53. Presseau J, Ivers NM, Newham JJ, Knittle K, Danko KJ, Grimshaw JM. Using a behaviour change techniques taxonomy to identify active ingredients within trials of implementation interventions for diabetes care. Implement Sci 2015;10:55 [FREE Full text] [doi: 10.1186/s13012-015-0248-7] [Medline: 25900104]
54. Steinmo S, Fuller C, Stone SP, Michie S. Characterising an implementation intervention in terms of behaviour change techniques and theory: the 'Sepsis Six' clinical care bundle. Implement Sci 2015;10:111 [FREE Full text] [doi: 10.1186/s13012-015-0300-7] [Medline: 26253306]
55. Morrison LG, Yardley L, Powell J, Michie S. What design features are used in effective e-health interventions? A review using techniques from Critical Interpretive Synthesis. Telemed J E Health 2012 Mar;18(2):137-144. [doi: 10.1089/tmj.2011.0062] [Medline: 22381060]
56. Conroy DE, Yang C, Maher JP. Behavior change techniques in top-ranked mobile apps for physical activity. Am J Prev Med 2014 Jun;46(6):649-652. [doi: 10.1016/j.amepre.2014.01.010] [Medline: 24842742]
57. Yang C, Maher JP, Conroy DE. Implementation of behavior change techniques in mobile applications for physical activity. Am J Prev Med 2015 Apr;48(4):452-455. [doi: 10.1016/j.amepre.2014.10.010] [Medline: 25576494]
58. Gollwitzer P. Implementation intentions: strong effects of simple plans. American psychologist Jul 1999;54(7):493.

59. Sniehotta FF, Scholz U, Schwarzer R. Action plans and coping plans for physical exercise: A longitudinal intervention study in cardiac rehabilitation. Br J Health Psychol 2006 Feb;11(Pt 1):23-37. [doi: 10.1348/135910705X43804] [Medline: 16480553]
60. Scholz U, Knoll N, Sniehotta FF, Schwarzer R. Physical activity and depressive symptoms in cardiac rehabilitation: long-term effects of a self-management intervention. Soc Sci Med 2006 Jun;62(12):3109-3120. [doi: 10.1016/j.socscimed.2005.11.035] [Medline: 16388882]
61. Sniehotta F, Schwarzer R, Scholz U, Schüz B. Action planning and coping planning for long-term lifestyle change: theory and assessment. European Journal of Social Psychology Jul 1 2005;35(4):565-576.
62. Sillence E, Hardy C, Briggs P. Why don't we trust health websites that help us help each other?: an analysis of online peer-to-peer healthcare. 2013 May 02 Presented at: In Proceedings of the 5th Annual ACM Web Science Conference. ACM; 2013 May 2; Paris, France p. 396-404.
63. Nielsen J. Too many topics, too little time. 2006 Oct 14. Participation inequality: lurkers vs. contributors in internet communities (Jakob Nielsen's Alertbox) URL: http://www.tmttlt.com/archives/5079 [accessed 2016-03-29] [WebCite Cache ID 6gMhWIGL7]
64. Bossen D, Buskermolen M, Veenhof C, de Bakker D, Dekker J. Adherence to a Web-based physical activity intervention for patients with knee and/or Hip osteoarthritis: a mixed method study. Journal of medical Internet research Oct 2013;15(10):e223. [doi: 10.2196/jmir.2742]
65. Bossen D, Veenhof C, Van Beek K, Spreeuwenberg P, Dekker J, de Bakker D. Effectiveness of a web-based physical activity intervention in patients with knee and/or hip osteoarthritis: randomized controlled trial. Journal of Medical Internet Research Nov 2013;15(11):e257. [doi: 10.2196/jmir.2662]
66. Li LC, Townsend AF, Badley EM. Self-management interventions in the digital age: new approaches to support people with rheumatologic conditions. Best Pract Res Clin Rheumatol 2012 Jun;26(3):321-333. [doi: 10.1016/j.berh.2012.05.005] [Medline: 22867929]

Abbreviations

BCT: behavioral change technique
ESCAPE-pain: Enabling Self-management and Coping with Arthritic Pain through Exercise
OA: osteoarthritis

Edited by G Eysenbach; submitted 16.12.15; peer-reviewed by D Bossen, N Dewan; comments to author 06.01.16; revised version received 27.01.16; accepted 28.01.16; published 19.05.16.

Please cite as:
Pearson J, Walsh N, Carter D, Koskela S, Hurley M
Developing a Web-Based Version of An Exercise-Based Rehabilitation Program for People With Chronic Knee and Hip Pain: A Mixed Methods Study
JMIR Res Protoc 2016;5(2):e67
URL: http://www.researchprotocols.org/2016/2/e67/
doi:10.2196/resprot.5446
PMID:27197702

Original Paper

Development of the Lupus Interactive Navigator as an Empowering Web-Based eHealth Tool to Facilitate Lupus Management: Users Perspectives on Usability and Acceptability

Carolyn Neville[1], BA, RN; Deborah Da Costa[1], PhD; Murray Rochon[2], BArch; Christine A Peschken[3], MD, MSc, FRCP; Christian A Pineau[4], MD, FRCPC; Sasha Bernatsky[4], MD, PhD, FRCPC; Stephanie Keeling[5], MD, MSc, FRCPC; Antonio Avina-Zubieta[6,7], MD, PhD; Elizabeth Lye[2], BSc; Davy Eng[8], MSc; Paul R Fortin[8,9], MD, MPH, FRCPC

[1]Division of Clinical Epidemiology, Department of Medicine, McGill University Health Centre, Montreal, QC, Canada
[2]Jack Digital Productions, Inc, Toronto, ON, Canada
[3]Division of Rheumatology, Department of Medicine, University of Manitoba, Winnipeg, MB, Canada
[4]Division of Rheumatology, McGill University Health Centre, Montreal, QC, Canada
[5]Division of Rheumatology, Department of Medicine, University of Alberta, Edmonton, AB, Canada
[6]Arthritis Research Centre of Canada, Vancouver, BC, Canada
[7]Division of Rheumatology, Department of Medicine, University of British Columbia, Vancouver, BC, Canada
[8]Axe Maladies Infectieuses et Immunitaires, Centre de recherche du CHU de Québec - Université Laval, Quebec City, QC, Canada
[9]Division of Rheumatology, Department of Medicine, CHU de Québec - Université Laval, Quebec City, QC, Canada

Corresponding Author:
Paul R Fortin, MD, MPH, FRCPC
Centre de recherche du CHU de Québec - Université Laval
Faculté de médecine
Université Laval
2705, boul. Laurier, Room H-1365
Quebec, QC, G1V 4G2
Canada
Phone: 1 418 654 2178
Fax: 1 418 654 2142
Email: Paul.Fortin@crhudequebec.ulaval.ca

Abstract

Background: Systemic Lupus Erythematosus (SLE) is a serious, complex, and chronic illness. Similar to most other chronic illness states, there is great interest in helping persons with SLE engage in their disease management.

Objective: The objectives of this study were to (1) develop the Lupus Interactive Navigator (LIN), a web-based self-management program for persons with SLE, and (2) test the LIN for usability and acceptability.

Methods: The LIN development platform was based on the results of preliminary comprehensive needs assessments and adapted from the Oncology Interactive Navigator, a web-based tool developed for persons with cancer. Medical researchers, writers, designers, and programmers worked with clinical experts and persons with SLE to develop content for the LIN. Usability and acceptability of the LIN was tested on individuals with SLE meeting American College of Rheumatology criteria, who were recruited from five Canadian SLE clinics. Participants were provided with access to the LIN and were asked to use it over a two-week period. Following the testing period, participants were contacted for a 30-minute telephone interview to assess usability and acceptability.

Results: The content for the LIN was subdivided into six primary information topics with interview videos featuring rheumatologists, allied health professionals, and persons with SLE. Usability and acceptability of the LIN was tested on 43 females with SLE. Of these, 37 (86%) completed telephone interviews. The average age was 43.6 (SD 15.9) years and disease duration averaged 14.1 (SD 10.8) years. Median time spent on LIN was 16.3 (interquartile range [IQR]:13.7, 53.5) minutes and median number of sessions was 2 (IQR: 1, 3). Overall, Likert ratings (0=strongly disagree; 7=strongly agree) of website usability and content were very high, with 75% scoring >6 out of 7 on all items. All participants agreed that LIN was easy to use, would

recommend it to others with SLE, and would refer to it for future questions about SLE. Very high ratings were also given to relevancy, credibility, and usefulness of the information provided. Overall, 73% of the participants rated all topics helpful to very helpful. Participants who reported more prior knowledge about SLE rated items regarding improvement in knowledge and helpfulness relatively lower than persons with less prior knowledge. Most participants commented that the LIN would be very useful to those newly diagnosed with SLE. Minor revisions were recommended.

Conclusions: This study furthers the understanding of the needs in the SLE community and delivers a unique eHealth tool to promote self-management in persons with SLE. The LIN was found to be highly acceptable in content and usability. The information provided on LIN may be most helpful for individuals with less experience with the disease, such as those newly diagnosed, indicating the need to tailor the content for persons with more SLE experience.

(JMIR Res Protoc 2016;5(2):e44) doi:10.2196/resprot.4219

KEYWORDS

Systemic lupus erythematosus; web-based eHealth tool; self-management; empowerment; usability; navigation

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease associated with multi-organ involvement and characterized by frequent flares. The unpredictable nature of the illness and complexity of treatment create serious challenges in disease management to persons with SLE and their health care providers [1]. Self-management interventions are essential to meet these challenges and they must be built on sound person-centered approaches and aimed at self-empowerment strategies. In chronic illness management there is an ever increasing need for patients to play more active roles in their health care, and work in partnership with their health care providers. However, for this to occur, patients need to be equipped with a technology that will provide them with appropriate information and accessible support tools. We used qualitative research methods to better define the information and support needs of persons with SLE and health care providers [2,3]. Oncology Interactive Navigator (OIN) is a web-based tool developed to build a sense of competence around living with cancer, support autonomy, and engage patients and families as partners in care. Based on the OIN and preliminary work in SLE, we developed the Lupus Interactive Navigator (LIN). The LIN was designed to provide education and to support self-management in persons with SLE. This paper reports on the development of the LIN and the results of the testing of usability and acceptability of the LIN.

Methods

Development of the Lupus Interactive Navigator

The results of the needs assessments were organized into topic groups to form the basis of the *Table of Contents* and guide content development of the LIN. By adapting the OIN platform and approach, medical researchers, writers, designers and programmers worked with clinical experts and persons with SLE to outline the *Table of Contents* and write the first plain-language draft for the LIN. Required graphics and interview videos featuring rheumatologists, allied health professionals, and persons with SLE were produced to complement the written content.

The content for the LIN was subdivided into six primary information topics that were derived from the qualitative analysis of the results of our focus groups and surveys [2,3]. Each primary topic was subdivided with pull-down tabs for further elaboration on each topic (Table 1).

Table 1. Summary of LIN *Table of Contents*.

About Lupus	Symptom Management & Treatments	Accessing Healthcare	Support Services	Family, Friends & Work	Living Well With Lupus
What is Lupus	Symptoms of Lupus	Your Care Team	Community Services search tool to locate available lupus- support resources in close proximity to the user's postal code	Family & Lupus	Managing Stress & Fatigue
What Causes Lupus?	Medications to Treat Lupus	Communicating with Your Care Team		Lupus & Work	Getting Enough Sleep
Lupus & the Immune System	Side Effects of Medications	Covering Medical Costs		Supporting Someone With Lupus	The Importance of Exercise
A Lupus Diagnosis	Preventing and Managing Flares	Transitioning From Pediatric to Adult Care		Resources for Family Members & Friends	Depression
Prognosis	Monitoring Your Lupus	Accessing Care in Rural Areas			Overcoming the Emotional Hurdles of Lupus
Flares and Remissions	Complementary Therapies				Maintaining a Healthy Diet
Lupus & The Body	Other Therapies				Vaccinations
FAQs/ Myths	Clinical Trials				Pregnancy & Lupus
					Young People & Lupus

Usability and Acceptability of the Lupus Interactive Navigator

Participants

Individuals meeting the 1997 SLE American College of Rheumatology criteria [4] were recruited from five Canadian SLE clinics based in university health centers in Vancouver, Edmonton, Winnipeg, Montreal and Quebec City. Each center had obtained prior approval from their local research ethics board for this study. Consenting participants were provided information on how to access the LIN website and were asked to use their devices (computers, tablets, or mobile phones) to browse LIN over a two-week period. The number of log-ins and the duration of each session were recorded for each participant. Following the two-week testing period, participants were contacted for a 30-minute telephone interview to assess their opinions about the LIN and to identify areas for improvement.

Telephone Interview

Content for the telephone interview was established following discussions with members of an expert panel including a rheumatologist, a psychologist, a nurse, the developer of the OIN, and an individual with SLE. The telephone interview consisted of a four-page document including (1) a script to be used as the introduction to each interview, (2) questions to assess demographics and participant characteristics, (3) Likert scales to rate website usability, content, and perceived helpfulness, and (4) open-ended questions to assess overall acceptability and usability of the LIN and to provide recommendations and comments.

Participant characteristics included age, marital status, education, disease duration, and factors related to computer usage, including ease with using computers, time spent on the Internet, time spent searching for health information, and type of device used.

Website Usability and Content

Likert scales were used to assess website usability and content quality and quantity. Participants were asked to rate 17 items on a 7-point Likert scale (0=strongly disagree; 7=strongly agree). Participants who scored items <3 were asked to elaborate. Scores equal to or >5 were considered moderate to strong agreements. Scores equal to or <4 were considered low to no agreement.

Helpfulness

Participants were asked to rate each of the six topic sections using a 5-point Likert scale in terms of how helpful each section was to them (1=not at all helpful; 5=most helpful). Scores equal to or >4 were considered *helpful* to *very helpful*. Scores equal to or <3 were considered low to *not at all helpful*.

Recommendations and Comments

Four open-ended questions were asked to further assess if there was information missing, and give participants the opportunity to comment on the overall experience and provide recommendations for improvement.

Statistical Analyses

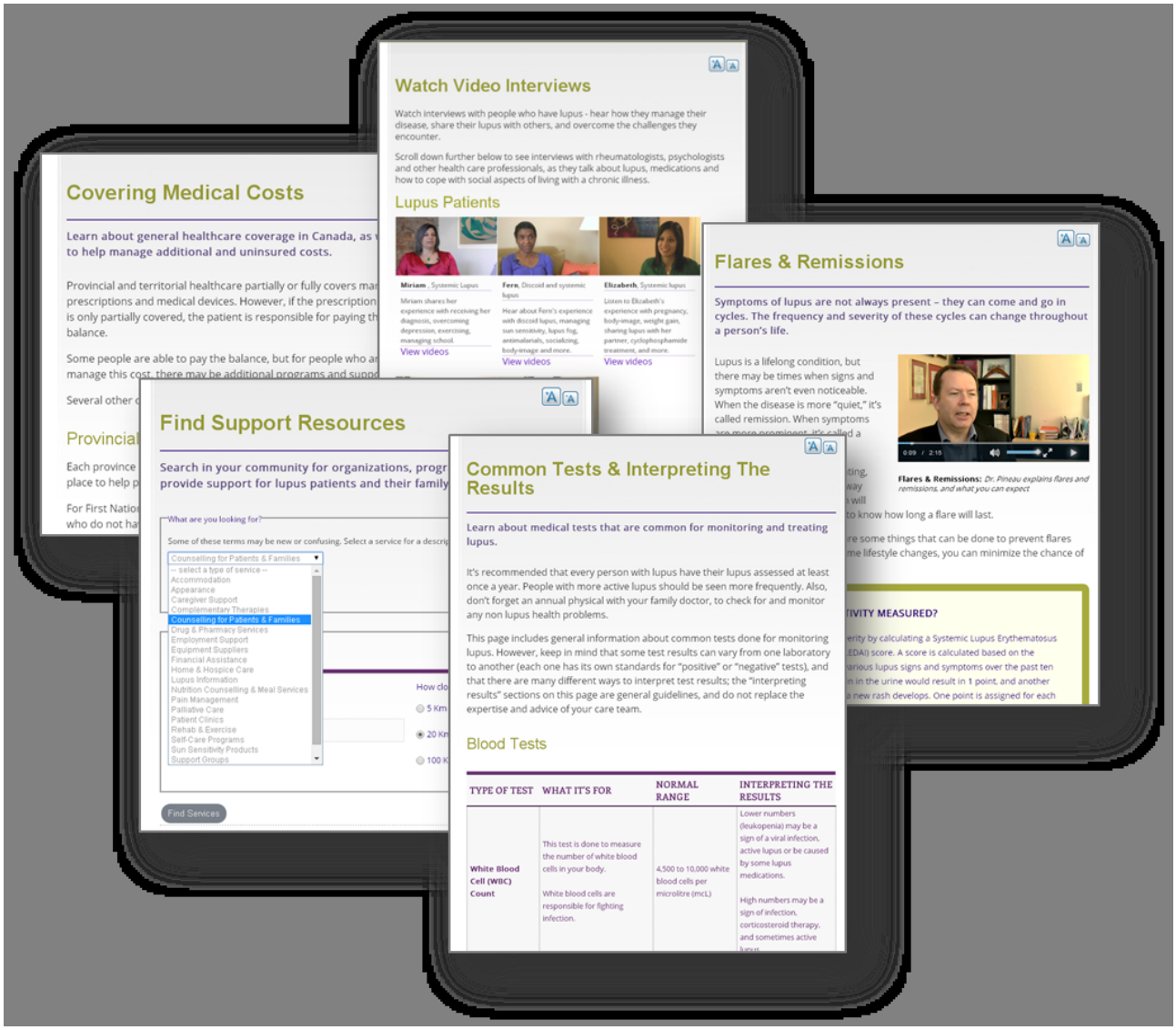
The data was transferred from the interview questionnaire to Microsoft Excel (2007). Means, medians, and percentages were calculated for continuous variables and percentages were calculated for categorical variables.

Results

Development of the Lupus Interactive Navigator

The LIN was constructed from a *Table of Contents* that was developed from the results of the prior focus group studies and surveys performed in preparation for this project [2,3]. An abbreviated *Table of Contents* is provided in Table 1, reflecting the topics that were prioritized by the focus groups and surveys. Figure 1 provides a glimpse of some of the web-based pages that persons with SLE can access once logged into the LIN.

Figure 1. Examples of LIN web pages.



Usability and Acceptability of the Lupus Interactive Navigator

Forty-three women with SLE were recruited. Of these, six participants did not complete the two-week follow-up telephone interview (time constraints, 2; illness, 2; could not be contacted, 2). Thirty-seven (86%) completed the telephone interviews. Median time spent on LIN was 16.3 (interquartile range [IQR]:13.7, 53.5) minutes and median number of sessions was 2 (IQR: 1, 3).

Characteristics of Participants

Table 2 describes the characteristics of the study participants. The average age was 43.6 (SD 15.9) years, disease duration averaged 14.1 (SD 10.8) years, 57% (21/37) were married, and 86% (32/37) had completed post-secondary education. Weekly reported average Internet usage was 15.8 (SD 24.6) hours with 2.8 (SD 0.9) hours used for health information. Ratings for overall experience, website usability, and content are shown in Table 3.

Table 2. Participant characteristics (N=37).

	Mean (SD)	n (%)
Age (years)	43.6 (15.9)	
Disease duration (years)	14.1 (10.8)	
Gender (% female)		37 (100)
Marital status (% married)		21 (57)
Education (% post-secondary)		32 (86)
Comfort with computers (% comfortable to very comfortable)		27 (73)
Internet usage per week (hours)	15.8 (24.6)	
Health information searches per week (hours)	2.8 (0.9)	
Preference for web searching		
Personal Computer		24 (65)
Tablet		7 (19)
Mobile Phone		6 (16)

Table 3. Ratings of website usability and content based on 37 participants (1=strongly disagree; 7=strongly agree).

Statement	Mean (SD)	% equal to or >5
Overall experience		
I would recommend this website to others seeking information about lupus	6.8 (0.5)	100
Would go to this website if I had a question about lupus	6.2 (1.5)	89
My friends and family would benefit by accessing this website	6.0 (1.8)	89
Website design		
Easy to learn how to use the website	6.7 (0.6)	100
Easy to find information on this website	6.6 (0.6)	97
Easy to read information	6.6 (0.7)	100
Easy to use the website	6.6 (0.6)	100
Content		
Information was credible	6.6 (0.8)	97
Information was relevant	6.6 (0.7)	97
Information was useful	6.5 (1.1)	97
Satisfied with the amount of information	5.9 (1.6)	87
Improved knowledge about lupus	5.8 (1.6)	87
Improved knowledge about coping	5.4 (1.9)	78
Improved knowledge about resources	5.4 (1.8)	77
Will help me maintain better health habits	5.3 (1.7)	69
Improved knowledge about medications	5.0 (1.8)	68
Will be useful to help me prepare for next doctor's visit	5.0 (1.9)	67

Overall Experience

All participants strongly agreed that they would recommend this website to other persons with SLE seeking information about SLE and 89% (33/37) would refer to it to answer their own future questions about SLE. Participants also agreed that family and friends would benefit from accessing the LIN.

Website Usability

All items assessing website usability received *high* to *very high* ratings. All participants were in *high* agreement that the website was easy to learn and use.

Content

Over 97% (36/37) of the participants were in *high* to *very high* agreement that the content was useful, credible, and relevant.

Additionally, 86% (32/37) of participants were satisfied with the amount of information provided. Ratings for items relating to gains in knowledge about lupus, coping, and resources were *high* (77-87%). Somewhat lower ratings were given for items relating to gains in knowledge about medications, helpfulness in maintaining good health habits, and preparing for clinic visits (67-69%). Participants stated that the reason for giving lower ratings was prior knowledge about these items. Participants with disease duration <5 years had similar ratings for these items as those with disease duration >5 years. However, there were only 11 participants with short disease duration in our sample.

Helpfulness

Table 4 shows the ratings of helpfulness of each of the six major information topics provided in LIN. Overall, 73% (27/37) of the participants rated all topics *helpful* to *very helpful*.

Ratings of perceived helpfulness for each individual major topic varied across topics. The topic *About Lupus* (providing general information about SLE) was perceived as the most helpful (91%) and the topic *Support Services* (providing information about available resources) was considered least helpful (57%). Once again, lower ratings were given by those who reported prior knowledge about SLE than those with less prior knowledge (62% versus 86%).

All participants voiced enthusiasm about LIN and were eager to offer comments and recommendations to further improve this website. None of the participants reported any information missing from the content. However, 26 participants would have preferred more information about specific topics. Of these, the most frequently requested were: more information regarding current research about new medications for SLE (n=9); coping strategies including yoga, meditation, psychosocial, and complementary/alternative treatments (n=9); and adding more support resources on the resource locator for Manitoba and Alberta, including support groups and social workers (n=7).

Minor changes were recommended to improve appearance and usability of the LIN, including changes to font and facilitating drop-down menus. Recommendations to improve content included (1) more videos of physicians and youths, (2) more pictures of rashes and medications, (3) the addition of social networking tools such as a chat room or forum, (4) updates on research and new medications using podcasts, tweets, newsletters, or message boards, and (5) providing a link to show the source of the information provided in the LIN. These adaptations are being implemented.

Overall, the comments were very positive. The most frequent comment was that this website would be most useful to those newly diagnosed with SLE (n=10). Many participants spoke of looking forward to the completed version of LIN that would include a forum for discussion.

Table 4. Ratings of helpfulness of the LIN content across information topics based on 37 participants (1=not at all helpful; 5=most helpful).

Section topic	Median (IQR)	% equal to or >4
About Lupus	5 (4,5)	91
Friends, family, and work	5 (4,5)	76
Symptom management and treatment	5 (3,5)	72
Living well with Lupus	5 (3,5)	71
Accessing health care	4 (3,5)	68
Support services	4 (3,4)	57

Discussion

Tailored web-based programs are becoming increasingly considered as a means of empowering individuals with chronic conditions with the tools and strategies needed to promote self-management. Our study furthers the understanding of needs in the SLE community, and allowed us to develop a web-based tool to build confidence, support autonomy, and empower persons with SLE toward self-management. As SLE is an uncommon yet important disease, this is also an important tool to support health providers caring for people with SLE.

There are a number of potential limitations of our work. First, the study participants were recruited from tertiary care centers and tended to be well educated, and thus may not be entirely representative of the full spectrum of persons with SLE. Second, participants were all females and we cannot generalize these findings to males, who represent 10% of the SLE population. Third, most participants had SLE for several years and their analysis of the LIN was affected by their own experience of living with SLE for that period of time. Many participants mentioned the usefulness of the LIN for persons newly diagnosed with SLE. Several participants also perceived that the LIN would have been most useful at the time of their diagnosis, although they agreed that they still learned from the LIN and would continue to use it to answer questions in the future. This suggests that the LIN could provide different points of entry based on disease duration and experience. Lastly, accessibility of a web-based tool may be suboptimal in some geographic, demographic, or socio-economic groups. However, the LIN can be used from any mobile device such as a tablet or mobile phone.

We assessed the acceptability and usefulness of the LIN as a tool to improve empowerment and self-management in persons with SLE. These results support the value of using a multi-method design that included surveys, focus groups, an expert panel, and interviews when developing programs tailored to specific populations. It is important to acknowledge that tools such as the LIN require ongoing updates and development to

respond to new information and user feedback. Other sections which we are already considering for further development include a personalized *SLE Tool Box* which will offer links to an electronic SLE *Health Passport* (personal profile to monitor aspects of health, such as blood pressure), printable information sheets, links to clinical trials, and a forum for discussions relating to SLE.

All participants agreed that the website was easy to navigate and functioned well. The quality and quantity of content were also rated highly. No topics were reported to be missing. This suggests the value of involving patients in the design phase by identifying their needs and preferences when developing eHealth websites tailored to specific populations. Nine participants suggested adding more information about research on new medications for SLE and six participants asked for more information about yoga and meditation as coping strategies. To address these needs, more information will be provided about ongoing research on SLE, and coping strategies delivered interactively via webinars with psychosocial experts are being considered.

Conclusion

As chronic disease models of care evolve toward self-management, it is increasingly important to develop and validate tools that support providers and engage patients. The LIN is an example of such a tool. It was very well received by patients, and considered easy to navigate with sufficient quantity and quality of content. The information provided on the LIN may be most helpful for individuals lacking experience with the disease, such as those newly diagnosed. Our results suggest the need to tailor the content for persons with more SLE experience.

Acknowledgments

We are thankful to all participants for their contributions in the telephone interviews for this study. We would like to acknowledge the contributions to the development of the content for LIN from our SLE patient collaborators, including Fern Davis, Wendy Singer, Claire Rodrigues, Ben Sherman, Miriam Gaudelli, and Elizabeth Vicente. We would also like to thank our colleagues from Health Care Providers, including Evelyne Vinet, Janet Pope, Monique Gignac, Lori Tucker, and Anne Cymet. We are grateful to: Kathryn Reimer, Vancouver, British Columbia; Asvina Bissonauth, Edmonton, Alberta; Mellissa Moyen, Winnipeg, Manitoba; and Alexandra GodBout, Quebec City, Quebec, for their help in coordinating the study, Jane Su for providing research assistance, and Julie Parrot for secretarial assistance.

This research was supported by Partnerships for Health System Improvement (PHSI) grant 238692 from the Canadian Institutes of Health Research (CIHR), with an in-kind contribution by Jack Digital Productions (JDP) and a partnership contribution to PHSI made by GlaxoSmithKline (GSK) Canada. Dr Fortin holds a Canada Research Chair in Systemic Autoimmune Rheumatic Diseases and is supported by Université Laval, Quebec, Canada.

Authors' Contributions

All authors contributed to the conceptual framework of this paper as well as to the development of the content of the surveys with their own expertise as rheumatologist (Paul R Fortin), psychologist (Deborah Da Costa), nurse (Carolyn Neville), and developer of the Oncology Interactive Navigator (Murray Rochon). This effort was coordinated by Davy Eng. The analysis was done by Carolyn Neville. Interpretation of the data was done by Carolyn Neville and Paul R Fortin. All authors contributed to, reviewed, and approved the paper.

Conflicts of Interest

Carolyn Neville, Deborah Da Costa, Christian Pineau, Antonio Aviña-Zubieta, and Davy Eng declare that they have no conflicts of interest. Murray Rochon has a patent copyright, trademark, and marketing rights with royalties paid to JDP and is the founder of JDP, a social innovation company that is a partner organization under the PHSI grant provided by CIHR for this work. As part of the mandate of this grant, corporations are asked to partner with researchers to help effect change in health systems. This alignment and collaboration is a criterion of the CIHR grant to extend the reach and application of innovation. JDP contributes funds and expertise to develop this tool, and retains rights to content, technology, dissemination, and licensing of the tool in all jurisdictions. Stephanie Keeling reports having participated in a Lupus Advisory Board for Eli Lilly. Paul R Fortin reports grants from the CIHR and an in-kind contribution from JDP during the conduct of this study, as well as other unrestricted funds from GSK Canada Inc., also as part of the PHSI CIHR grant partnership program. He also reports having participating on Lupus Advisory Boards for Eli Lilly, AbbVie and GSK.

References

1. Hale ED, Treharne GJ, Lyons AC, Norton Y, Mole S, Mitton DL, et al. "Joining the dots" for patients with systemic lupus erythematosus: personal perspectives of health care from a qualitative study. Ann Rheum Dis 2006 May;65(5):585-589 [FREE Full text] [doi: 10.1136/ard.2005.037077] [Medline: 16219711]
2. Neville C, Da CD, Mill C, Rochon M, Aviña-Zubieta JA, Pineau CA, et al. The needs of persons with lupus and health care providers: a qualitative study aimed toward the development of the Lupus Interactive Navigator. Lupus 2014 Feb;23(2):176-182. [doi: 10.1177/0961203313517154] [Medline: 24335012]

3. Neville C, DaCosta D, Rochon M, Eng D, Fortin PR. Toward the development of a Lupus Interactive Navigator to facilitate patients and their health care providers in the management of lupus: results of web-based surveys. JMIR Res Protoc 2014;3(4):e65 [FREE Full text] [doi: 10.2196/resprot.3349] [Medline: 25533760]
4. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997 Sep;40(9):1725. [doi: 10.1002/1529-0131(199709)40:9<1725::AID-ART29>3.0.CO;2-Y] [Medline: 9324032]

Abbreviations

CIHR: Canadian Institutes of Health Research
GSK: GlaxoSmithKline
IQR: interquartile range
JDP: Jack Digital Productions
LIN: Lupus Interactive Navigator
OIN: Oncology Interactive Navigator
PSHI: Partnerships for Health System Improvement
SLE: Systemic lupus erythematosus

Edited by G Eysenbach; submitted 16.01.15; peer-reviewed by M Jolly, J Prescott; comments to author 23.06.15; revised version received 06.01.16; accepted 07.01.16; published 30.05.16.

Please cite as:
Neville C, Da Costa D, Rochon M, Peschken CA, Pineau CA, Bernatsky S, Keeling S, Avina-Zubieta A, Lye E, Eng D, Fortin PR
Development of the Lupus Interactive Navigator as an Empowering Web-Based eHealth Tool to Facilitate Lupus Management: Users Perspectives on Usability and Acceptability
JMIR Res Protoc 2016;5(2):e44
URL: http://www.researchprotocols.org/2016/2/e44/
doi:10.2196/resprot.4219
PMID:27240666

Original Paper

A Web-Based Platform for Patients With Osteoarthritis of the Hip and Knee: A Pilot Study

Leif E Dahlberg[1], MD, PhD; Daniel Grahn[2]; Jakob E Dahlberg[2]; Carina A Thorstensson[3,4], PhD

[1]Orthopedics, Department of Clinical Sciences Lund, Skåne University Hospital, Lund University, Lund, Sweden

[2]Joint Academy, Malmö, Sweden

[3]Institute of Neuroscience and Physiology, Sahlgrenska Academy, Department of Clinical Neuroscience and Rehabilitation, University of Gothenburg, Gothenburg, Sweden

[4]BOA Registry, Registercentrum Västra Götaland, Gothenburg, Sweden

Corresponding Author:
Leif E Dahlberg, MD, PhD
Orthopedics
Department of Clinical Sciences Lund, Skåne University Hospital
Lund University
Skåne University Hospital
Lund, SE-221 85
Sweden
Phone: 46 46171540
Fax: 46 46130732
Email: leif.dahlberg@med.lu.se

Abstract

Background: Chronic conditions are the leading cause of disability throughout the world and the most expensive problem facing the health care systems. One such chronic condition is osteoarthritis (OA), a frequent cause of major disability.

Objective: To describe the effect on joint pain for the first users of a newly developed Web-based osteoarthritis self-managing program, Joint Academy, and to examine whether these patients would recommend other OA patients to use the program.

Methods: Patients with clinically established knee or hip OA according to national and international guidelines were recruited from an online advertisement. A trained physiotherapist screened the eligible patients by scrutinizing their answers to a standardized questionnaire. The 6-week program consisted of eight 2- to 5-minute videos with lectures about OA, effects of physical activity, self-management, and coping strategies. In addition, exercises to improve lower extremity physical function were introduced in daily video activities. During the course of the program, communication between physiotherapist and patients was based on an asynchronous chat. After 6 weeks, patients were able to continue without support from the physiotherapist. Patients reported their current pain weekly by using a numeric rating scale (range 0-10; 0=no pain, 10=worst possible pain) as long as they were in the program. In addition, after 6 weeks patients answered the question “What is the probability that you would recommend Joint Academy to a friend?”

Results: The eligible cohort consisted of 53 individuals (39 women; body mass index: mean 27, SD 5; age: mean 57, SD 14 years). With the continued use of the program, patients reported a constant change in pain score from mean 5.1 (SD 2.1) at baseline to mean 3.6 (SD 2.0) at week 12. Six patients participated for 30 weeks (mean 3.2, SD 2.1). Overall, the patients would highly recommend Joint Academy to other OA patients, suggesting that the platform may be useful for at least some in the vast OA population.

Conclusions: Joint Academy, a Web-based platform for OA therapy, has the potential to successfully deliver individualized online treatment to many patients with OA that presently lack access to treatment.

(JMIR Res Protoc 2016;5(2):e115) doi:10.2196/resprot.5665

KEYWORDS

osteoarthritis; exercise therapy; mobile apps; digital therapeutics

Introduction

Chronic conditions are the leading cause of disability throughout the world and collectively they represent the most expensive problem facing health care systems [1]. One prevalent condition among these noncommunicable diseases is osteoarthritis (OA), which is one of the leading causes of global disability [2]. Approximately 27 million individuals live with OA in the United States [3], estimated to cost US $189 billion annually [4,5] highlighting the financial and societal burden attributed to OA.

Osteoarthritis primarily affects the elderly. The prevalence in the age group 60 years and older is 10% among men and 18% among women [6]. Ongoing demographic changes, particularly in developed countries, and a growing number of elderly individuals suggest that the number of people with OA will increase.

Like other chronic diseases, OA progresses slowly. Before individuals are eligible for total joint replacement (TJR) surgery, incubation time is some 10 to 15 years with increasing joint pain, decreasing function, and reduced quality of life. Accordingly, cross-sectional Swedish and UK data show that only 20% of the OA population qualifies for TJR in spite of debilitating symptoms [7-9]. For those in earlier stages of OA when the diagnosis should be based on clinical symptoms, the primary treatment is nonsurgical, based on exercise, information, and—in relevant cases—weight loss according to all international and national guidelines [10-13]. Unfortunately, this evidence-based treatment is not reflected in present OA management administered by the health care system [14]. Rather, joint pain is considered by health care professionals as a normal part of the aging process (ie, “wear and tear of the body”) and is therefore not manageable until TJR becomes an option. As a result, many suffering from OA are not aware of or offered well-established evidence-based nonsurgical treatment.

The Swedish national initiative “Better Management of Patients with OsteoArthritis” (BOA), a national quality registry and an evidence-based supported self-management program for patients with OA, was developed to facilitate the implementation of guidelines [9,14]. Of Sweden’s 9 million inhabitants, more than 50,000 individuals have participated in the BOA program between 2008 and 2015. Still, they represent less than 20% of people in need of treatment due to joint problems [9,14]. Thus, despite the systematic and thorough work put into BOA, most individuals suffering from OA have not yet received access to the program, which may be due to lack of health care resources or people having trouble fitting their schedule to primary care opening hours. Therefore, alternative methods are required to reach these individuals.

One appealing method that leverages technology into health care is digital therapeutics. In this context, digital therapeutics can be viewed as software functioning as “medication” that is delivered via the Web. This treatment focuses on behavioral changes with long-term improvements in contrast to the short-term gain of taking a pill or other interventions presently used in health care. A crucial point to achieve the effect of any treatment is compliance. Using digital therapeutics that utilize the Internet to deliver cost-effective treatment around the clock has the potential to increase adherence. Allowing for people to administer their treatment at a suitable time point probably increases compliance and the likelihood of improved health and quality of life for patients with chronic conditions. An interesting and successful example is the translation of the Diabetes Prevention Program into an online treatment [15,16]. With respect to OA, we have developed Joint Academy [17], which is a digital platform for individuals with clinically verified OA. The platform is based on the BOA program [9,11,14]. It includes a Web-based patient interface that provides individualized exercises, a personal physiotherapist, peer-to-peer support, education about lifestyle and behavioral changes, and a physiotherapist interface that provides necessary information on the patient’s progress in the program for support and encouragement.

The aim of this pilot study was to describe the effect on joint pain for the first users of a newly developed Web-based OA self-managing program, Joint Academy, and to examine whether these patients would recommend other OA patients to use the program. Collectively, the objectives aimed at deciding (1) whether it seemed feasible to deliver Web-based OA treatment and (2) whether the results would support further development of the platform.

Methods

Patients and Study Design

Participants with knee or hip joint pain were recruited from an online advertisement on the home page of the Swedish Rheumatology Association during two weeks in January 2015. However, single patients were eligible for inclusion until December 2015. The potential participants were directed to a website where they were asked to create a user account and fill in a screening questionnaire. Participants were not compensated for their participation but were enrolled in the program at no cost.

A trained physiotherapist (CT) screened the questionnaires and, whenever relevant, asked additional questions to patients through their user interface. To be included, the physiotherapist ensured that described symptoms were in agreement with clinical OA according to national guidelines [9,11,14]. Exclusion criteria included chronic widespread pain or other, more severe diseases, such as inflammatory joint disease, cancer, sequel after hip fracture, or due to major trauma.

Participants were informed that the program lasts for 6 weeks. Included participants (referred to as patients subsequently) were asked to answer some demographic questions according to the International Consortium for Health Care Measurement (ICHOM) initiative as well as those in the BOA registry [9,14,18] and reported their current baseline of pain using the Numeric Rating Scale (NRS; range 0-10, 0=no pain, 10=worst possible pain). After 6 weeks, patients were asked “What is the probability that you would recommend Joint Academy to a friend?” (range 0-10, 0=not likely, 10=most likely). For this study, patients were not asked to specify what joint was affected by their disease.

Description of the Intervention

The basis for Joint Academy is the Supported Osteoarthritis Self-management Program (SOASP) used in BOA. The BOA program consists of theory sessions held by a physiotherapist, sometimes in collaboration with an occupational therapist and an OA communicator (ie, a patient with OA who has been educated by the Swedish Rheumatology Association to talk about the daily experience of OA and good coping strategies including physical activity). After completing the theory sessions, patients can opt for an individually adapted and physiotherapist-supervised exercise program [14]. The SOASP content was based on existing evidence, national and international treatment guidelines, as well as patients' views, thoughts, and tolerability of treatment and exercise for OA. Patients in the SOASP rate their pain on a visual analog scale at baseline and again after 3 and 12 months.

The Joint Academy program that was used in this study started on Sunday and ran for 6 weeks. The program consisted of eight videos of 2- to 5-minute lectures about OA, effects of physical activity, self-management, and coping strategies. After each lecture, the patient took a quiz to confirm that the take-home messages of the lecture were correctly understood. Parallel to these lectures, four neuromuscular exercises were introduced to improve lower extremity physical function. Each exercise had 3 to 5 levels of intensity. The level of intensity was based on an algorithm taking into account individual progress and the patient's perceived ability to perform the exercise without exacerbating pain. The week's exercises and lessons (12-14 exercises, two lessons, and one pain report per week) were divided into daily packages and delivered in video format to the patient during the 6-week period by push email. In each email, there was a link to the embedded videos within the Web-based platform. These videos showed how to properly perform the exercises. The short video lectures also included key OA issues important for understanding the delivered treatment to be fully motivated for the exercises. Each package was designed to take no more than 5 to 15 minutes per day. After having performed an exercise, the patient registered it as complete. When needed, the patient was able to communicate questions to the personal physiotherapist. This communication between the physiotherapist and patient within the Joint Academy platform was asynchronous and based on a chat during the 6-week program. To have a comparable benchmark over time, pain was always reported on Sundays and referred to the average pain during the week. An "active week" was defined as a week when patients reported their pain level. If a patient reported pain values for four consecutive weeks, skipped two weeks, and finally reported pain for three additional weeks, this was defined as seven active weeks in the program.

Software Programming

The software was compatible with all platforms and worked on personal computers, tablets, and mobile phones. It was built as a single-page Web app with a responsive user interface to facilitate user experience. The Web app was connected to our proprietary back-end service for OA treatment. The back-end was built on the framework Ruby on Rails and the front-end on Angular JS.

Statistical Analyses

The statistical analysis was performed using a longitudinal random effects model. A random intercepts and slopes model was fitted with using the restricted maximum likelihood approach and with the underlying assumption of an unstructured variance-covariance matrix and degrees of freedom estimated using Satterthwaite's method. The calculations were performed using the mixed command in Stata version 14.

Ethical Consideration

Patients gave informed consent when entering the program.

Results

The study cohort consisted of 53 individuals (39 women; body mass index [BMI] mean 27, SD 5; age mean 57, SD 14 years). Of these 53 patients, 36 (68%) registered their pain levels for 6 active weeks (Table 1). On average, patients needed 7 to 8 weeks to complete a 6-week active period (Table 1). During these weeks, patients received 113 activities in total, of which they performed a mean 83 (SD 13) activities.

Table 1. Study results summary.

Result	Number of active weeks					
	Baseline	6	12	18	24	30
Number of patients in program, n	53	36	19	12	9	6
Time to complete active weeks (days), mean (SD)		53 (18)	112 (53)	154 (32)	201 (39)	246 (49)
Activities per week, mean (SD)		14 (2)	13 (2)	13 (2)	14 (1)	14 (1)
NRS pain score, mean (SD)[a]	5.1 (2.1)	4.5 (1.8)	3.6 (2.0)	3.3 (2.5)	2.7 (1.7)	3.2 (2.1)
Change in mean NRS pain score vs baseline, %		–11	–28	–35	–47	–38
Patients with >15% improvement in NRS pain score, n (% of remaining patients) [19]		17 (47)	12 (63)	7 (58)	8 (89)	5 (83)

[a] Numeric Rating Scale: range 0-10.

We observed that 33 patients voluntarily continued using the program after 6 weeks utilizing the same weekly instructions as in week 6, but without the support of a personal physiotherapist.

Furthermore, 19 patients (36%) voluntarily continued to exercise and report their pain level for a total of 12 active weeks. After 18 and 24 active weeks, there were 12 and nine patients remaining, respectively, and six patients completed 30 active weeks in the program (Figures 1 and 2,Table 1). The longest participating patient continued for a total period of 50 weeks (data not shown). Pain according to the NRS was markedly reduced over a 30-week period (Figures 1-3,Table 1). The mean weekly change in pain during follow-up was estimated to be –0.074 (95% CI –0.118 to –0.030, *P*=.002), which corresponds to a pain reduction of one unit every 14 weeks.

Figure 2 shows that baseline values were similar regardless of how long patients participated in the program (ie, patients engaged in the program for a longer time period did not have less severe pain at baseline compared to baseline values for patients who participated for a shorter period of time). There were no obvious demographic differences (ie, sex, age, BMI) between patients who were active for less than 6 weeks compared to those who were active for more than 6 weeks (data not shown). At all weeks during the 30-week period, the mean pain score of the active patients was similar to the reported pain score of the patients that discontinued the program after that week (data not shown).

At week 6, 18 of the 36 active patients had a lower absolute value in pain score, eight were unchanged, and 10 had an increase compared to baseline. The mean NRS pain score for the 36 active patients changed from mean 5.1 (SD 2.1) at baseline to mean 4.5 (SD 1.8) (Table 1). Sixteen patients (68%) were classified as responders with an individual improvement of more than 1.5 in NRS pain score [19].

The NRS pain data showed that at weeks 6 and 30, 47% (17/36) and 83% (5/6) were responders, respectively (Table 1).

In all, 31 patients (five were lost due to technical reasons) answered the question “What is the likelihood that you would recommend Joint Academy to a friend?” The median score was 10 (range 6-10).

Figure 1. Mean NRS pain score for active patients (●) and number of patients (○) remaining in the program at each week. Due to decreasing number of patients during the course of the program, individual weekly changes may have a disproportional effect on the mean pain level.

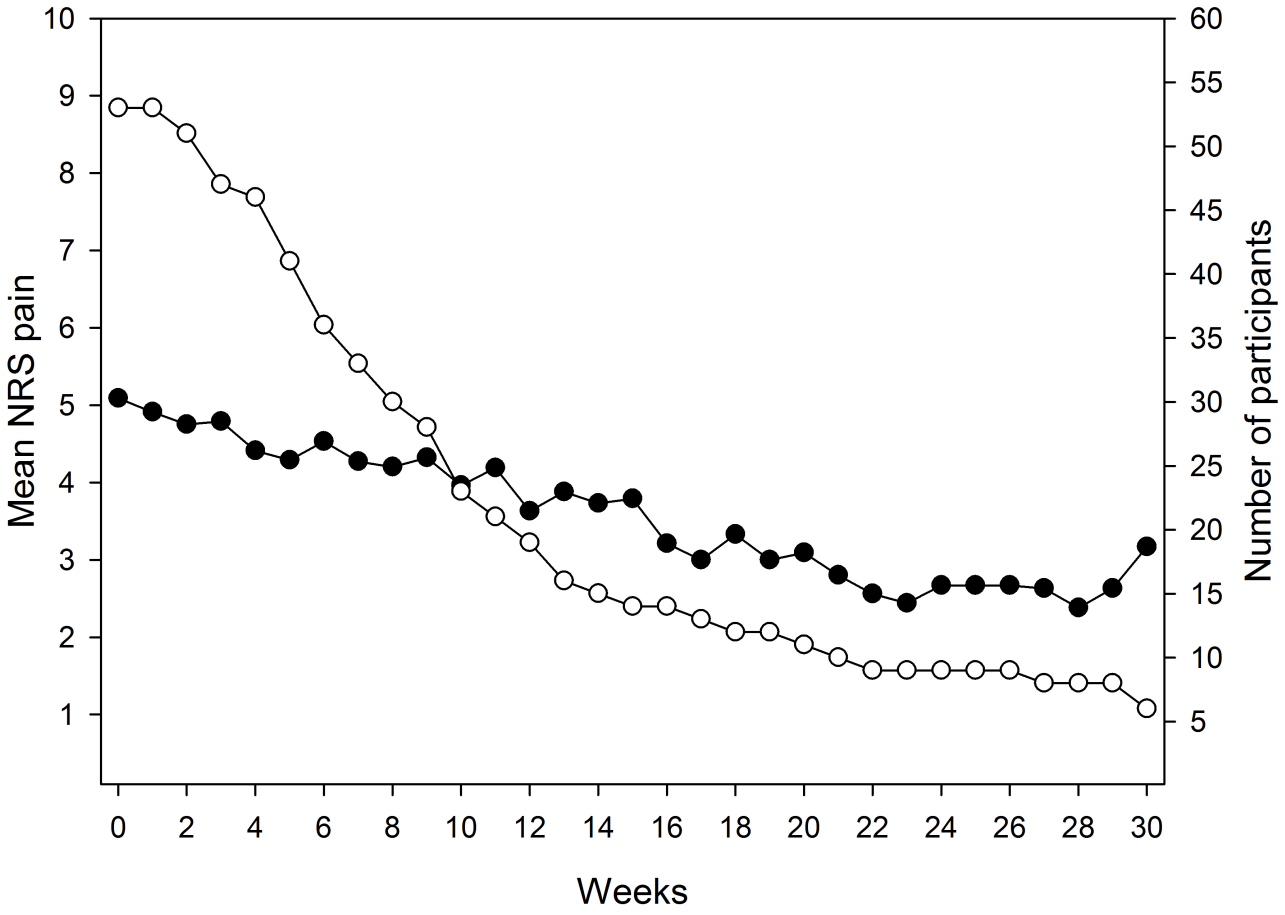


Figure 2. Box plots of the NRS pain values (the horizontal line in the middle of each box indicates the median and the top and bottom borders of the box mark the 75th and 25th percentiles, respectively; the whiskers above and below the box mark the 90th and 10th percentiles; the black dots beyond the whiskers are outliers) at different time points. Baseline is baseline mean NRS for all 53 patients. For each subsequent time point, data are presented for those patients that participated in the program at the indicated time period (6 weeks: n=36; 12 weeks: n=19; 18 weeks: n=12; 24 weeks: n=9; 30 weeks: n=6). White boxes: baseline NRS; gray boxes: NRS after the indicated time period.

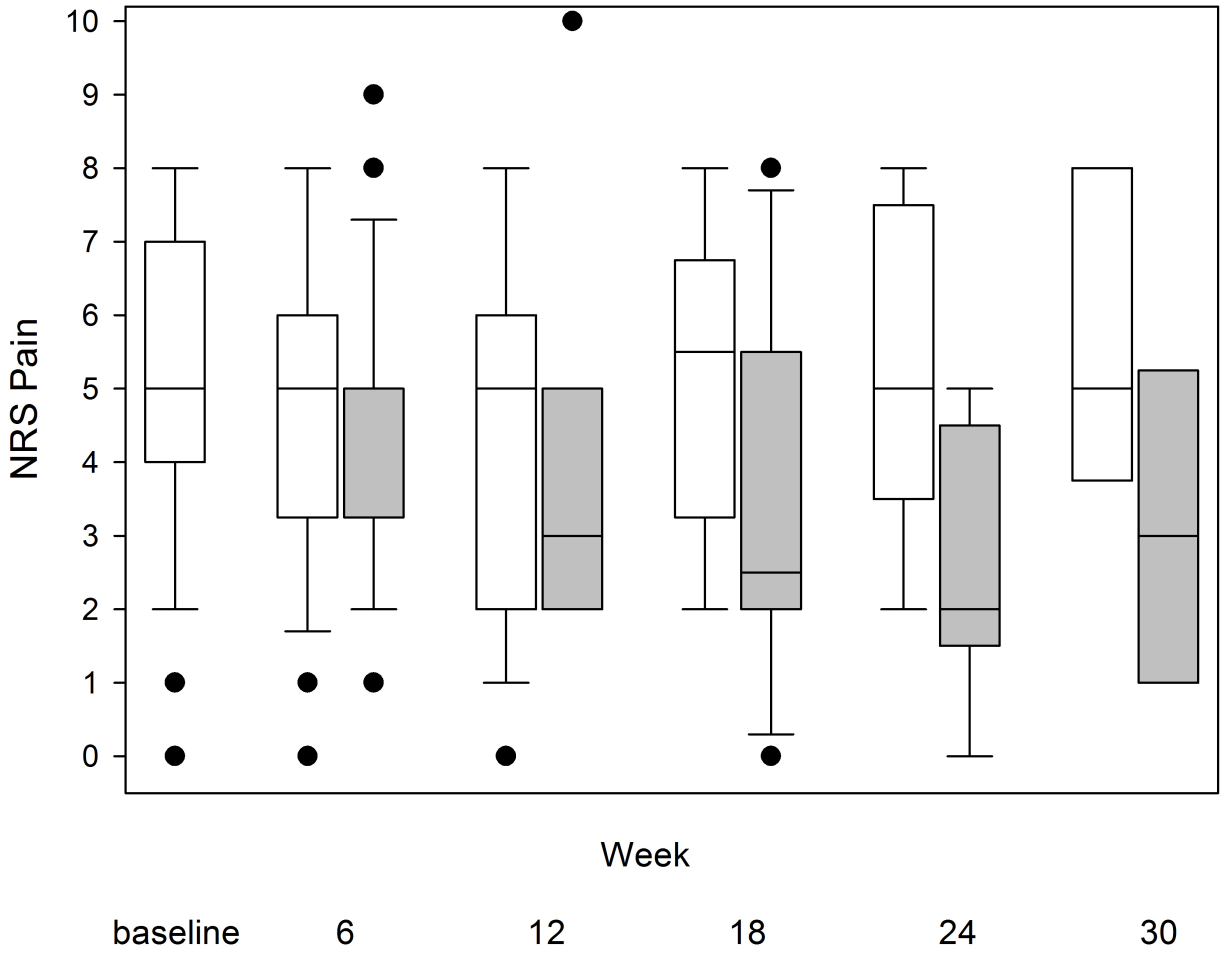
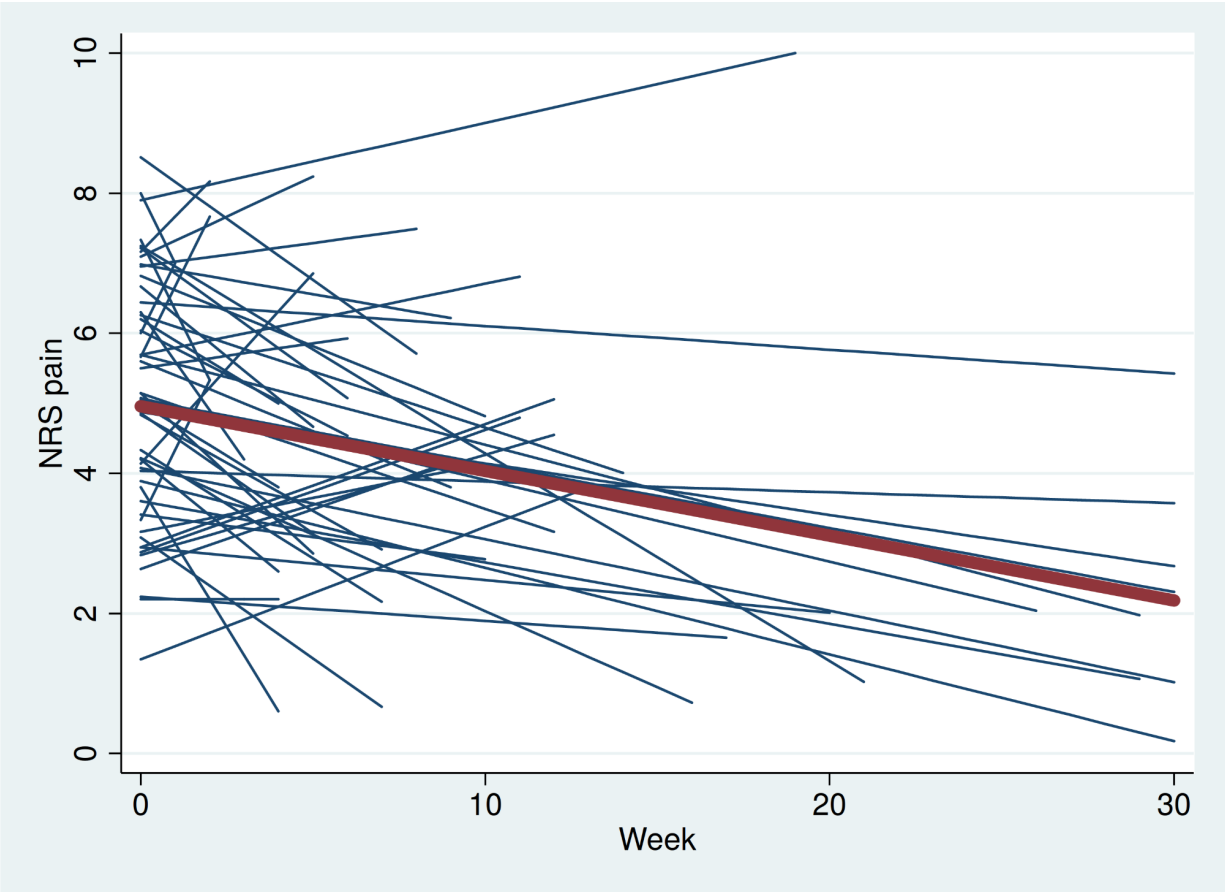


Figure 3. Spaghetti plot showing NRS pain. Each blue line represents a single patient. The red line represents change in mean pain over time for all 53 patients.



Discussion

In this study, we demonstrate that Joint Academy, a Web-based platform for OA therapy, has the potential to successfully deliver individualized digital treatment to patients with clinical OA in the hip or knee. Many experienced an improvement in pain and would recommend the program to others. This is one of few exercise intervention studies following patients for a longer period of time [20,21]. This study shows similar pain improvement as those in previous face-to-face studies [13,14,22,23]. Furthermore, although a definitive cause relationship could not be established, the degree of improvement seems to be associated with duration of stay in the program. Although not designed to determine reasons for discontinuing the program, the study revealed that patients who discontinued the program within 6 weeks showed similar pain scores at baseline (Figure 2) compared to those that remained in the program. Of note, patients consecutively entered the program during the 12 months of recruitment meaning that not all patients had the opportunity to participate for 30 weeks and that the lower number of patients by time is not a true measure of compliance.

Even though several patients discontinued the program, results suggest that pain fluctuates over time (Figure 1). This is in agreement with the clinical profile of OA showing relapsing intervals of pain and impaired function. Another possible explanation for the fluctuating pain level may be that as patients improve (ie, their symptoms become less severe), they increase exercise time and intensity. This suggests that patients may have similar or increased pain but, at the same time, they have increased physical function. Future studies will explore the relationship between pain and function by assessing physical function, which was recently included in Joint Academy.

In SOASP, patients rate their pain on a visual analog scale (VAS) at baseline and again after 3 and 12 months [13,14]. On average, the VAS pain score decreases by 10 points (from 48 to 38) and 12 points (from 48 to 36) for patients with hip and knee OA, respectively. These results are similar to the results reported at 12 weeks in this study (5.1 to 3.6) (Table 1) indicating that a Web-based means to deliver evidence-based health care to OA patients seems to work as well as the “analog” face-to-face predecessor.

In the United States, US $40 billion per year is allocated to the more than 600,000 TJR operations conducted annually, making TJR one of the most expensive interventions today [4]. The number of TJRs is expected to increase by more than 100% by 2030 due to the increasing prevalence of OA in an aging population, together with the decreasing age of intervention for TJR in the baby boomer generation [24]. Without doubt, TJR is a very successful intervention when performed on the right patient at the right time point. However, recent studies have shown that many TJRs, as well as other surgical interventions in patients with OA, are often unnecessary and that indication for surgery is not well validated. For instance, a study that compared pre- and post-health care costs for OA patients that underwent a TJR in the United States showed that although the

total number of outpatient visits declined after surgery, the percentage of patients hospitalized after TJR increased. The result was a higher total cost during follow-up compared to before surgery [25]. In addition, TJR patients may need revision surgery (ie, a new prosthesis) and TJR is associated with an increased risk for adverse events compared to nonsurgical treatment [24]. Furthermore, 15% to 20% of the TJR population has sustained disabilities after surgery, which generates suffering, costly visits, and unnecessary diagnostics and treatments [26].

Another common operative procedure in middle-aged patients with knee pain is arthroscopy. In the United States alone, 400,000 arthroscopies are performed annually due to the popular belief that pain in the degenerative knee is caused by a meniscal tear [27-30]. As concluded by Katz and Jones [28], a reasonable initial strategy for these patients is physiotherapy rather than arthroscopy. This conclusion is supported by a recent study that contradicts the prevailing consensus that mechanical symptoms justify an arthroscopic intervention [31]. Furthermore, partial meniscectomy may be associated with increased risk of incident radiographic osteoarthritis [32]. That physiotherapy indeed has an effect, and that the results of this study shows similar effect, is further demonstrated by a recent Cochrane review [22] as well as results from the Danish GLA:D program, which is based on the BOA program [23]. The positive effect of exercise, weight control, and information can be explained by the biomechanical origin of OA as well as the importance of patients having accurate knowledge about their disease [22,33].

Two randomized controlled trials are of interest with respect to nonsurgical options to treat OA patients eligible for total knee replacement [34,35]. One of these studies showed that supervised exercise before surgery is associated with a faster postoperative recovery [34]. The second study compared knee TJR with a nonsurgical treatment program and showed substantial improvement in both groups with respect to most outcomes. However, only 26% of the patients who were assigned to receive nonsurgical treatment alone underwent total knee replacement in the year following the procedure [35]. That education and individually adapted exercise have the potential to reduce the need for TJR is further enforced by Svege et al [36].

To our knowledge, Joint Academy is the first platform to deliver digital health care to OA patients. The fact that the program may reverse the course of symptoms for some patients to the degree observed in the current study is very encouraging, suggesting that Joint Academy may be feasible at least for some OA patients. For the subgroup of the OA population volunteering for participation in this program, a pragmatic approach with 5 to 15 minutes of exercise a few days per week seemed sufficient to achieve significant results. Interestingly, the program motivated the patients to perform approximately 80 activities in a 7- to 8-week period. This suggests that Joint Academy may play an important role in OA treatment. In addition, Joint Academy may also increase equity in OA treatment by offering evidence-based health care for people living with clinical hip or knee OA in the developing world.

That a digital health program may have significant effects on health is also shown by the Prevent program targeting patients with prediabetes. By combining weekly theoretical lessons and individualized health coaching, patients lowered their body weight as well as their blood glucose levels [15,16]. The great advantage of a Web-based platform that works on personal computers, tablets, and mobile phones, is that it can be used wherever and at a time point of the patient's own choice, minimizing the interruption of daily life activities and the need for scheduled appointments at a clinic. This may be particularly relevant for patients in rural areas with limited access to and/or living far away from health care facilities as well as for working people who may find it difficult to allocate time for a visit to a primary care practice. In addition, Internet availability is increasing rapidly as the price of a basic mobile phone decreases. Ultimately, digital health care may save financial resources and increase quality of life for many people living with chronic diseases.

There are limitations to this study. This is a pilot study without a control group and with a small study population, especially at later time points, limiting the establishment of a definitive cause relationship between length of participation in Joint Academy and improvement in pain. However, patient attrition over time is not due to demographic differences between those patients who discontinued the program and those patients that continued the program. When using this study design, there is a risk that the cohort is not representative of the general OA population. However, both the OA pathology and the clinical disease patterns are similar around the world. The relative ease with which you can enter the study (eg, patients do not need to visit a general physician to have a diagnosis or a physiotherapist to perform the exercises), may result in a higher-than-average dropout rate. Alternatively, those signing up may be more motivated to change their present situation and/or have an interest in digital technology and, consequently, show better results. It can also be argued that patients that enroll in the program are currently experiencing an exacerbation in pain and, therefore, are more motivated than the average OA patient. However, this did not seem to be the case for all patients in this study. Patients that enrolled in Joint Academy had a baseline mean NRS pain of 5.1 (SD 2.1) meaning that the pain level of at least some patients was relatively low. Overall, we believe it can be argued that patients in the study cohort are well suited to be the future target group for digital OA management. Despite these limitations, the results encouraged us to further develop Joint Academy. In the current version, we have included extended assessments at inclusion and also during the course of the program. Furthermore, we have included a functional test, comorbidities, and additional demographics to enable an improved user definition in order to further individualize the program. With respect to the enormous OA population, we believe that Joint Academy has the potential to attract people who are more motivated by digital health than by visits to a primary care practice.

In conclusion, we demonstrate that Joint Academy, a Web-based platform for OA therapy, has the potential to successfully deliver individualized Web-based treatment to many patients with OA who presently lack access to treatment.

Acknowledgments

Joint Academy has received financial support from Lund Innovation System.

Conflicts of Interest

Jakob Dahlberg and Daniel Grahn are employees of Joint Academy. Carina Thorstensson is a part-time consultant of Joint Academy. Leif Dahlberg is a board member of Joint Academy.

References

1. Pruitt S, Annandale S, Epping-Jordan J, Fernández DJ, Khan M, Kisa A, et al. Innovative Care for Chronic Conditions: Building Blocks for Action: Global Report. Geneva: World Health Organization; 2002. URL: http://www.who.int/chp/knowledge/publications/icccglobalreport.pdf [accessed 2016-02-01] [WebCite Cache ID 6ey6h109K]
2. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis 2014 Jul;73(7):1323-1330. [doi: 10.1136/annrheumdis-2013-204763] [Medline: 24553908]
3. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 2008 Jan;58(1):26-35 [FREE Full text] [doi: 10.1002/art.23176] [Medline: 18163497]
4. Kotlarz H, Gunnarsson CL, Fang H, Rizzo JA. Insurer and out-of-pocket costs of osteoarthritis in the US: evidence from national survey data. Arthritis Rheum 2009 Dec;60(12):3546-3553 [FREE Full text] [doi: 10.1002/art.24984] [Medline: 19950287]
5. Centers for Disease Control and Prevention. 2015. Osteoarthritis URL: http://www.cdc.gov/arthritis/basics/osteoarthritis.htm [accessed 2016-02-01] [WebCite Cache ID 6ey2DBqhj]
6. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. Bull World Health Organ 2003;81(9):646-656 [FREE Full text] [Medline: 14710506]
7. Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. Ann Rheum Dis 2001 Feb;60(2):91-97. [Medline: 11156538]
8. Turkiewicz A, Gerhardsson de Verdier M, Engström G, Nilsson PM, Mellström C, Lohmander LS, et al. Prevalence of knee pain and knee OA in southern Sweden and the proportion that seeks medical care. Rheumatology (Oxford) 2015 May;54(5):827-835. [doi: 10.1093/rheumatology/keu409] [Medline: 25313145]
9. BOA: Better Management of Patients with Osteoarthritis. URL: http://utv.boaregistret.se/en [accessed 2016-02-16] [WebCite Cache ID 6fKxUsQyd]
10. Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, et al. OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthritis Cartilage 2010 Apr;18(4):476-499 [FREE Full text] [doi: 10.1016/j.joca.2010.01.013] [Medline: 20170770]
11. The Swedish National Board of Health and Welfare. The National guidelines for Musculoskeletal Diseases - summary URL: http://www.socialstyrelsen.se/nationalguidelines/nationalguidelinesfororthopaedicconditions [accessed 2016-02-08] [WebCite Cache ID 6f9225Ams]
12. American Academy of Orthopedic Surgeons. Treatment of Osteoarthritis of the Knee. Evidence-based guideline. 2nd edition. 2013 May 18. URL: http://www.aaos.org/research/guidelines/TreatmentofOsteoarthritisoftheKneeGuideline.pdf [accessed 2016-02-01] [WebCite Cache ID 6ey5NNPqE]
13. National Institute for Health and Care Excellence. 2014 Feb. Osteoarthritis: care and management URL: https://www.nice.org.uk/guidance/cg177 [accessed 2016-02-01] [WebCite Cache ID 6ey5ZMeln]
14. Thorstensson CA, Garellick G, Rystedt H, Dahlberg LE. Better management of patients with osteoarthritis: development and nationwide implementation of an evidence-based supported osteoarthritis self-management programme. Musculoskeletal Care 2015 Jun;13(2):67-75. [doi: 10.1002/msc.1085] [Medline: 25345913]
15. Sepah SC, Jiang L, Peters AL. Long-term outcomes of a Web-based diabetes prevention program: 2-year results of a single-arm longitudinal study. J Med Internet Res 2015;17(4):e92 [FREE Full text] [doi: 10.2196/jmir.4052] [Medline: 25863515]
16. Prevent by Omada Health. URL: https://preventnow.com/ [accessed 2016-02-01] [WebCite Cache ID 6ey5stgJh]
17. Joint Academy. URL: https://www.jointacademy.com/ [accessed 2016-02-16] [WebCite Cache ID 6fKyiutC1]
18. The International Consortium for Health Outcomes Measurement (ICHOM). URL: http://www.ichom.org/ [accessed 2016-02-01] [WebCite Cache ID 6ey65idFi]
19. Tubach F, Ravaud P, Baron G, Falissard B, Logeart I, Bellamy N, et al. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. Ann Rheum Dis 2005 Jan;64(1):29-33 [FREE Full text] [doi: 10.1136/ard.2004.022905] [Medline: 15208174]

20. Thomas KS, Muir KR, Doherty M, Jones AC, O'Reilly SC, Bassey EJ. Home based exercise programme for knee pain and knee osteoarthritis: randomised controlled trial. BMJ 2002 Oct 5;325(7367):752 [FREE Full text] [Medline: 12364304]
21. Jenkinson CM, Doherty M, Avery AJ, Read A, Taylor MA, Sach TH, et al. Effects of dietary intervention and quadriceps strengthening exercises on pain and function in overweight people with knee pain: randomised controlled trial. BMJ 2009;339:b3170 [FREE Full text] [Medline: 19690345]
22. Kroon FP, van der Burg LR, Buchbinder R, Osborne RH, Johnston RV, Pitt V. Self-management education programmes for osteoarthritis. Cochrane Database Syst Rev 2014;1:CD008963. [doi: 10.1002/14651858.CD008963.pub2] [Medline: 24425500]
23. English Summary GLA:D Annual Report 2014. URL: https://www.glaid.dk/pdf/English%20Summary%20annual%20report%202014%20GLAD.pdf [accessed 2016-04-19] [WebCite Cache ID 6gsv3JRHe]
24. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am 2007 Apr;89(4):780-785. [doi: 10.2106/JBJS.F.00222] [Medline: 17403800]
25. Bozic KJ, Stacey B, Berger A, Sadosky A, Oster G. Resource utilization and costs before and after total joint arthroplasty. BMC Health Serv Res 2012;12:73 [FREE Full text] [doi: 10.1186/1472-6963-12-73] [Medline: 22443109]
26. Beswick AD, Wylde V, Gooberman-Hill R, Blom A, Dieppe P. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. BMJ Open 2012;2(1):e000435 [FREE Full text] [doi: 10.1136/bmjopen-2011-000435] [Medline: 22357571]
27. Sihvonen R, Englund M, Turkiewicz A, Järvinen TL, Finnish Degenerative Meniscal Lesion Study Group. Mechanical symptoms and arthroscopic partial meniscectomy in patients with degenerative meniscus tear: a secondary analysis of a randomized trial. Ann Intern Med 2016 Feb 9. [doi: 10.7326/M15-0899] [Medline: 26856620]
28. Katz JN, Jones MH. Treatment of meniscal tear: the more we learn, the less we know. Ann Intern Med 2016 Feb 9. [doi: 10.7326/M16-0049] [Medline: 26856759]
29. Englund M, Guermazi A, Gale D, Hunter DJ, Aliabadi P, Clancy M, et al. Incidental meniscal findings on knee MRI in middle-aged and elderly persons. N Engl J Med 2008 Sep 11;359(11):1108-1115 [FREE Full text] [doi: 10.1056/NEJMoa0800777] [Medline: 18784100]
30. Sihvonen R, Paavola M, Malmivaara A, Itälä A, Joukainen A, Nurmi H, Finnish Degenerative Meniscal Lesion Study (FIDELITY) Group. Arthroscopic partial meniscectomy versus sham surgery for a degenerative meniscal tear. N Engl J Med 2013 Dec 26;369(26):2515-2524. [doi: 10.1056/NEJMoa1305189] [Medline: 24369076]
31. Sihvonen R, Englund M, Turkiewicz A, Järvinen TL. Mechanical symptoms as an indication for knee arthroscopy in patients with degenerative meniscus tear: a prospective cohort study. Osteoarthritis Cartilage 2016 Mar 31 [FREE Full text] [doi: 10.1016/j.joca.2016.03.013] [Medline: 27038490]
32. Roemer FW, Kwoh CK, Hannon MJ, Hunter DJ, Eckstein F, Grago J, et al. Partial meniscectomy is associated with increased risk of incident radiographic osteoarthritis and worsening cartilage damage in the following year. Eur Radiol 2016 Apr 27. [doi: 10.1007/s00330-016-4361-z] [Medline: 27121931]
33. Felson DT. Osteoarthritis as a disease of mechanics. Osteoarthritis Cartilage 2013 Jan;21(1):10-15 [FREE Full text] [doi: 10.1016/j.joca.2012.09.012] [Medline: 23041436]
34. Villadsen A, Overgaard S, Holsgaard-Larsen A, Christensen R, Roos EM. Postoperative effects of neuromuscular exercise prior to hip or knee arthroplasty: a randomised controlled trial. Ann Rheum Dis 2014 Jun;73(6):1130-1137. [doi: 10.1136/annrheumdis-2012-203135] [Medline: 23661494]
35. Skou ST, Roos EM, Laursen MB, Rathleff MS, Arendt-Nielsen L, Simonsen O, et al. A randomized, controlled trial of total knee replacement. N Engl J Med 2015 Oct 22;373(17):1597-1606. [doi: 10.1056/NEJMoa1505467] [Medline: 26488691]
36. Svege I, Nordsletten L, Fernandes L, Risberg MA. Exercise therapy may postpone total hip replacement surgery in patients with hip osteoarthritis: a long-term follow-up of a randomised trial. Ann Rheum Dis 2015 Jan;74(1):164-169 [FREE Full text] [doi: 10.1136/annrheumdis-2013-203628] [Medline: 24255546]

Abbreviations

BMI: body mass index
ICHOM: International Consortium for Health Care Measurement
NRS: Numeric Rating Scale
OA: osteoarthritis
SOASP: Supported Osteoarthritis Self-management Program
TJR: total joint replacement
VAS: visual analog scale

Edited by G Eysenbach; submitted 19.02.16; peer-reviewed by S Lohmander, D Bossen, N Dewan, R Osbourne, D Pach; comments to author 16.03.16; revised version received 20.04.16; accepted 13.05.16; published 03.06.16.

Please cite as:
Dahlberg LE, Grahn D, Dahlberg JE, Thorstensson CA
A Web-Based Platform for Patients With Osteoarthritis of the Hip and Knee: A Pilot Study
JMIR Res Protoc 2016;5(2):e115
URL: http://www.researchprotocols.org/2016/2/e115/
doi:10.2196/resprot.5665
PMID:27261271

Original Paper

Developing an Evidence-Based Epilepsy Risk Assessment eHealth Solution: From Concept to Market

Craig Newman[1], BSc (Hons), PhD, DClinPsy; Rohit Shankar[2], MBBS, MRCPsych; Jane Hanna[3]; Brendan McLean[4], PhD, FRCP; Alex Osland[3]; Cathryn Milligan[5]; Abbie Ball[5]; Caryn Jory[6]; Matthew Walker[7], PhD, FRCP

[1]Neuro-Cognitive Research Group (NeuroCoRe), Plymouth University Peninsular School of Medicine and Dentistry (PUPSMD), Plymouth, United Kingdom

[2]Exeter Medical School, Exeter, United Kingdom

[3]SUDEP Action, Oxfordshire, United Kingdom

[4]Royal Cornwall Hospital Trust, Truro, United Kingdom

[5]Neuro-Cogntivie Research Group (NeuroCoRe), Plymouth University Peninsular School of Medicine and Dentistry (PUPSMD), Plymouth, United Kingdom

[6]Cornwall Partnership NHS Foundation Trust, Bodmin, United Kingdom

[7]UCL Institute of Neurology, London, United Kingdom

Corresponding Author:
Craig Newman, BSc (Hons), PhD, DClinPsy
Neuro-Cognitive Research Group (NeuroCoRe)
Plymouth University Peninsular School of Medicine and Dentistry (PUPSMD)
N13 ITTC Building
Plymouth Science Park,
Plymouth, PL6 8BX
United Kingdom
Phone: 44 1752315264
Fax: 44 1752792560
Email: craig.newman@plymouth.ac.uk

Abstract

Introduction: Sudden unexpected death in epilepsy (SUDEP) is possibly the most common cause of death as a result of complications from epilepsy. The need to educate and regularly review risk for all patients with epilepsy is paramount, but rarely delivered in actual clinical practice. Evidence suggests that education around SUDEP and modifiable risk variables translate into better self-management of epilepsy.

Objective: We aimed to develop and implement an eHealth solution to support education and self-management of risks, in epilepsy.

Methods: We undertook an innovation pathways approach, including problem identification, feasibility assessment, design, implementation, and marketing. People with epilepsy were provided a smartphone-based app (Epilepsy Self-Monitor, EpSMon), which translates the clinical risk assessment tool into an educational and self-monitoring platform, for the self-management of epilepsy.

Results: Results include the success of the marketing campaign, and in what areas, with an estimated reach of approximately 38 million people. EpSMon has proved a success in academic and clinical circles, attracting awards and nominations for awards. The number of users of EpSMon, after 3 months, turned out to be lower than expected (N=221). A 4-month trial of the app in use in the United Kingdom, and the success of the marketing strategy, point to necessary changes to the model of delivery and marketing, summarized in this paper. These include the marketing message, user cost model, and need for the availability of an Android version.

Conclusions: EpSMon has proven a success in respect to its reception by academics, clinicians, stakeholder groups, and the patients who use it. There is work needed to promote the model and increase its acceptability/attractiveness, including broadening the marketing message, increasing its availability, and reducing its cost. Future development and promotion of the tool will hopefully inform iterative design of its core features for a receptive audience and lead to increased uptake as it is launched worldwide in 2016.

(JMIR Res Protoc 2016;5(2):e82) doi:10.2196/resprot.5389

KEYWORDS

eHealth; mhealth; mobile app; epilepsy; SUDEP; self-management; self-monitoring; smartphone

Introduction

Background

Epilepsy is one of the most common neurological disorders globally affecting 5 to 40 people per 1000 population [1]. Epilepsy affects approximately 50 million people throughout the world. It has been estimated that 10% of the burden of brain and mental disorders in the world is caused by epilepsy. This calculation includes premature deaths and the loss of healthy life due to disability [2].

Sudden unexpected death in epilepsy (SUDEP) is the most important direct epilepsy-related cause of death [3]. SUDEP is possibly the most common cause of death as a result of complications from epilepsy, accounting for between 7.5% and 17% of all epilepsy-related deaths and [4] 50% of all deaths in refractory epilepsy [5]. Sudden death is 20 times higher in people with epilepsy (PWE) than the general population. Epilepsy is the 5th highest cause of life-years lost and the public health burden of SUDEP alone is estimated as second only to stroke among neurological conditions [6]. Forty-two percent of all deaths are considered avoidable [7]. Consequently, the National Institute for Health and Care Excellence epilepsy guidelines 2004 and 2012 [8] recommend discussion of SUDEP with newly diagnosed PWE. This is rarely delivered and until recently only 4% of PWE had a recorded SUDEP discussion [9].

There is robust evidence to suggest that knowledge relating to modifiable risk factors would help empower the patient to take responsibility toward his well-being in managing his condition [10-12]. Recent studies have shown that factors influencing SUDEP and other direct causes of epilepsy death overlap [13-15].

Aim

Development of a patient-centered eHealth solution to reduce risk of SUDEP and educate PWE around risk. Utilization of quality improvement and iterative cycles of development to evidence the proposed solution.

Methods

App Conceptualization

In the conceptualization stage of a patient-administered eHealth alternative to the consultant-administered checklist, it was important to identify how this might fit alongside existing care pathways and where, if anywhere, a clear gap in service delivery was observed. Consultation was undertaken with a specialist national Epilepsy charity (SUDEP Action), a specialist general practitioner (GP) commissioning group in Cornwall, UK and both national academic and consultant specialists in epilepsy.

This steering group identified the removal of the primary care–based Quality Outcomes Framework financial support for annual epilepsy reviews, provided by GPs, would likely translate into a significant reduction in epilepsy reviews in the community for patients not identified as at risk. A service pathway was drafted, which included an eHealth self-monitoring option, for patients to self-administer, which could act as a triaging tool alongside existing primary care models.

Stepped-Care Model Approach

A rapid informal review of eHealth solutions delivered in other sectors revealed a range of options for support, including general education, risk-specific educational interventions, prompts to seek help, and automated triggering of community or secondary care service support. Against the current level of support for PWE with ongoing seizures, where it is currently their own responsibility to seek help when they perceive a need, the steering group perceived that support in the ability to identify when this need is present was most relevant. This is reinforced by earlier reported findings [16] in which coroner data for SUDEP-related deaths identified that only 20% of patients had sought medical contact with an epilepsy specialist in the period of 12 months prior to their deaths. The evidence indicated a 3-month high-risk period for people whose risk profile deteriorates, as identified by the checklist, and so the identified eHealth need was the provision of an informative risk assessment at prompted 3-monthly intervals.

Technology Identification

The steering group assessed the potential risks and benefits of differing technologies to support this eHealth solution, including a systematic review of existing seizure detection methods [17]. Primarily, the goals of the project required ease of use, accessibility, effortless international dissemination, notification capabilities, and data collection capabilities (to support the ongoing development of the checklist). A mobile app was selected due to the ongoing surge of take-up of these devices (6.9 billion mobile phone prescriptions worldwide with a forecast of 5.6 billion smartphone subscriptions by 2019, Global mobile statistics report - 2014 [18]), the tendency for owners to carry their device at all times, the numerous notification options and the expansive range of data collection options including take-up and user retention data.

App Design (EpSMon – Epilepsy Self Monitor)

The development of the App content was iterative, cycling on the basis of specialist input across a range of development themes: the consultant steering group, a patient-representative group (recruited by the charity), University information technology (IT) support services and patients of volunteer clinicians were repeatedly involved in providing feedback across a range of development stages, (summarized in Figure 1)

A wire-frame (flowchart of screens, features, and server activity) was initially developed by a local University-based team who specialize in the development of apps for neurology and clinical services. Following this, a graphical representation mock-up

was produced providing, first versions of the graphics in situ in a functioning App and the final Beta version prerelease (a Beta version being the version that is tested for coding bugs, all other features assumed complete). The target users for this tool span all ages and demographics and so the development team strived to access a diverse feedback group.

Usability testing (public and patient involvement, PPI): explored and observed how users experienced and used the app naturally and across a series of identified tasks. This research was led independently by the charity (to be published separately), software team, and specialist clinicians in clinics with patients. Feedback was reviewed by the steering committee with design modifications to the app when deemed appropriate.

In order to generate the content of the app, the translation of the checklist into a self-administered tool, supported by educational material, was led by the charity in liaison with a specialist patient consultation group and specialist clinicians and academics in this field. This content was reviewed in the first version of the app, by volunteer patient representatives, with edit recommendations made when deemed appropriate by the steering committee. The steering committee decided upon a minimum governance standard for the project, requiring that the checklist be taken through an annual update, requiring ongoing reviews of the literature. An update cycle was undertaken during the build of the app and the app content was updated accordingly.

Once version 1 of the app was built, beta testing was completed for bugs in its functioning by all supporting partners, and a range of patient representatives who had registered to support this activity on a prerelease invitation hosted on the charity's website. Prior to release of the app to iTunes, the app's code, user policies, terms of use, data protection protocols, and security protocols (data encryption, secure transfer, etc) were all reviewed by an IT specialist and legal services provided by the University partner.

Given the heterogeneous characteristics of the potential user population, being any individual with epilepsy and so any age, sex, or race – speculations about user preference or accessibility to devices seemed uninformative beyond national update statistics. Rather, it was decided to aim to release the app to the most popular platforms (Apple and Android) with the aspiration to expand to provide to Windows phones if resources allow.

Key Feature Selection

Following the iterative design process, the app was completed with a range of features that are supportive to patients, service delivery and future research. The features included represent the minimum required to rapidly meet identified user needs and research model of the project, with additional features to be considered in future updates.

It was considered valuable to develop capability to support users in self-triaging their need to seek clinical contact, following an assessment of risk. The translation of the checklist into a self-assessment provides a robust evidence-based self-triaging tool that identifies risk change across regular time intervals. Rather than providing a binary health care approach, a stepped-care approach was designed into the app. EpSMon initially educates PWE around variables related to risk through regular exposure to the checklist. Secondly, succinct educational content is provided to support further queries around identified risk with the app designed to encourage access to this information. Finally, the app encourages contact with a GP when appropriate and queries whether this was adhered to at the next assessment. As an additional safety precaution, a telephone number is provided for people who are distressed or confused, direct to SUDEP Action.

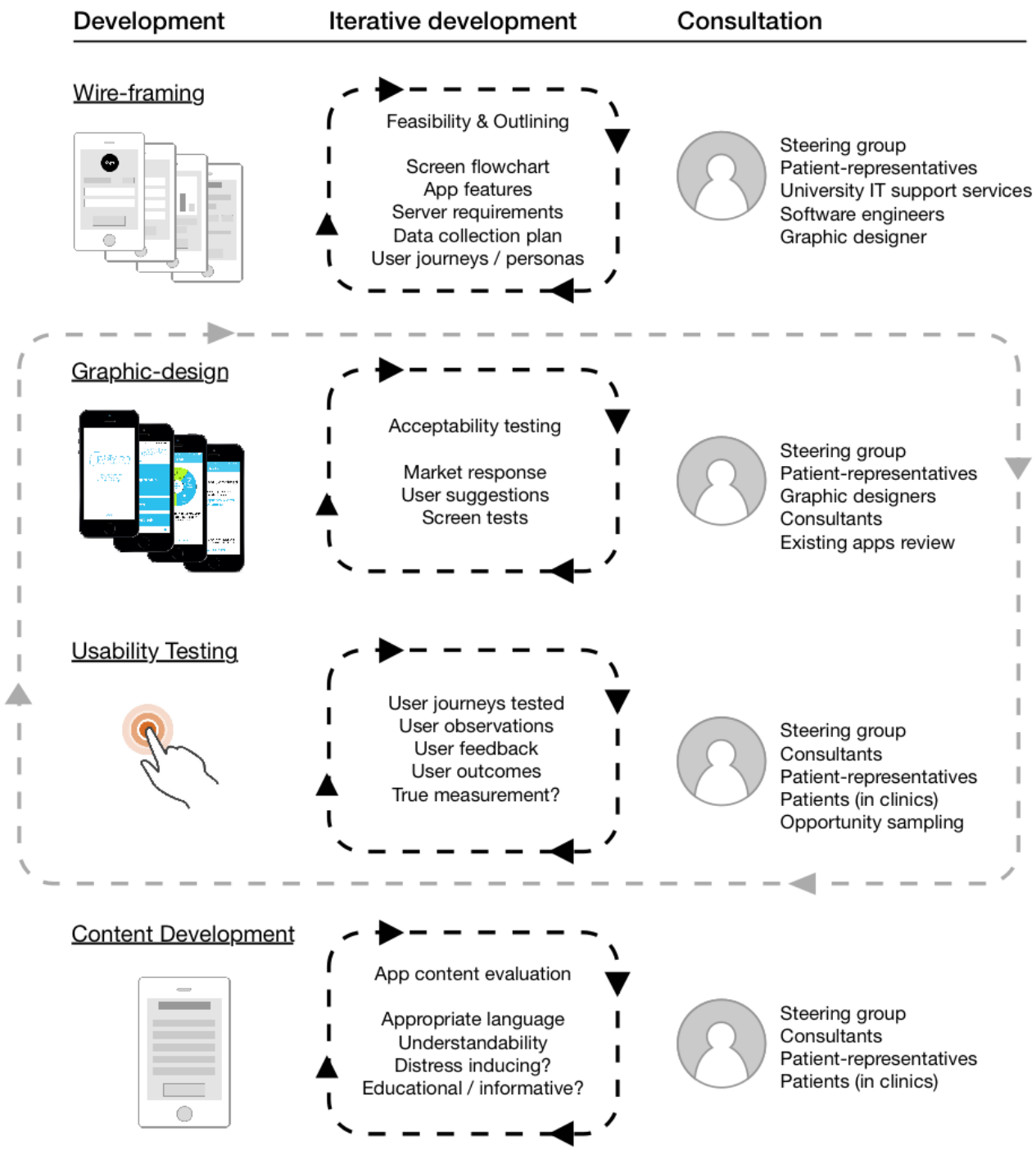
Interventions in other disease areas frequently use a stratified approach, cutting off access to services at a particular percentage of risk of serious disease or death. The Checklist and EpSMon do not do this. The app replicates the checklist, in that it is designed to not include a cumulative score or percentage of risk so there is no cut off of risk, hopefully maximizing doctor and patient empowerment and risk-management. To maintain a quality risk-management and clinical governance approach, the app is designed to support research by consenting users into research and collecting data relating to user demographics, comorbidity, medication use (epilepsy, depression, and psychosis), risk profiles over time, and app usage.

App Governance

After reviewing the government's criteria for app medical device registration [19], it was considered that EpSMon does not meet entry requirements. EpSMon does not diagnose, monitor, prevent, treat, or alleviate a disease. Although the tool is called a monitor, this is a reference to the tool supporting the self-report of user's perceptions about their current state that is used to prompt education or conversation with a clinician, no raw data is interpolated for clinical use. The app is not an alternative to standard treatment and nor does it interfere with or recommend any treatment plan, which is a stipulation (not met) for medical device status required by the Medicines and Healthcare products Regulatory Agency. It informs its users that the results are not to be considered as anything but suggestive. This position could change if the underlying questionnaire responses are developed into statistically weighted factors and the report process becomes more interpretative. This may also need further consideration when EpSMon is released to other countries, such as the United States.

While the safety checklist was developed for SUDEP, risk factors such as nonadherence and depression are relevant to epilepsy mortality generally. They bring a set of questions to the fingertips of doctors and patients that were developed from research on SUDEP. Many of the questions overlap with epilepsy mortality generally and the 2015 version of the Checklist agreed by a UK development group of experts includes the latest research on epilepsy fatality. These include questions on wellbeing as well as seizures. The Checklist will be reviewed annually to enable updating with evidence on fatality. A question on comorbidity has already been identified as an area for recommended inclusion in 2017. Country versions outside the United Kingdom will need additional information and country contextualization if there are no national guidelines in place.

Figure 1. Cycles of iterative development undertaken in creating EpSMon.



Results

Launching the Epilepsy Self-Monitor App

EpSMon was launched to iPhone (UK only) in July 2015 at a cost of £1.49 for life-time access. A strategic marketing communications campaign supported the launch of the app, with public relations support from all partner organizations. Coverage achievements included 5× regional television news reports (audience estimates unavailable), 7× regional radio reports (estimated 1.5 million audience), 27× national and regional newspaper articles (estimated 33.2 million audience), 625 Facebook likes, 424 shares, and 255 clicks to the website (from a potential Facebook reach of 360, 000) and 110,300 ‘EpSMon’ retweets and 14,900 mentions. In total, the marketing communications campaign attained an overall reach of approximately 38 million people.

A full-time support phone line was indicated in the app, provided by SUDEP Action. Very little activity has been generated, with contact mostly relating to enquiries for an Android version of the tool.

Releasing EpSMon has been a very positive experience with unanimous support from clinicians, academics, and patients who have had contact. It has received awards at the International League Against Epilepsy conference, mass media interest, and

two nominations to the Health Service Journal Innovation awards (HSJ) despite its infancy in respect to project duration. The almost nonexistent need for support, by users, encourages further expansion of the user base.

Since the launch, 221 users have downloaded the tool and registered, with 218 having assessed their risk. In addition, EpSMon has also been adopted into the National Epilepsy Commissioning Toolkit, alongside its parent checklist for clinicians. The app collects, with consent, users' age, sex, epilepsy diagnosis duration, seizure type, medications use, questionnaire responses, and app-use frequency data for all users. This data will be used to both better understand the existing user base, for purposes of further project delivery, and to support the research that will further develop the risk checklist's ongoing development.

APP Modifications

The current user base, while modest, represents a test base for the project and has supported the identification of areas in which further work is needed. The first of these is cost. The introduction of a £1.49 fee was driven by a desire to test whether this would increase trust in the product, rather than a need to fund the project. Data indicates that 80% of visitors to the app download page do not purchase the app, which may be a consequence of this fee structure. The steering committee has chosen to remove this fee and to provide the app at no cost. This may, in addition, encourage GPs and other organizations to promote the tool without fear that there is a profit motive for the partners involved.

There is an imminent need to provide an Android version of the tool, based on feedback to the charity and the fact that 79% of smartphone ownership is Android [20]. This could translate into an immediate rapid uptake of EpSMon, especially in the context of this being provided at no cost.

The marketing campaign for EpSMon was built on earlier epilepsy work relating to safety, 'Safety in your pocket.' Feedback since the launch suggests that we may need to consider a multipronged approach. Marketing strategies are currently being explored, with potential but resistant users. A second marketing communications campaign is planned for mid 2016, with news of the app now being free and available for Android and new Apple users.

Discussions are underway with potential US supporters who can provide marketing support into a US market in early 2016. This will involve the bundling of a Spanish translation of the tool. A translation proforma has been developed, which will be provided to a translation agency in the near future.

Discussion

Principal Findings

The development of EpSMon and its first phase of implementation has been successful. In only 4 months the tool has been adopted into the commissioning toolkit for the National Health Service and has been nominated as a finalist in two categories of the UK's prestigious HSJ. The project has also received recent prizes at the International League Against Epilepsy for best poster and best presentation. The reception from academics, clinicians, families, and users is to date unanimously positive and supportive.

The take up of the app has been modest, although this likely reflects a cocktail of challenges that will require a responsive and reflective approach, beyond the need for an Android version summarized above. The literature relating to SUDEP in many ways characterizes both community and clinical level denial or ignorance as to the need to monitor risk of death in PWE. Marketing to a potential user base who are unaware of, or disconnect from, the narrative of risk in epilepsy is a challenge. The EpSMon project will seek to engage with clinicians, who already appear very receptive, and user groups to develop marketing strategies that engage people in the community, GPs, and specialist clinicians. In addition, work is underway to embed EpSMon into standard advice practice of GPs, through research trials to demonstrate the efficacy of this approach and specialist GP e-training (expected implementation in spring 2016).

Conclusions

Although this project appears U-centric, SUDEP is a global phenomenon. There is a higher prevalence of epilepsy in economically poorer and developing countries than economically developed countries [21]. In such poor countries, priority of safety and ignorance is rife. Presence of a cost-effective solution such as the app could save lives. The initiative toward making this app free to use, and housed within a research collaborative model, will hopefully invite opportunities to create impact in these contexts, through further development and uptake of EpSMon. Further usability research, academic publication of the tool's merits, and developments alongside a strong research strategy will hopefully further support the success of this project into the future and beyond the United Kingdom.

Conflicts of Interest

None Declared.

References

1. Hauser AW, Hesdorffer DC. Epilepsy: Frequency, Causes, and Consequences. New York: Demos Medical Publishing; 1990.
2. World Bank. World Development Report: Investing in Health. Oxford: Oxford University Press; 1993.

3. Tomson T, Walczak T, Sillanpaa M, Sander Josemir W A S. Sudden unexpected death in epilepsy: a review of incidence and risk factors. Epilepsia 2005;46 Suppl 11:54-61 [FREE Full text] [doi: 10.1111/j.1528-1167.2005.00411.x] [Medline: 16393182]
4. Terra VC, Cysneiros R, Cavalheiro EA, Scorza FA. Sudden unexpected death in epilepsy: from the lab to the clinic setting. Epilepsy Behav 2013;26:415-420. [doi: 10.1016/j.yebeh.2012.12.018] [Medline: 23402930]
5. Devinsky O. Sudden, unexpected death in epilepsy. N Engl J Med 2011;365:1801-1811. [doi: 10.1056/NEJMra1010481] [Medline: 22070477]
6. Thurman DJ, Hesdorffer DC, French JA. Sudden unexpected death in epilepsy: assessing the public health burden. Epilepsia 2014;55:1479-1485 [FREE Full text] [doi: 10.1111/epi.12666] [Medline: 24903551]
7. Hanna NJ, Black M, Sander J, Smithson W, Appleton R, Brown S. The Stationery Office. Fish DR The National Sentinel Clinical Audit of Epilepsy-Related Death: Epilepsy-death in the shadows 2002 URL: https://www.sudep.org/files/sudepaction/national-sentinel-clinical-audit-of-epilepsy-related-death-2002-summary.pdf [accessed 2016-04-18] [WebCite Cache ID 6grDfxW7o]
8. NICE Clinical Guideline 137 - Partial Pharmacological Update of Clinical Guideline 20: The epilepsies: the diagnosismanagement of the epilepsies in adultschildren in primarysecondary care. National Clinical Guideline Centre. 2012. URL: https://www.nice.org.uk/guidance/cg137/evidence/cg137-epilepsy-full-guideline-185134861 [accessed 2016-04-18] [WebCite Cache ID 6grDriXzu]
9. Waddell B, McColl K, Turner C, Norman A, Coker A, White K, et al. Are we discussing SUDEP?--A retrospective case note analysis. Seizure 2013;22:74-76 [FREE Full text] [doi: 10.1016/j.seizure.2012.09.017] [Medline: 23099115]
10. Shankar R, Cox D, Jalihal V, Brown S, Hanna J, McLean B. Sudden unexpected death in epilepsy (SUDEP): development of a safety checklist. Seizure 2013;22:812-817 [FREE Full text] [doi: 10.1016/j.seizure.2013.07.014] [Medline: 23962523]
11. Shankar R. SUDEP Global Conversation. 2014. SUDEP - are we as safe as we can be? URL: http://www.sudepglobalconversation.com/ [accessed 2016-04-18] [WebCite Cache ID 6grE65aBQ]
12. Brown S, Shankar R, Cox D, M. McLean B, Jory C. Clinical governance: risk assessment in SUDEP. Clinical Governance: An Intl J 2013;18:325-331. [doi: 10.1108/CGIJ-12-2012-0045]
13. Ridsdale L. Avoiding premature death in epilepsy. BMJ 2015;350:h718-h718. [doi: 10.1136/bmj.h718]
14. Ridsdale L, Charlton J, Ashworth M, Richardson MP, Gulliford MC. Epilepsy mortality and risk factors for death in epilepsy: a population-based study. Br J Gen Pract 2011;61:e271-e278 [FREE Full text] [doi: 10.3399/bjgp11X572463] [Medline: 21619751]
15. Ostler A, Cousins S, Ridsdale L. SUDEP Action January 2015.www.sudep.org. 2015. The Causes of Death in Epilepsy: A Systematic Review URL: https://www.sudep.org/files/sudepaction/the_causes_of_death_in_epilepsy_0.pdf [accessed 2016-04-18] [WebCite Cache ID 6grEkVzq9]
16. Shankar R, Jalihal V, Walker M, Laugharne R, McLean B, Carlyon E, et al. A community study in Cornwall UK of sudden unexpected death in epilepsy (SUDEP) in a 9-year population sample. Seizure 2014;23:382-385 [FREE Full text] [doi: 10.1016/j.seizure.2014.02.005] [Medline: 24630808]
17. Jory C, Shankar R, Coker D, McLean B, Hanna J, Newman CGJ. Safe and sound? A systematic literature review of seizure detection methods for personal use. Seizure 2016;36:4-15. [doi: 10.1016/j.seizure.2016.01.013] [Medline: 26859097]
18. mobiThinking. Global Mobile Statistics 2014 Part A: Mobile Subscribers; Handset Market Share; Mobile Operators. 2014. URL: https://mobiforge.com/research-analysis/global-mobile-statistics-2014-part-a-mobile-subscribers-handset-market-share-mobile-operators [accessed 2016-04-18] [WebCite Cache ID 6grYR7fol]
19. Medicine & Healthcare products Regulatory Agency. Guidance -Medical Device Stand-Alone Software Including Apps. 2014. URL: https://www.gov.uk/government/publications/medical-devices-software-applications-apps/medical-device-stand-alone-software-including-apps [accessed 2016-04-18] [WebCite Cache ID 6grEv77ai]
20. engadget. Android climbed to 79 percent of smartphone market share in 2013, but its growth has slowed URL: http://www.engadget.com/2014/01/29/strategy-analytics-2013-smartphone-share/ [accessed 2016-04-18] [WebCite Cache ID 6grF1d0O9]
21. Ngugi AK, Kariuki S, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Incidence of epilepsy: a systematic review and meta-analysis. Neurology 2011;77:1005-1012 [FREE Full text] [doi: 10.1212/WNL.0b013e31822cfc90] [Medline: 21893672]

Abbreviations

EpSMon: epilepsy self-monitor
GP: general practitioner
HSJ: Health Service Journal Innovation awards
IT: information technology
PPI: public and patient involvement
PWE: people with epilepsy
SUDEP: sudden unexpected death in epilepsy

Edited by G Eysenbach; submitted 27.11.15; peer-reviewed by R Ho, V Patterson, RK B; comments to author 07.01.16; revised version received 01.02.16; accepted 20.02.16; published 07.06.16.

Please cite as:
Newman C, Shankar R, Hanna J, McLean B, Osland A, Milligan C, Ball A, Jory C, Walker M
Developing an Evidence-Based Epilepsy Risk Assessment eHealth Solution: From Concept to Market
JMIR Res Protoc 2016;5(2):e82
URL: http://www.researchprotocols.org/2016/2/e82/
doi:10.2196/resprot.5389
PMID:27269382

Protocol

Towards a Mobile-Based Platform for Traceability Control and Hazard Analysis in the Context of Parenteral Nutrition: Description of a Framework and a Prototype App

Víctor M Alonso Rorís[1*]; Luis M Álvarez Sabucedo[1*], PhD Eng; Carmina Wanden-Berghe[2*], PhD; Juan M Santos Gago[1*], PhD Eng; Javier Sanz-Valero[3*], PhD

[1]E E Telecomunicación, University of Vigo, Vigo, Spain

[2]Foundation for the Promotion of Health and Biomedical Research from the Valencian Community (FISABIO), University General Hospital of Alicante, Alicante, Spain

[3]Department of Public Health & History of Science, University Miguel Hernandez, Alicante, Spain

[*]all authors contributed equally

Corresponding Author:
Javier Sanz-Valero, PhD
Department of Public Health & History of Science
University Miguel Hernandez
Campus Sant Joan
Alicante,
Spain
Phone: 34 666840787
Fax: 34 965919506
Email: jsanz@umh.es

Abstract

Background: The parenteral nutrient (PN) mixtures may pose great risks of physical, microbiological, and chemical contamination during their preparation, storage, distribution, and administration. These potential hazards must be controlled under high levels of excellence to prevent any serious complications for the patients. As a result, management control and traceability of any of these medications is of utmost relevance for the patient care, along with ensuring treatment continuity and adherence.

Objective: The aim of this study is to develop a mobile-based platform to support the control procedures and traceability services in the domain of parenteral nutrient (PN) mixtures in an efficient and nonintrusive manner.

Methods: A comprehensive approach combining techniques of software engineering and knowledge engineering was used for the characterization of the framework. Local try-outs for evaluation were performed in a number of application areas, carrying out a test/retest monitoring to detect possible errors or conflicts in different contexts and control processes throughout the entire cycle of PN. From these data, the absolute and relative frequencies (percentages) were calculated.

Results: A mobile application for the Android operating system was developed. This application allows reading different types of tags and interacts with the local server according to a proposed model. Also, through an internal caching mechanism, the availability of the system is preserved even in the event of problems with the network connection. A set of 1040 test traces were generated for the assessment of the system under various environments tested. Among those, 102 traces (9.81%) involved conflictive situations that were properly taken care of in this paper by suggesting solutions to overcome them.

Conclusions: A mobile oriented system was generated and tested in order to allow enhanced control and quality management of PN mixtures that is easy to integrate into the daily praxis of health care processes.

(JMIR Res Protoc 2016;5(2):e57) doi:10.2196/resprot.4907

KEYWORDS

parenteral nutrition; quality control; process assessment; information management

Introduction

Mixtures of parenteral nutrition (PN) enable intravenous delivery of essential nutrients to patients who cannot be fully fed orally. The PN mixture may contain more than 50 components with a high potential for physicochemical interaction among its ingredients, the bag, oxygen, temperature, and light. These interactions are potentially iatrogenic and, in some cases, may even compromise the patient's life [1,2]. Therefore, PN is considered a high-alert medication that must be controlled throughout its life cycle [3].

In such contexts, in order to minimize errors and problems in the procedures involved, clinical practice guidelines and recommendations for action are generated [4]. A properly defined protocol ensures a high degree of theoretical viability, quality, and safety of the intended process. Thus, it is possible to adapt the context to strict quality requirements of the health care environment and compliance, in the elaboration and control of PN, with current regulations [5].

The criterion that determines whether those goals are achieved is adherence to the protocol of the different operations performed by the agents involved. Thus, in this type of high-risk context, to ensure proper execution of the processes, it is mandatory to check that the protocols are being applied and the results are the expected ones. In line with this, certain time points and places within processes need to be monitored. These elements are known as control points (CP) and allow for verification of the defined requirements [6]. Additionally, depending on the probability of the event, and especially the severity of the potential damage, those CP that require special supervision, which are referred to as critical control points (CCP), should be identified [7].

At the CP, and especially the CCP, data records from the applied monitoring system are generated, which are known as traces [8]. Gathered traces allow explicit statement to be made about the states or interactions, or both, between the different elements involved in the various processes that are being carried out. A thorough and complete log of traces makes full awareness of the history, usage, or location of an entity possible. This ability is known as traceability [9].

In the context of PN, traceability makes following the movement of a mixture through all the stages of its life cycle possible. Specifically, traceability is aimed at determining with certainty which vendors and products are part of a PN mixture's composition (traceability back), tracking the PN in production time (internal traceability), and tracing the mixture once it is produced and distributed (traceability forward) [10]. Thus, an efficient system of traceability should be able to react quickly and appropriately to any quality risks identified or to hazards related to the safety of medicines.

Various technological proposals are focused on traceability, particularly in the logistics area [11]. But, unfortunately, this type of deployment is based on automatic recording from the temporary location of the product and cannot cover all immediate demands, requirements, and needs of comprehensive management control in a context such as that of the PN. Nevertheless, mobile technologies are providing new solutions, based on comprehensive patient-focused care models, which make them very attractive for clinical care applications [12,13].

Having noted the benefits of a management and traceability platform for PN using mobile technologies, we proposed the design and implementation of a holistic service architectural framework to fill the gaps in traceability and to provide flexible and effective telematic mechanisms for monitoring PN in a health care setting. We describe a technology platform to support control procedures and traceability of PN mixtures in an efficient and nonintrusive way.

Methods

Models

We used a comprehensive approach combining software engineering and knowledge engineering techniques to characterize our framework. In particular, we generated three initial models to fully define the system from different perspectives. Together they provide a complete description of the solution. We tested these models [14], which are a business model (high-level description of conditions, agents, and general behavior of the platform); a semantic model (formalization of the knowledge within the system using technologies that facilitate automatic processing and interpretation of information); and a reference architecture (the definition of a framework for the development of a software solution).

Business Model

The business model is intended to identify the basic features of the technological platform. This characterization offers a vision, not necessarily formal, of how the whole system works in this context.

To conduct this modelling, in addition to consulting the opinion of experts, we reviewed the available literature (science, technology, legal, etc) and generated different usage scenarios for analysis and validation.

By using this model, we were able to identify, manage, and freely modify on run time the data attached to CP, CCP, and the monitoring parameters associated with the entire life cycle of a PN mixture. We also labelled the elements involved in the context (pumps, filters, etc) with matrix barcodes (quick response, or QR, and data matrix codes) and near field communication (NFC) tags to identify them uniquely.

Semantic Model

The semantic model formalized the proposed traceability mechanisms, which facilitated the analysis and automatic processing of the history of each PN mixture. In this sense, it was essential to establish a formal scheme that would describe the information in a way that would enable the efficient application of reasoning or complex queries.

This modelling allowed formal conceptualization of the universe of applications and of relationships, which would be easily readable and interpretable by machines. Having semantic support in the model enabled the application of advanced information technologies and added-value solutions and tools,

such as inference engines that perform logical reasoning (or make inferences). Such reasoning enabled us to extract new facts and knowledge and to answer specific and complex queries.

Following this line of reasoning, we defined an open and generic data model focused on the definition of common concepts (with their properties) for related scopes of the domain of interest: users, institutions, CP, CCP, services, and parameters to monitor, for example traces and context variables. This semantic model provided us with an abstract representation of the whole application domain. To this end, we generated specific internal vocabularies and, as much as possible, reused vocabularies that are widely accepted in the field of semantics (eg, friend of a friend, resource description framework schema).

Uniform resource identifiers (URIs) [15] univocally identify semantic concepts and entities. This usage is derived from the HTTP paradigm and makes it possible to reference resources. This feature allowed us to attach the URI of each element in the semantic model to the information on the label on each actual item. Thus, by reading a label, regardless of the agent involved, it was possible to directly access a representation of the information stored in the system for the specific entity.

Reference Architecture

The next step in the comprehensive modelling of the system was to define a reference architecture that would provide a guide or framework for the development and final implementation of the software platform. In general, we used a client-server architecture. Thus, the business logic was hosted on servers accessible over the network and, as a result, the complexity of the agents was simplified.

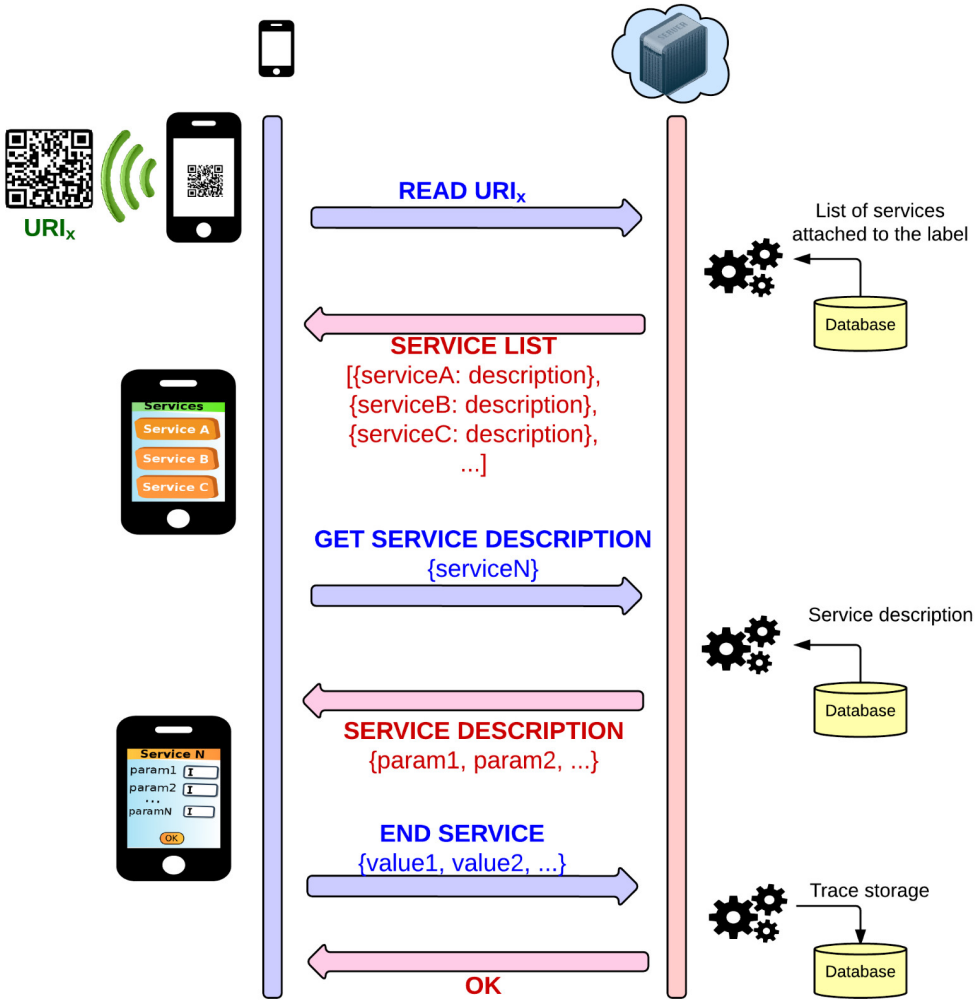
In this methodology, the reference architecture is described from different perspectives that compose a comprehensive view of the platform. The aim is to be able to speak to the characteristics and peculiarities defined in the business model and the semantic modelling.

Client-Server Interaction

To carry out a successful interaction with the frame of the proposal, the client (the software that runs on the end user device) and server must interact according to the established model. In particular, this interaction must be compliant with the model presented in Figure 1. In this example, after reading the label on a PN bag, the client launches a request to the server. The server then responds with a list of services associated with the element depending on the requesting user and other related variables of context.

Afterward, the client must select the actual service to invoke using an on-screen interface. On selection, the server sends back a full description of the service under consideration. Using this description, the client software generates a form in the display with the parameters required by the service and that the user must provide. Finally, the values entered into the form are sent to the server according to the software interface and become a trace in the system.

Figure 1. Model representation of a regular interaction between client (software) and server.



Reference Model

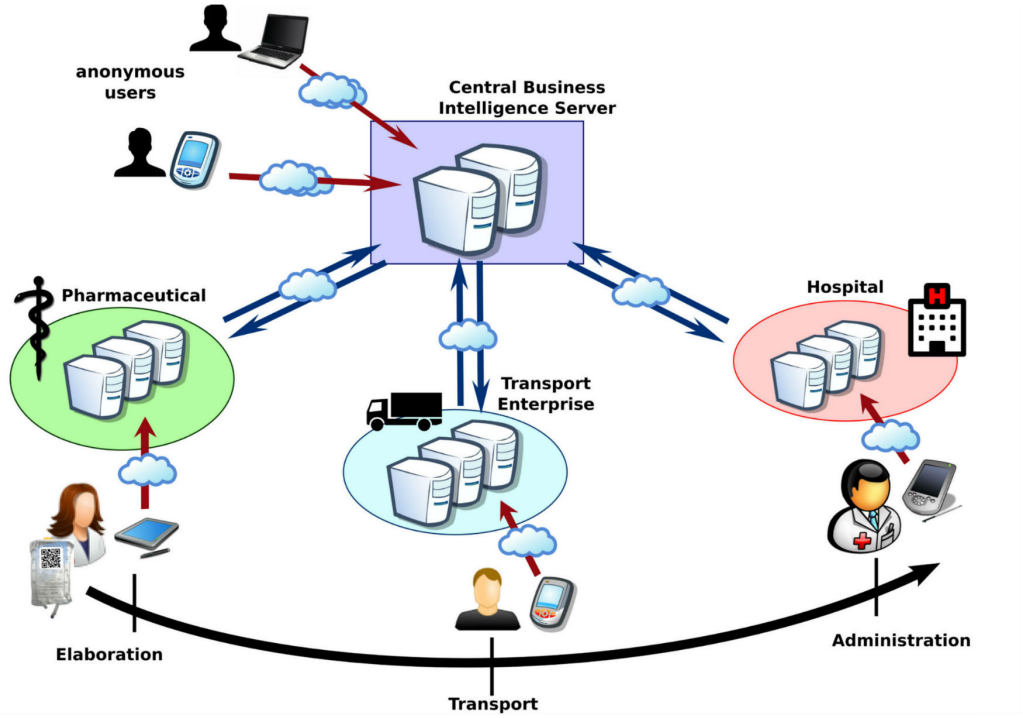
During the life cycle of a PN mixture, management and control of the traces may concern different institutions or companies (eg, pharmaceutical industry, hospitals, transport companies). Given the sensitive nature of the information processed, these organizations are compelled to store the information generated in its ecosystem under rigorous security measures to ensure compliance with legal and ethical regulations.

To achieve the required security levels, each organization may deploy its system locally according to its own standards of security. This decentralized scenario is achieved through the use of specialized agents (running mobile apps for the final clients) that have the appropriate logic to establish direct connections with servers in their organizations.

By means of this modelling, different servers may record different traces throughout the life cycle of the product (see Figure 2). Consequently, if an unregistered user accesses the system, the central server is responsible for redirecting the request to the proper agent that possesses the requested information.

The central server acts, from the point of the client agent, as the single access point and coordinator for the existing local system. In this way, the fragmented system appears seamless to the user.

Figure 2. Reference structure for the different components and communication models.



Modular Architecture

The architecture model for the server was designed following a modular approach. Thus, it was possible to divide the overall complexity of the system, and the logic layer was distributed according to the nature of each component. Figure 3 shows the high-level architecture of a server and different interfaces and management layers. We describe the main modules below.

Open Information Provider

This provides a universal access point for public information about semantic records. In particular, it responds to HTTP requests on the URI that uniquely identifies the elements within the domain of the application.

Tracking Application Programming Interface

This provides the functionality that is available for interaction with the specialized customer software. These features include services for discovering control services, accessing information about a concrete item, downloading service descriptions (eg, describing how to monitor variables), invoking a specific service for registration of the relevant traces, and recovering useful material for human users (videos, manuals, etc).

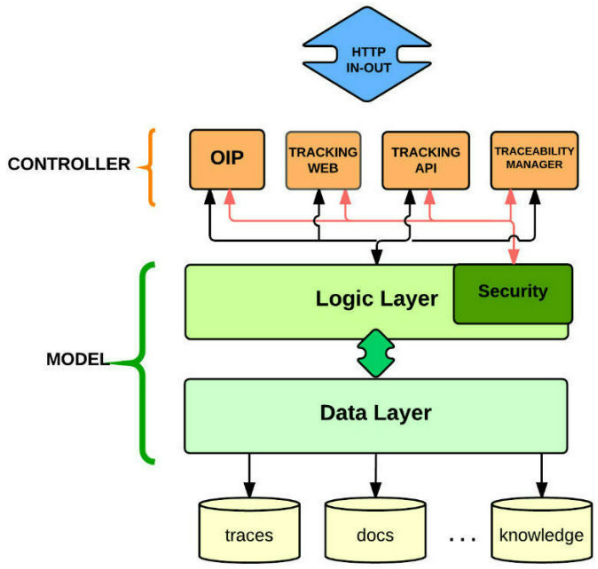
Tracking Web

This provides similar functionalities to those offered by the tracking application programming interface using just the support of a Web browser.

Traceability Manager

This provides a Web interface designed to support 1) functionalities related to traceability, such as checking historical traces according to user preferences, date, location, and related services, 2) an advanced search engine supporting advanced queries, 3) facilitating the definition of logical inference patterns and automatic analysis of procedures, problems, alerts, etc, 4) statistical analysis of existing traces to enable high-value services, and 5) automatic verification of adherence to protocols according to existing traces.

Figure 3. General architecture including server modules.



Evaluation of the Platform

We developed simulation testbeds to test the validity of the prototype we developed. A test-retest control detected possible errors or conflicts in different contexts and control processes throughout the entire cycle of the PN mixture. From these data, we calculated the absolute and relative frequencies (percentages). We controlled information quality by double entering data; we corrected inconsistencies by consulting the original data.

Results

Prototype

We generated a mobile app for the Android operating system according to our presented models. This app reads different types of labels and tags, and interacts with the local server under the proposed schema. Also, the above-mentioned app ensures operability of the system, even in case of network disconnection, by means of an internal caching mechanism.

During the prototype implementation process, the following elements were provided: the central server, to redirect requests to the proper local server responsible; the local servers, to provide the necessary functionality for control and traceability; and the client app that supports efficient mechanisms for the discovery of CP and CCP.

Within the frame of the proposed model (see Figure 4), on reading the QR tag associated with a nutrition bag, the client software retrieves the list of invokeable services (offered by the system) and displays them to the user. To select the desired service, the user accesses a form on the device screen to submit the variables to be monitored. Finally, the information is sent to the server, which processes the new information and records it as a trace.

In this way, after reading a label attached to a PN bag using a mobile device with Internet access, the user can discover the control operations related to the identified element, at run time. That is, the platform dynamically retrieves control operations that can be invoked by the user according to the role assigned in the system (nurse, pharmacist, doctor, etc), the element under consideration, and other context variables such as time and location. All collected data are stored on a server that acts as a repository of information. And, using data mining techniques, the server can reuse these data and generate new knowledge by applying inference and discovery processes.

Use of the software is very intuitive and user centric, as the user interfaces are generated dynamically and ad hoc according to the descriptions provided by the server. Figure 5, for example, shows the list of services that the user can access after reading a label as the software agent generates it. In the same way, Figure 6 illustrates how the dynamically generated form is displayed to invoke service control.

Summing up, the developed prototype server covers the functionality required for the proper functioning of the overall process control and traceability support. Consequently, we have implemented mechanisms for logical reasoning that allow for the application of advanced processing methods on traces generated in this framework. Figure 7 is a screenshot showing the list of historical traces available in the system. In addition, this log of traces can be customized through various search filters (eg, prescription, type of nutrition, responsible for delivery, composition).

During the evaluation process, we collected 1040 test traces in different testbed scenarios. Table 1 lists the issues we identified, along with their proposed solutions.

To achieve the desired results and functionalities from the point of view of the final users, we identified several functional and nonfunctional requirements.

Table 1. Frequency (f) and percentage of errors (undesired situations) identified in the assessment of the management and traceability platform and their suggested corrections.

Undesired situation	f_0	%	Solution
The QR[a] tag was stained and not readable.	9	0.87	Laminate labels.
QR tag was attached to a surface with a large curvature and was not readable (the camera was not able to capture a defined image of the whole QR code).	11	1.06	Reduce the size of the label to minimize the curvature radius or change its location to a nearby flat surface.
In poorly lit places, the camera was not able to read the QR tag.	5	0.48	While reading, the app triggers a flash to illuminate the corresponding surface.
The NFC[b] tag could not be read because it was attached to a metallic surface.	9	0.87	Replace basic NFC tags with special NFC tags designed to be used on metallic surfaces or place them on another spot.
The NFC tag was located behind a plastic sign on the door and could not be read.	14	1.35	Remove any surface between the mobile and NFC tag.
User was unable to log on to the app when offline the first time the app was used on that mobile device (no preexisting cache contents).	6	0.58	The system requests the user to log in, at least the first time, in an online context.
The user, trying to read the tag, noted that the battery was drained	2	0.19	User training (no solution in the app).
The user typed a decimal value by entering a comma instead of a period. As a result, data were misinterpreted.	21	2.02	Unblock use of the comma button in the app.
The system noted that it was impossible to invoke the service when the form was including incorrect values. No hints on the wrong values were provided.	6	0.58	Update the app to display a warning message when wrong data are detected. Also, present information about accurate expected values.
In the input form, when trying to send multiple documents (eg photographs) with the same name, the server could only recover the last one.	4	0.38	Implement a mechanism in the app to avoid file name conflicts.
Leaving the input form by mistake was possible, resulting in losing all data entered so far.	1	0.10	Modify the app so that trying to leave the input form prompts a message that the entered data would be lost and that requests explicit confirmation to leave the form.
The implementation required activating the GPS[c] service to inform the server of the location of the operator in each of the traces generated. This circumstance caused high battery consumption.	14	1.35	Replace the initial mechanism to recover coordinates based on continuous queries with an intelligent mechanism that checks the GPS service according to the user's mobility over time.
Total	102	9.81	

[a]QR: quick response.

[b]NFC: near field communication.

[c]GPS: global positioning system.

Figure 4. Outlining the interaction with the platform through the QR code attached to a bag of PN mixture.

Figure 5. Screenshot of the mobile application showing the interface for selecting associated services to a concrete label.

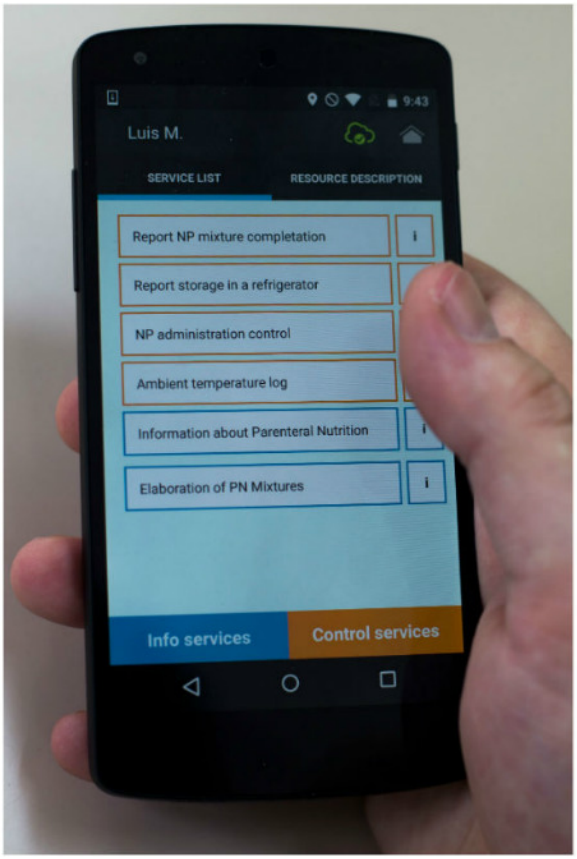


Figure 6. Screenshot of the mobile application showing the form for invoking a control service.

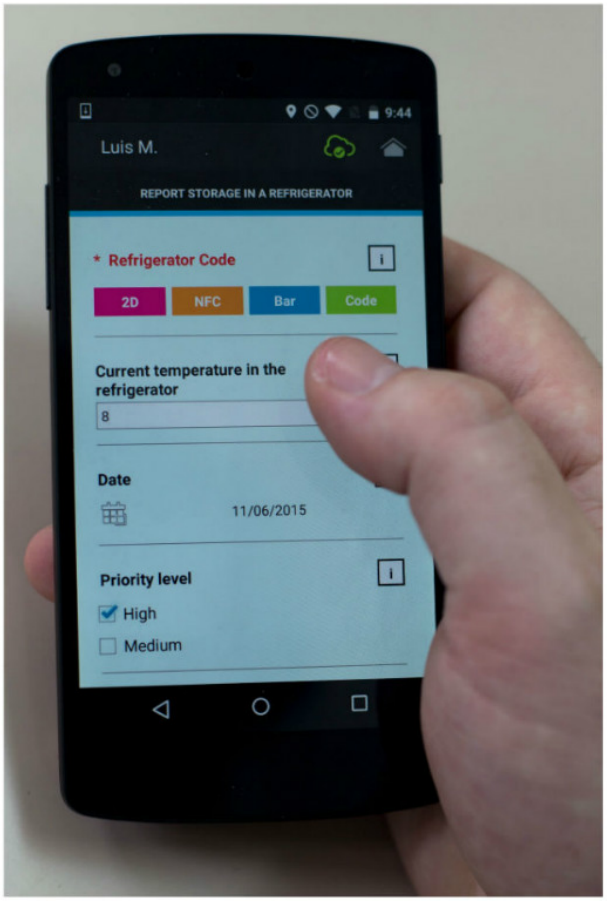
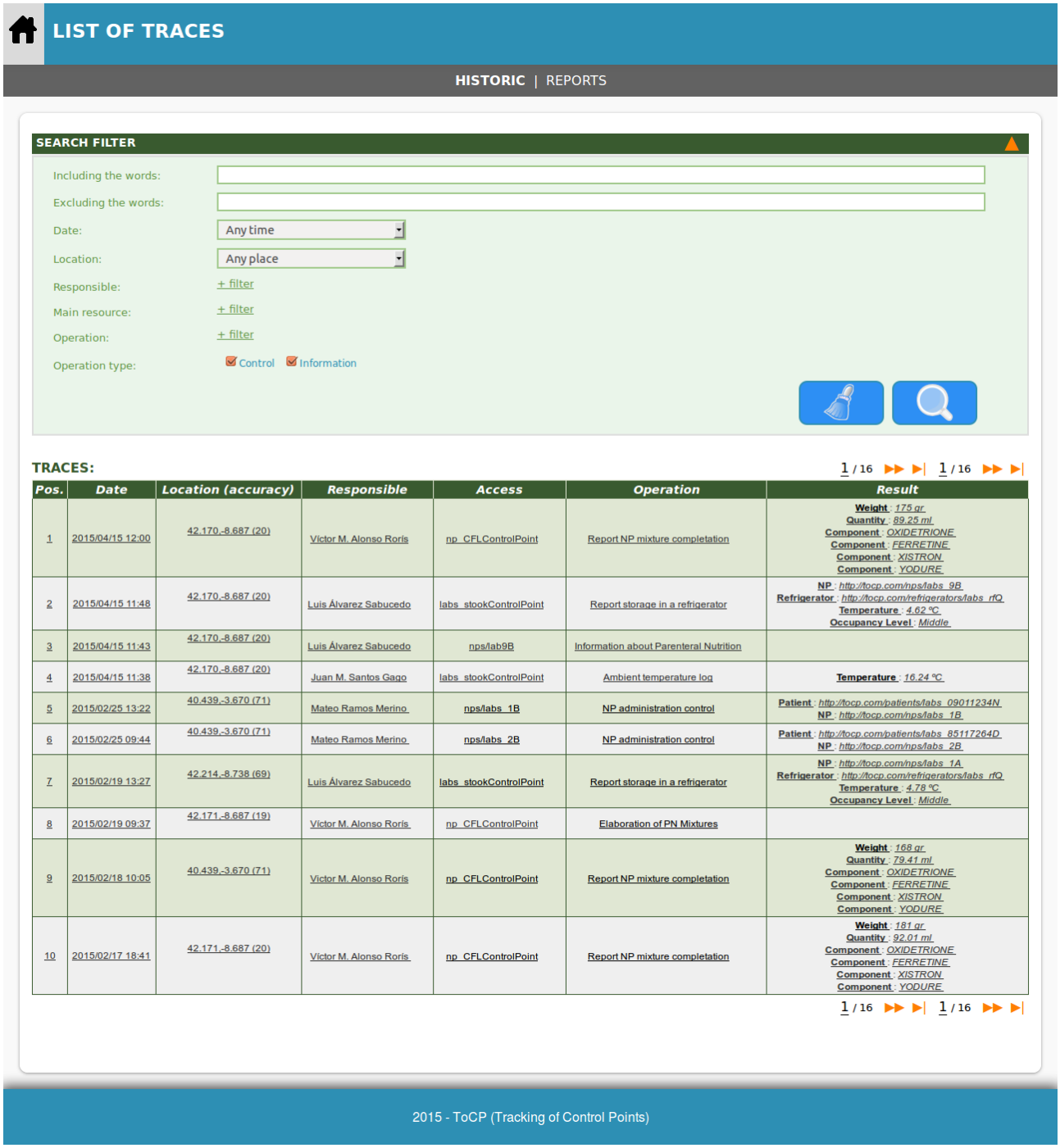


Figure 7. Screenshot regarding traceability functionality showing the trace log according to the search filter options.



Requirements

Simple and Unobtrusive Use

Use of the platform should fit into the existing standard operating procedures, which should not intrude on or misuse the platform.

Availability Throughout the Entire Life Cycle

The platform must include a highly adaptable and configurable framework. Thus, it would be possible to support a large range of organizations and to enable them to establish and manage their own procedures and services for the whole life cycle of the products.

Support for Different Types of Labels

The labels we used allowed for unique identification of the elements in the domain. Due to their popularity and low cost, we used 2-dimensional labels (QR and data matrix code) and NFC.

Mobile Devices

Smart mobile devices (mobile phones and tablets) offer the capacity and portability required for client use. Moreover, they are simple and intuitive to use and are highly available among potential users.

Different Types of Services

Services that could be generated and supported within the platform were of two types: control and information. Control services allow monitoring of one or more variables, while information services provide access to suitable pieces of information relevant to the context.

Support for Different Roles

The platform provides customization mechanisms. Thus, it was possible to filter the services available according to the role of the current user.

Security

Given the sensitive nature of the information exchanged, it is essential that the platform offer mechanisms to ensure the confidentiality of the exchanged information.

Offline Operability

Due to the nature of the problem, it is of the utmost relevance that no trace be lost at any point of the processes being monitored. Therefore, we developed software capabilities to make use of the platform possible even without a network connection.

Discussion

Principal Findings

We outlined the provision of a holistic computerized control and verification system, for the entire process of production and distribution of a PN mixture. Our solution meets the recommendation of the consensus on the preparation of parenteral nutrient mixtures of the Spanish Society of Hospital Pharmacy [1] and is in line with clinical guidelines on guarantees and rational use of PN [16].

Nevertheless, the key point to using labels as described to uniquely identify the items under consideration in any stage is related to the platform's application in the analysis and monitoring of hazards (by means of CCP) within a system of hazard analysis and critical control points (HACCP) implemented in the whole process of preparation and administration of PN mixtures. Intravenous therapy management is a critical process in clinical patient safety involving traceability, accountability, and security. Thus, the use of HACCP-based systems ensures excellence in its control [17]. This tag, attached to the PN bag, can be very useful in ensuring links with the prescription, reporting about its proper use according to established standards, and providing data such as elaboration, issue or expiration date, dosage, and possible side effects [18]. Regarding home care, these labels integrated into PN containers facilitate the exchange of information between caregivers and the medical team, and in emergency care this platform contributes to immediate patient identification and comprehensive knowledge of medical history. This model provides, at the same time, security features in clinical data transmission [19,20].

In addition, the software developed for the Android operating system supports an internal cache mechanism that makes regular operation of the system possible even if the network connection is not available [21]. Among its capabilities, the central server acts as a repository of publicly accessible information that enables the reuse of existing knowledge in an open and free manner. To make this feature possible, the central server periodically retrieves the public records of each of the deployed servers. Then, this information is automatically enriched with external information gathered over the Web using semantic enrichment mechanisms that we have already deployed successfully in previous work [22].

Besides features related to control management and traceability, the prototype system we developed has the following advantages: improved management of patient care and quality of care, empowerment of the actors involved, and ensured continuity of the action planned. The association of these characteristics with reducing the rate of patients with missing data and better monitoring of adherence to treatments and of iatrogenic risks has been previously proven [23]. Regarding adherence to PN treatments, it has been found that only intensive care units met established goals, with adherence being especially problematic in monitoring patients admitted to home care units [24]. This problem can be addressed by using the platform we have developed.

The evaluation tests showed a low rate for the unfavorable situations we observed. Also, we were able to solve most of them fully except for those related to lack of user training. Nevertheless, this was an expected issue. We were well aware that training and user feedback should always be present in the deployment of mobile technologies [25,26].

In addition to the good evaluation results, an advantage that must be considered is the positive adoption of mobile apps due to their low cost and simplicity of use. Previous studies have shown that these apps are feasible for real life, and are productive for clinical application [27].

Limitations

Among possible limitations of this study, it must be mentioned that, although we conducted the evaluation in a testbed designed in a realistic way from the point of view of prescription logistics, preparation, and delivery, the overall evaluation would benefit from an actual usage scenario in a heavy load condition to ensure optimal application [28].

Conclusions

The prototype platform is fully operational and ready to be tested in a real context. Consequently, we have generated and tested a system based on mobile technology that allows better monitoring and management of the quality of PN mixtures and that is easy to incorporate into the daily praxis of health care processes.

Acknowledgments

This work has been partially funded by the Instituto de Salud Carlos III (Spain) under project PI13/00464, and by the European Regional Development Fund “A way of making Europe.”

Conflicts of Interest

None declared.

References

1. Cardona Pera D, Cervera Peris M, Fernández Arévalo M, Gomis Muñoz P, Martínez Tutor M, Piñeiro Corrales G, et al. Spanish consensus on the preparation of parenteral nutrient mixtures. National Work Group “Pharmaceutic aspects of nutrition”. Nutr Hosp 1997;12(1):15-19. [Medline: 9147533]
2. Sacks G. Safety surrounding parenteral nutrition systems. JPEN J Parenter Enteral Nutr 2012 Mar;36(2 Suppl):20S-22S. [doi: 10.1177/0148607111434776] [Medline: 22301322]
3. Boullata JI. Overview of the parenteral nutrition use process. JPEN J Parenter Enteral Nutr 2012 Mar;36(2 Suppl):10S-13S. [doi: 10.1177/0148607111433624] [Medline: 22275321]
4. Boullata JI, Gilbert K, Sacks G, Labossiere RJ, Crill C, Goday P, American Society for ParenteralEnteral Nutrition. A.S.P.E.N. clinical guidelines: parenteral nutrition ordering, order review, compounding, labeling, and dispensing. JPEN J Parenter Enteral Nutr 2014;38(3):334-377. [doi: 10.1177/0148607114521833] [Medline: 24531708]
5. Llop Talaverón J M, Martorell PC, Mercadal OG, Badía Tahull M B, Rancaño I, Abascal N, et al. Automation of parenteral nutrition elaboration: adaptation to in force legislation. Nutr Hosp 2006;21(2):184-188. [Medline: 16734071]
6. Curbera F, Doganata Y, Martens A, Mukhi N, Slominski A. Business provenance - a technology to increase traceability of end-to-end operations. In: Meersman R, Tari Z. , editor. On the Move to Meaningful Internet Systems: OTM. Monterrey, Mexico: Springer; 2008:2008-2540.
7. Iyengar V, Elmadfa I. Food safety security: a new concept for enhancing food safety measures. Int J Vitam Nutr Res 2012 Jun;82(3):216-222. [doi: 10.1024/0300-9831/a000114] [Medline: 23258403]
8. García García H, Santos Menéndez E, Windels B. International Journal on Information Technologies and Knowledge (4 Suppl). 2008. Traceability management architectures supporting total traceability in the context of software engineering URL: http://oa.upm.es/2753/1/INVE_MEM_2008_57995.pdf [accessed 2016-03-10] [WebCite Cache ID 6fvCi6zqR]
9. Miana Mena M T, Fontanals Martínez S, López Púa Y, López Suñé E, Codina Jané C, Ribas Sala J. Description of the ISO 9001/2000 certification process in the parenteral nutrition area. Farm Hosp 2007;31(6):370-374 [FREE Full text] [Medline: 18348667]
10. Kelepouris T, Pramatari K, Doukidis G. RFID‐enabled traceability in the food supply chain. Industr Mngmnt & Data Systems 2007 Mar 20;107(2):183-200. [doi: 10.1108/02635570710723804]
11. Brock D. The Electronic Product Code (EPC) - A naming scheme for physical objects. In: White Paper - Massachusetts Institute of Technology (MIT). Cambridge, MA: Massachusetts Institute of Technology (MIT); 2001.
12. Nasi G, Cucciniello M, Guerrazzi C. The role of mobile technologies in health care processes: the case of cancer supportive care. J Med Internet Res 2015;17(2):e26 [FREE Full text] [doi: 10.2196/jmir.3757] [Medline: 25679446]
13. Semple JL, Sharpe S, Murnaghan ML, Theodoropoulos J, Metcalfe KA. Using a mobile app for monitoring post-operative quality of recovery of patients at home: a feasibility study. JMIR Mhealth Uhealth 2015;3(1):e18 [FREE Full text] [doi: 10.2196/mhealth.3929] [Medline: 25679749]
14. Santos J, Anido L, Llamas M. Design of a Semantic Web-based Brokerage Architecture for the E-learning Domain: A Proposal for a Suitable Ontology. In: IEEE/ASEE, editor.: IEEE Computer Society; 2005 Presented at: 35th Frontiers in Education Conference; 19-22 October 2005; Indianapolis, IN p. 1-6.
15. Sauermann L, Cyganiak R, Völkel M. Künstliche Intelligenz. Kaiserslautern, FRG: Deutsches Forschungszentrum für Künstliche Intelligenz; 2007. Cool URIs for the semantic web monograph on the Internet URL: http://scidok.sulb.uni-saarland.de/volltexte/2011/3944/pdf/TM_07_01.pdf [accessed 2016-03-14] [WebCite Cache ID 6g0cQkbg0]
16. Dreesen M, Foulon V, Vanhaecht K, De PL, Hiele M, Willems L. Guidelines recommendations on care of adult patients receiving home parenteral nutrition: a systematic review of global practices. Clin Nutr 2012 Oct;31(5):602-608. [doi: 10.1016/j.clnu.2012.02.013] [Medline: 22424704]
17. Sanz-Valero J, Álvarez Sabucedo L, Wanden-Berghe C, Martínez de Victoria E. QR codes: Outlook for food science and nutrition. Ann Nutr Metab. (Suppl 1) 2013;63:366.
18. Lin C, Tsai F, Tsai W, Wen H, Hu M. The feasibility of QR-code prescription in Taiwan. J Clin Pharm Ther 2012 Dec;37(6):643-646. [doi: 10.1111/j.1365-2710.2012.01358.x] [Medline: 22612397]
19. INTECO National Institute of Communication Technologies. Instituto Nacional de Ciberseguridad. Madrid, Spain: INTECO - Ministry of Industry and Energy; 2012. Study on security on mobile devices and smartphones URL: https://www.incibe.es/file/rdj_9ad_DHM_jZcyjTYRlw [accessed 2016-03-14] [WebCite Cache ID 6g0ckVwXM]

20. Meruga JM, Cross WM, Stanley MP, Luu Q, Crawford GA, Kellar JJ. Security printing of covert quick response codes using upconverting nanoparticle inks. Nanotechnology 2012 Oct 5;23(39):395201. [doi: 10.1088/0957-4484/23/39/395201] [Medline: 22968045]
21. Mummert L, Ebling M, Satyanarayanan M. Exploiting weak connectivity for mobile file access. In: ACM. 1995 Presented at: SOSP '95 Proceedings of the fifteenth ACM symposium on Operating systems principles; 3-6 Dec, 1995; Copper Mountain Resort, Colorado p. 143-155 URL: http://www.cs.cmu.edu/~coda/docdir/s15.pdf [doi: 10.1145/224056.224068]
22. Alonso Rorís VM, Santos Gago J, Pérez Rodríguez R, Rivas Costa C, Gómez Carballa M, Anido Rifón L. Information extraction in semantic, highly-structured, and semi-structured Web sources. Polibits;(49) 2014:69-76 [FREE Full text]
23. Le Divenah A, David S, Brignone M, Chau I, Segouin C, Kauffmann C, et al. Management and follow-up of patients treated with antiretroviral prophylaxis: an evaluation of professional practices. Sante Publique 2010;22(4):393-403. [Medline: 20858338]
24. van den Broek Paulina W J H, Rasmussen-Conrad E, Naber Anton H J, Wanten Geert J A. What you think is not what they get: significant discrepancies between prescribed and administered doses of tube feeding. Br J Nutr 2009 Jan;101(1):68-71. [doi: 10.1017/S0007114508986852] [Medline: 18768101]
25. Farrell MJ, Rose L. Use of mobile handheld computers in clinical nursing education. J Nurs Educ 2008 Jan;47(1):13-19. [Medline: 18232610]
26. Trangenstein PA. Electronic toolkit for nursing education. Nurs Clin North Am 2008 Dec;43(4):535-46, vi. [doi: 10.1016/j.cnur.2008.06.004] [Medline: 18940410]
27. Zhang M, Cheow E, Ho CS, Ng BY, Ho R, Cheok CC. Application of low-cost methodologies for mobile phone app development. JMIR Mhealth Uhealth 2014;2(4):e55 [FREE Full text] [doi: 10.2196/mhealth.3549] [Medline: 25491323]
28. Jung K, Jang J. Development of a two-step touch method for website navigation on smartphones. Appl Ergon 2015 May;48:148-153. [doi: 10.1016/j.apergo.2014.11.006] [Medline: 25683542]

Abbreviations

CP: control points
CPP: critical control points
HACCP: hazard analysis and critical control points
NFC: near field communication
PN: parenteral nutrition
QR: quick response
URI: uniform resource identifier

Edited by G Eysenbach; submitted 06.07.15; peer-reviewed by M Zhang; comments to author 20.08.15; revised version received 28.08.15; accepted 20.09.15; published 07.06.16.

Please cite as:
Alonso Rorís VM, Álvarez Sabucedo LM, Wanden-Berghe C, Santos Gago JM, Sanz-Valero J
Towards a Mobile-Based Platform for Traceability Control and Hazard Analysis in the Context of Parenteral Nutrition: Description of a Framework and a Prototype App
JMIR Res Protoc 2016;5(2):e57
URL: http://www.researchprotocols.org/2016/2/e57/
doi:10.2196/resprot.4907
PMID:27269189

Original Paper

Informing Patients About Placebo Effects: Using Evidence, Theory, and Qualitative Methods to Develop a New Website

Maddy Greville-Harris[1], MSc, PhD; Jennifer Bostock[2], MA; Amy Din[3], BSc (Hons), MSc, MBAcC; Cynthia A Graham[1], BA, MAppSci, PhD; George Lewith[4], MA, DM, FRCP, MRCGP; Christina Liossi[1], BA, MSc, MPhil, DPsych, AFBPsS, CPsychol; Tim O'Riordan[5], MA, MSc; Peter White[3], BSc, PhD; Lucy Yardley[1], BSc, MSc, PhD, CPsychol; Felicity L Bishop[1], MA, MSc, PhD, AFBPsS, CPsychol

[1]Psychology Department, Faculty of Social and Human Sciences, University of Southampton, Southampton, United Kingdom
[2]Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom
[3]Centre for Innovation & Leadership in Health Sciences, Faculty of Health Sciences, University of Southampton, Southampton, United Kingdom
[4]Primary Care and Population Sciences, Faculty of Medicine, University of Southampton, Southampton, United Kingdom
[5]ZeMedia, Southampton, United Kingdom

Corresponding Author:
Felicity L Bishop, MA, MSc, PhD, AFBPsS, CPsychol
Psychology Department
Faculty of Social and Human Sciences
University of Southampton
Building 44
Highfield Campus
Southampton, SO17 1BJ
United Kingdom
Phone: 44 2380599020
Fax: 44 2380594597
Email: f.l.bishop@southampton.ac.uk

Abstract

Background: According to established ethical principles and guidelines, patients in clinical trials should be fully informed about the interventions they might receive. However, information about placebo-controlled clinical trials typically focuses on the new intervention being tested and provides limited and at times misleading information about placebos.

Objective: We aimed to create an informative, scientifically accurate, and engaging website that could be used to improve understanding of placebo effects among patients who might be considering taking part in a placebo-controlled clinical trial.

Methods: Our approach drew on evidence-, theory-, and person-based intervention development. We used existing evidence and theory about placebo effects to develop content that was scientifically accurate. We used existing evidence and theory of health behavior to ensure our content would be communicated persuasively, to an audience who might currently be ignorant or misinformed about placebo effects. A qualitative 'think aloud' study was conducted in which 10 participants viewed prototypes of the website and spoke their thoughts out loud in the presence of a researcher.

Results: The website provides information about 10 key topics and uses text, evidence summaries, quizzes, audio clips of patients' stories, and a short film to convey key messages. Comments from participants in the think aloud study highlighted occasional misunderstandings and off-putting/confusing features. These were addressed by modifying elements of content, style, and navigation to improve participants' experiences of using the website.

Conclusions: We have developed an evidence-based website that incorporates theory-based techniques to inform members of the public about placebos and placebo effects. Qualitative research ensured our website was engaging and convincing for our target audience who might not perceive a need to learn about placebo effects. Before using the website in clinical trials, it is necessary to test its effects on key outcomes including patients' knowledge and capacity for making informed choices about placebos.

(JMIR Res Protoc 2016;5(2):e106) doi:10.2196/resprot.5627

KEYWORDS

placebo effect; informed consent; qualitative research; health attitudes; consumer health information

Introduction

Clinical trials must be conducted in accordance with Good Clinical Practice guidelines [1] and ethical principles espoused in the Declaration of Helsinki [2]. In particular, patients should be fully informed about the interventions they might receive and must give written informed consent. In a placebo-controlled randomized clinical trial this means that all participants should be fully informed about both the new intervention being tested and the placebo control. However, a content analysis of participant information leaflets from United Kingdom–based placebo-controlled trials found that written information about placebos is typically incomplete and at times misleading [3]. For example, despite strong evidence of placebo effects and mechanisms in the scientific literature, [4-7] only 1 of 45 leaflets explicitly stated that patients might experience beneficial effects from the placebo [3]. Using placebos in clinical trials appears to be generally acceptable to patients, but crucially this depends not only on the severity of the condition being treated and available alternative controls, but also the adequacy of informed consent [8]. Furthermore, evidence from surveys and qualitative studies shows that clinical trial participants often have false beliefs about, and partial understanding of, placebos and their possible effects [9-11]. Examples of such false beliefs include the belief that placebo effects are fake, or illusory, and that people who respond to placebos are gullible or foolish [11-13]. This might explain why the inclusion of placebo controls can deter people from volunteering to participate in trials [14]. Overall, it seems that a significant proportion of clinical trial participants might have inadequate understandings of the potential clinical effects of placebo interventions [9-13], thus jeopardizing the ethical validity of informed consent [3] and potentially hampering recruitment [14]. More accurate and complete information about placebos could usefully address this ethical shortcoming, could combat patient anxiety about placebo effects [12], and reduce distress at being debriefed in placebo condition participants [15,16].

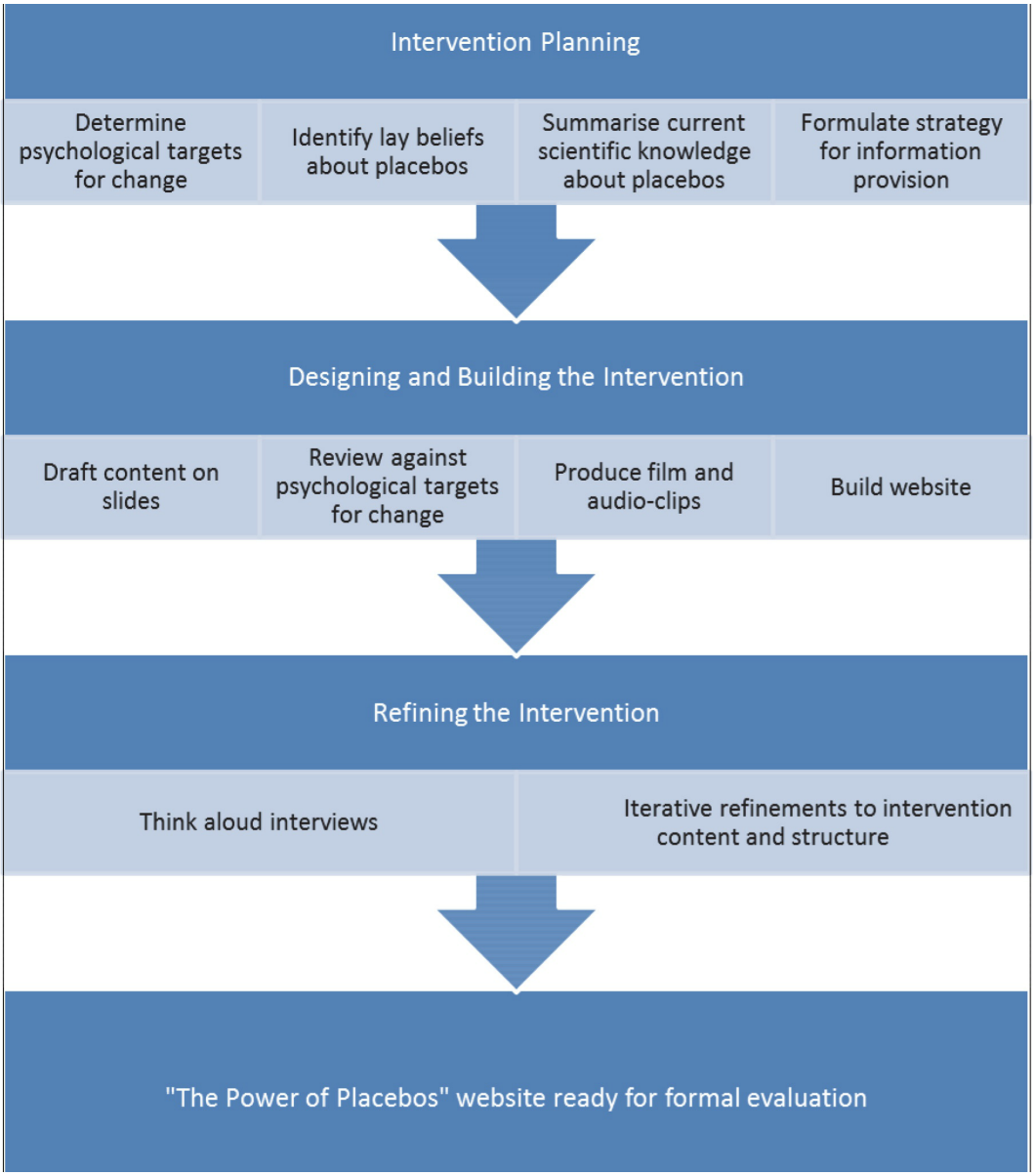
This paper describes the development of an educational website about placebo effects. We aimed to create an informative, scientifically accurate, and engaging website that could be used to improve understanding of placebo effects among patients who might be considering taking part in a placebo-controlled clinical trial. We chose to develop a website rather than a traditional printed information leaflet because websites (1) are increasingly popular sources of consumer health [17-20], suggesting that this format reflects consumer preferences, (2) easily incorporate interactive features [21], which can enhance engagement and effective education[22], (3) are easily and cheaply disseminated for widespread access [21] (86% of UK households had Internet access and 78% of adults accessed the Internet daily or almost daily in 2015 [23]), and (4) can be readily adapted and/or tailored to different subgroups [21]. Our intention was to develop a resource that could potentially be used across a large number of clinical trials and/or adapted for use in specific trials. However, because the effects and mechanisms of placebos differ across symptoms and diseases [24], we chose one clinical target to focus on for this version of the website. We chose placebo analgesia as pain is relevant to a large number of clinical conditions and placebo analgesia is a well-documented placebo effect [4,25-27]. The target audience for this website was thus adults experiencing pain symptoms (from any clinical condition).

Methods

An Evidence-, Theory-, and Person-Based Approach

We drew on existing evidence and theory, and conducted qualitative research to develop our website using an approach derived from evidence-based, theory-based [28,29], and incorporating elements of person-based [30] intervention development. In the context of a website about placebos, we felt this combined approach was more valuable than any single approach. It was important to use existing evidence and theory about placebo effects to ensure our content was scientifically accurate. Drawing on existing evidence and theory about health behavior was essential to ensure our content would be communicated persuasively to an audience who might currently be ignorant or misinformed about placebo effects. Conducting our own qualitative research was necessary to ensure our website was engaging and convincing for our target audience who might not have a perceived need to learn about placebo effects. Figure 1 provides an overview of the process of developing the website.

Figure 1. Overview of methods used to develop the website.



Planning the Intervention

To plan the content and structure of the website we considered four key questions:

What psychological targets are relevant to providing information about placebos? In other words, what would we expect to change as a result of viewing our website?

What do patients typically believe about placebos and placebo effects?

What is the current scientific understanding of placebos and placebo effects?

How should information about placebos and placebo effects be provided to be most effective?

Psychological Targets

Given current partial understandings, misunderstandings, and poor quality information about placebos [3,9-11], we decided our website should focus on promoting informed choices about placebos. Making an informed choice can be understood as choosing to act in a way that is based on one's knowledge and one's values [31-33]. According to this definition, it is incorrect to specify that a particular option is the correct choice for everyone: what counts as the informed choice will differ across equally knowledgeable individuals according to their values. To make an informed choice, a person needs to have an accurate understanding of the options available, have formed an opinion about the options based on their values, and make a decision (or otherwise act in a way) that is consistent with their knowledge and values. We chose to focus on informed choice, rather than informed consent, because the process of informed consent to take part in a placebo-controlled clinical trial would typically involve a face-to-face interaction between trial personnel and potential participants and would involve the provision of trial-specific information (eg, about the trial intervention). Our website is intended to provide a generic resource to educate and inform members of the public who may be considering receiving placebos as part of a clinical trial.

In the context of placebos, an informed choice to receive a placebo (eg, by taking part in a trial) requires knowledge about the possible effects of placebos, a positive attitude to taking placebos, and a decision to take placebos. An informed choice not to receive a placebo requires knowledge about the possible effects of placebos, a negative attitude to taking placebos, and a decision not to take placebos. To promote informed choice our website thus needed to improve people's knowledge of placebos. Therefore, knowledge about placebos and their effects was our primary target for change.

Making an informed choice to receive placebos can be understood as a volitional behavior, and thus can be modelled using the Theory of Planned Behavior [34]. According to the Theory of Planned Behavior, patients' intentions to take placebos are driven by attitudes, subjective norms, and perceived behavioral control. These, in turn, are determined by beliefs [34]. Thus, patients will be more likely to make an informed choice to receive placebos if they (1) believe that placebos are effective/good for them and value these effects (attitudes), (2) believe that people whose opinion they value would approve of placebos (subjective norms), and (3) believe that they control whether or not they receive placebos (perceived behavioral control). While we did not want to encourage people to decide to receive placebos (except in the context of an informed choice), we did want to provide information that was consistent with people's existing cognitive structures. Therefore, we designed the website to address the following: consequences of receiving placebos for the individual (attitudes), other people's views on placebos (subjective norms), and practicalities around receiving placebos (perceived behavioral control).

Typical Beliefs About Placebos

To understand typical beliefs about placebos we reviewed qualitative studies of patients' experiences of placebos in clinical trials. This literature showed that people are interested in but often anxious about or confused by placebos [35,36]. For example, in qualitative studies embedded in acupuncture trials patients described interest or anxiety as to whether they receive placebo or real treatment [37], and the knowledge that they may receive placebo made them doubt any perceived improvements in symptoms [12,13]. Patients conceptualize placebos and their effects in various ways, dominant among which are understandings of placebos: as fake treatments that fool people into thinking they are better; as tools that are necessary for scientific research; and as interventions that have real effects mediated by psychological mechanisms [11]. Patients' reactions to being told they had been in the placebo arm of one clinical trial included surprise and disbelief. Some worried that they would 'throw the trial off' and interpreted their experiences in a way that affirmed their understanding of their illness or emphasized the positive effect of social support from trial staff [15].

Based on these findings, we devised website content to describe the possible (positive and negative) effects and experiences of placebo ('can it help?', 'what is it like?'). The website also addresses common concerns about placebos ('what concerns me'), debunks myths that placebo responders are malingerers or gullible ('who does it help?'), and explains the mechanisms underpinning placebo effects ('how could it work?').

Scientific Understanding of Placebo Effects

To ensure scientific accuracy we consulted systematic and narrative reviews and seminal studies concerning the effects and mechanisms of action of placebos [4,6,7,24]. We selected key evidence-based facts about placebo effects to convey in the website including: placebos can relieve pain and stiffness in osteoarthritis [27]; placebos can improve reported pain across a number of painful conditions [25]; and placebos can elicit side effects in what is called a 'nocebo' effect [38] (ie, the negative aspect of the placebo effect that occurs when an adverse event, such as experiencing side effects, is triggered by negative expectations [39]). The website also conveyed that it is difficult to know how many people placebos will work for, but they seem to improve pain for between 26% and 51% of people in placebo studies [6].

The mechanisms of action of placebos have been described in neurobiological, psychological, and anthropological terms. Patients also appear to develop understandings of placebo effects at different levels, with some focusing on psychological processes and others emphasizing social processes [11,15]. To accurately represent the scientific literature and appeal to different patients, we therefore chose to convey a number of different theories of placebo effects, specifically neurobiological pathways [40], expectancy [41], conditioning [42], meaning response [43], and the therapeutic relationship [44].

We also drew on scientific literature when developing material on other aspects of placebos outlined in the previous section. For example, in addressing concerns that doctors have to lie to patients to give them placebos, we drew on evidence about open-label placebo prescribing, suggesting that doctors do not have to lie to patients to elicit placebo effects [5].

Effective Information Provision

To plan how to provide information effectively to educate people about placebos and thus improve their knowledge, we considered a selection of relevant theories. In particular, we drew on theories of motivation, learning, and attitude formation.

We drew on Self-Determination Theory [45] to plan how to design our website so that it would be maximally engaging for people. Self-Determination Theory distinguishes between intrinsic motivation (eg, curiosity) and extrinsic motivation (eg, payment) as drivers for action; our website relies on intrinsic motivation as we do not anticipate eventual users to receive external rewards for using it. Cognitive Evaluation Theory (1 of 6 'mini-theories' within Self-Determination Theory) elaborates on how social contexts can impact on intrinsic motivation, and suggests that intrinsic motivation can be enhanced by satisfying basic human needs of competence and autonomy [45]. Thus, if the website supports people's perceptions of themselves as competent and autonomous it should enhance intrinsic motivation and be more engaging. To promote perceptions of competence, we designed easy quizzes (using the word 'surprise' rather than 'wrong' to give feedback on incorrect answers) and used simple and consistent navigation. To promote perceptions of autonomy, we allowed users as much

freedom of choice as possible, for example in terms of the order in which to view different pages.

Educational theory suggests that people have different learning styles [46]; therefore, we decided to provide information in different formats: written text, photographs and images, audio clips, and film. We used quizzes to engage readers in active learning [47] and to test readers' knowledge (tests are an effective means of improving learning [48]). We also considered to whom to attribute different sources of information. According to Social Learning Theory, when we identify with another person (a 'model') and perceive them to be competent and similar to us, we may learn from observing them [49-51]. Therefore, we decided to use actors to narrate first-person accounts of patients' experiences of taking placebos, and to choose actors of various ages, genders, and ethnicities. We drew on qualitative studies of real patients' experiences in clinical trials to develop the first-person accounts [11-13,15].

While our focus was on educating people by providing accurate information about placebos, attitude formation and change processes might also occur in response to information provision. According to leading theories of attitude change, there are both central and peripheral routes to attitude formation and change [52]. Central routes are well-described by the Elaboration Likelihood Model and entail highly-motivated individuals engaging in an effortful way with substantive messages, assessing new information in relation to previously held beliefs, and coming to a reasoned conclusion [53]. Peripheral routes, as described by the Heuristic Systematic Model of persuasion, entail the use of simple heuristics or 'rules of thumb' based on superficial cues such as source credibility and number of arguments presented [54,55]. To encourage the development of more informed attitudes toward placebo effects, we described scientific evidence to support our substantive message that placebos can have effects, presented multiple scientific theories about how placebos produce effects, and bolstered the credibility of the message source by describing the website and study authors' academic credentials.

We followed guidance for developing patient-focused health information by considering five key issues: information needs, accessibility, quality, readability and comprehensibility, and usefulness [56]. To ensure we addressed different needs for information, we allowed readers a choice about whether to access basic or more complex information. In other words, we used simple text to convey basic information about a topic (based on the literature), then offered a click-through to a more detailed evidence summary describing a specific study or review, and then offered another click-through to access the actual scientific paper. To provide access to scientific evidence we wrote accurate text, evidence summaries, and in some cases, provided full papers. We considered color blindness and dyslexia in our choice of colors and formatting; for example, using clear, plain text and consistent formatting throughout. We also ordered the items on the pages to make them more accessible for people using text-reader software. To ensure we provided high-quality information we used peer-reviewed publications and reviews. To enhance readability we wrote in short sentences with simple sentence construction and used readability indices to guide our writing. To enhance usefulness, we provided information on relevant topics (according to the literature on patients' views of placebos), included patient representatives in the research team, and conducted a think aloud study to elicit users' feedback.

Designing and Building the Intervention

We used the insights gained during the planning phase to write the content and map out the initial structure of our website using PowerPoint slides. Content was based on published evidence, as described above. To ensure content was relevant to our primary targets for change (knowledge, informed choice) and mapped onto existing cognitive structures (attitudes, subjective norms, perceived behavioral control), we reviewed each draft page for relevance to these targets and structures. We then built the website using LifeGuide open source software to facilitate the design and scientific testing of Web-based behavior change interventions [57].

Audio clips were produced for first-person narratives about the phenomenology of placebo effects. A film was scripted and produced to illustrate a placebo effect in an experimental context (using a cold pressor task) and to describe the effects and mechanisms of action of placebos. As a visual medium that lends itself well to linear narrative, film provides an unrivalled, vivid view of the world and may capture events, people, and performances with detail and richness. Koumi [58] suggested a number of considerations for writing instructional film scripts including: the 'hook' (an element which captures viewers' attention), asking questions, synergy between image and narration, clarity of argument, audio/visual cues to denote changes, and argument consolidation. The film we produced integrated these steps through the use of animated infographic, live action, interview, and narration to reinforce key messages. While there is no hard-and-fast rule as to how many messages a video can contain, studies show that people can store approximately four discrete 'chunks' of information in short-term memory [59], and some writers advise that a 30-minute video can comfortably elucidate three essential points in some detail. As the placebo video has a running time of 4 minutes 20 seconds, the script was written to focus on two key points: that placebos have significant, measurable, positive effects on health, and that these effects are present in conventional treatments.

Korakidou and Charitos [60] asserted that film involves viewers on an emotional as well perceptual level, employing empathy to facilitate engagement and retention. In addition, in productions that include the spoken word it is believed that viewers prefer and empathize more readily with conversational language that is easily understood [61]. To facilitate this, the video used live action sequences to encourage viewers to imagine themselves in similar situations, and simple, jargon free narration to ease comprehension and reduce cognitive load.

Think Aloud Study

A small qualitative study during this phase informed the final content and structure of the website. Ethical approval was obtained from the host institution (reference: ergo id 10933) and all participants gave written informed consent. Posters and Web-based advertisements were used to recruit 10 participants

from the host institution (9 female, a mix of staff and students, aged 19-35 years, 4 with musculoskeletal pain). They worked through the website in the presence of the researcher, speaking aloud their thoughts and answering specific, probing questions (eg, "what do you think this page is about?", "What did you think about navigating through the site?"). The mean interview duration was 32 minutes (range, 22-40) and interviews were audio-recorded. Interviewees' comments were reviewed and coded according to the topic to which they referred using deductively derived codes based on aspects of the website (eg, "placebos in clinical practice", "patients' stories") and inductively derived codes for comments that did not relate directly to specific contents (eg, "technical terms"). Comments were further categorized as primarily related to content, style, or navigation. Two researchers were involved in interpreting interviewees' comments, which avoided an idiosyncratic focus on particular issues and enabled discussion of which comments to prioritize when deciding on modifications to the website (eg, in cases where interviewees provided divergent and/or conflicting perspectives). Interviews proceeded iteratively, with early interviews being analyzed first and used to inform changes to the website that were then presented in later interviews.

Results

Comments from participants in the think aloud study highlighted aspects of the website that participants felt were engaging as well as occasional misunderstandings and stylistic and structural features that were off-putting and/or confusing, and thus needed improving. Elements of content, style, and navigation were therefore modified to improve participants' experiences of using the website. Table 1 presents selected quotes from participants, illustrating how their perspectives were used to inform website modifications. Content changes included: elaborating on 'mind-body healing processes' as participants found this vague and wanted more information about how placebo effects might work; adding reassurance that pain is still real even if it reduces with placebo; adding specific details and evidence from scientific papers about how many doctors use placebos; and adding an example to address participants' concerns about how doctors can justify using placebos clinically: "For example, sometimes doctors may listen to a patient's chest, even when it is not essential for making a medical diagnosis, because it can be reassuring for the patient." Stylistic changes included: choosing photos (for patient's stories) that look more realistic as participants felt some looked like stock photos, and thus lacked authenticity; ensuring alignment and consistent logo placement throughout as participants noticed minor misalignments and saw them as unprofessional, reducing the credibility of the website; and modifying patients' stories to always use convincing lay language, and thus avoid the off-putting impression of advertising. Navigation changes included: adding a menu bar to all pages to make each page accessible from any other page, and page buttons changing color once viewed.

Table 1. Illustrative Quotes from Participants Used to Refine the Website

Topic	Quote	Modification
Content: information on placebo effects	So it's basically asking a question that yes it can help with your pain. And obviously there's been quite a big study that shows that it can definitely relieve pain and stiffness. There's obviously useful information. (Participant 2)	None needed
Content: patients' stories	I think it's good to have a case study. I didn't realize you could do placebo surgeries so that's quite interesting. (…) It's nice to have a picture of the person as well. It's good to have the option to read what he says as well, so if you don't want to read it, you can listen to it. (Participant 3)	None needed
Content: technical terms	Maybe explain what 'mind-body self-healing processes' are. Um otherwise I think like I understand what it says, yeah. (Participant 1)	Expand on 'mind-body self-healing'
Content: placebos in clinical practice	What is going through my mind maybe a little bit is maybe kind of if I was to receive the placebo and not actually know. So maybe something that addresses that, how common it is to be given a placebo in the health care sector. (Participant 8)	Add specific details about how many doctors use placebos
Style: patients' stories	Are these the pictures of the actual people who are talking or are they stock pictures? (Participant 6)	Change photos
Navigation: menu	Like usual websites have everything on the same page, so it'd have a menu at the side that you always see. So is a bit confusing because I'm going back, but I cannot remember what I've clicked on necessarily. It's all like a flow, you have to go through it, and back again. I think it might be more useful to have a menu at the edge or something. (Participant 5)	Add a side menu bar that is always available

The final structure and main content of the website is shown in Figure 2. Nine topics are covered across 10 main pages (the last page offering a summary of key facts), which can be accessed in any order. Text and images are supplemented by scientific evidence summaries (on 4 pages), audio clips with photos and transcripts of patients' experiences (on 4 pages), a film, and 2 quizzes (with immediate feedback). Figure 3 shows one page ("Can a placebo help with my pain"), annotated with key features that illustrate the contribution of evidence-, theory-, and person-based approaches.

Figure 2. Overview of structure and contents of website.

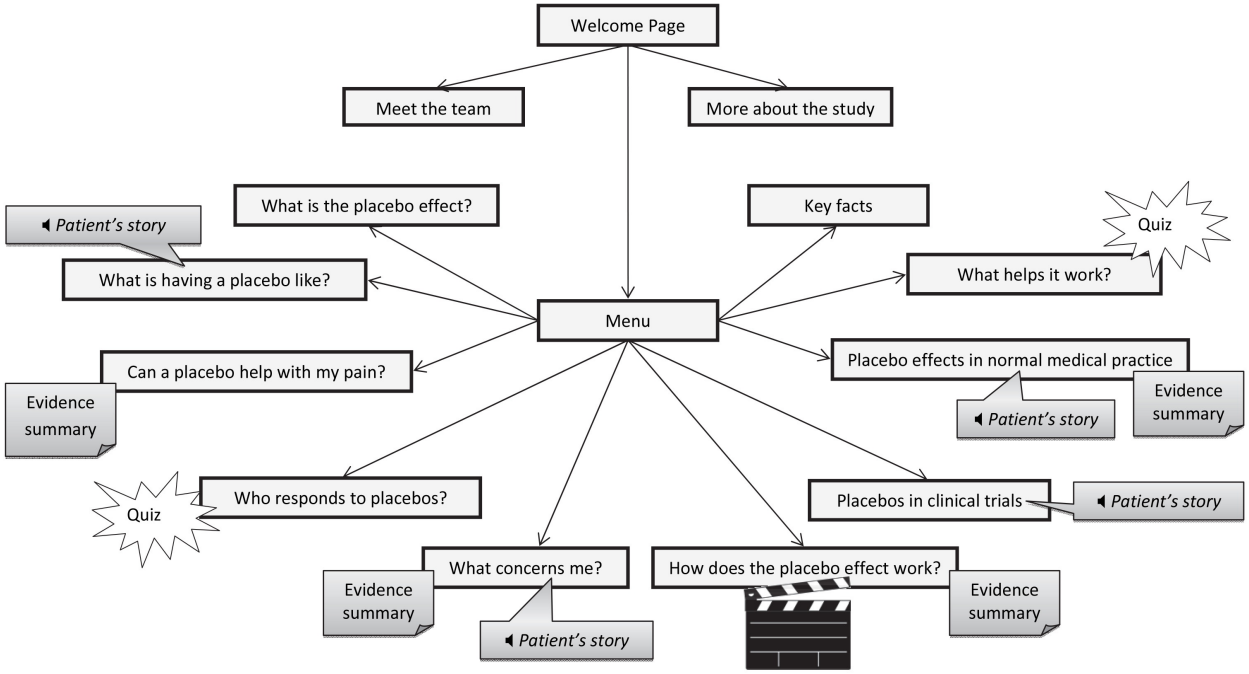
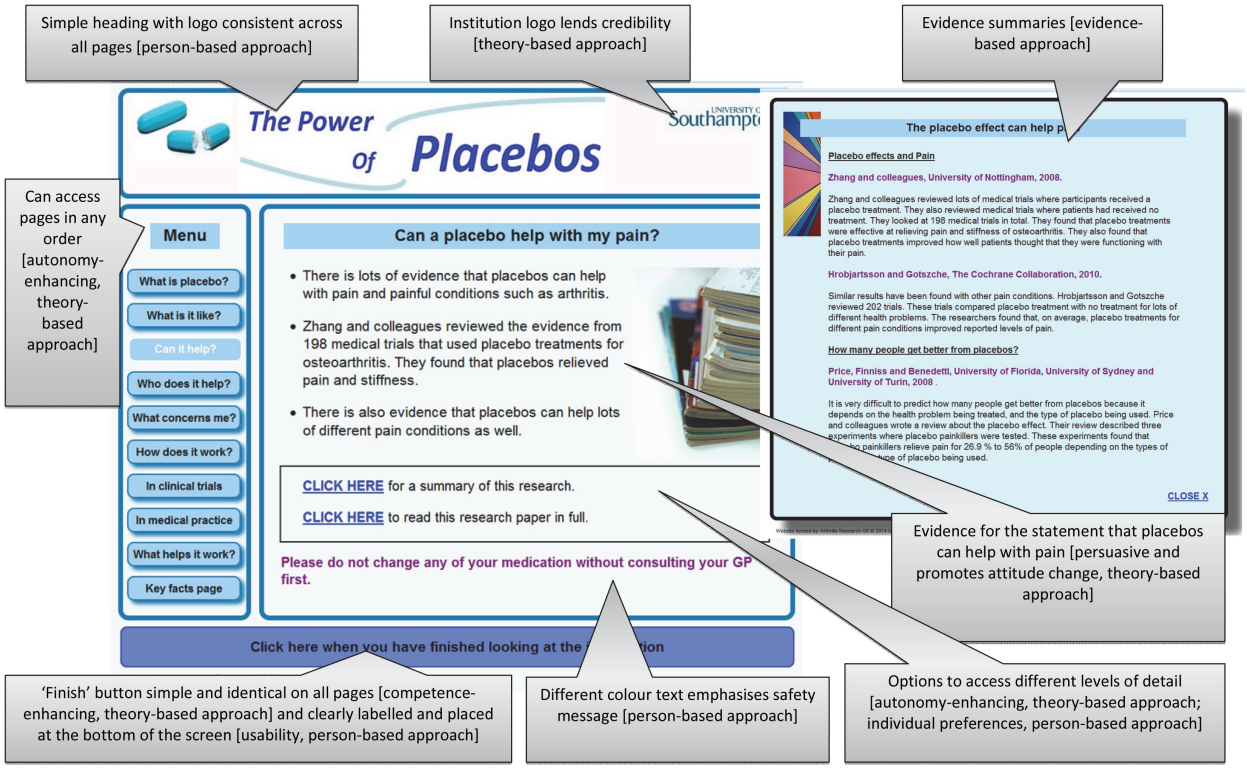


Figure 3. Example page annotated to highlight key features and their development from evidence-, theory-, and person-based approaches.



Discussion

Summary

We have developed a new website about placebos that conveys scientifically accurate information in a way that should engage members of the public and enable them to make informed choices about placebos. The development process drew on evidence about placebo effects, theory about education, attitudes and motivation, and qualitative research to maximize the website's likely effects.

Strengths and Limitations

Strengths of this project include the multidisciplinary team and the combination of evidence-, theory-, and person-based approaches [28-30]. Team members shared expertise in topics, including placebo effects, digital interventions, film, and chronic pain, and contributed diverse professional perspectives (eg,

psychology, general practice, physiotherapy, acupuncture). Two team members were patient representatives whose input helped ensure our website addressed important issues in an accessible and nonpatronizing manner. By drawing on a combination of approaches we were able to incorporate evidence, theory, and users' perspectives in a flexible manner throughout the intervention development process.

The main limitation of the study was the homogeneous sample of participants. Involving a more diverse sample of patients in our think aloud study would have allowed us to better gauge the comprehensibility of the website among members of our target audience, adults with experience of pain symptoms. The same issues were raised repeatedly across the 10 interviews, suggesting additional interviews would have produced diminishing returns for additional cost. However, additional interviews with people with other characteristics (eg, more severe chronic pain conditions) might have elicited novel comments. While participants' views on the format and structure of the website were vital for improving its usability, these issues may have been particularly pertinent for our sample because, from their comments, they appeared to be experienced Internet users with a good baseline understanding of placebo effects. A more diverse sample might have uncovered additional issues and/or misunderstandings about placebos and placebo effects. Future think aloud studies for website development would benefit from sampling diverse participants from the population of likely end-users and finding ways to encourage them to focus on the substance of the website as well as its style and structure. The full person-based approach includes guidance on how to achieve this to ensure qualitative research goes beyond user-testing to focus on participants' perspectives on substantive issues [30].

Applications

Using our website to inform potential clinical trial participants about placebos could have both beneficial and detrimental consequences. For example, it might improve the validity of informed consent [3], alleviate anxiety about placebos, ease the process of unblinding to placebo allocation at the end of trials [15,16], reduce adverse effects [62], and/or enhance recruitment [14]. However, increasing patients' expectations of benefit during trials by encouraging positive beliefs about placebos might increase the size of the placebo effect [63,64]. This could introduce bias [65] particularly if placebo and intervention effects are not additive [66] and/or could reduce estimated treatment effects [11]. It is therefore vital to test the effects of providing comprehensive information about placebos before changing research practice. To contribute to this much-needed evidence base, we will report separately a randomized experiment testing the effects of our new website on knowledge and informed choice about placebos.

Conclusions

In conclusion, we have developed an evidence-based website that incorporates theory-based techniques to inform members of the public about placebos and placebo effects. Before using the website in clinical trials it is necessary to test its effects on key outcomes, including patients' knowledge and capacity for making informed choices about placebos.

Acknowledgments

This project was funded by a grant from Arthritis Research UK (grant reference 20113). The funder had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

The authors would like to thank the participants who took part in the think aloud study, Christine Bagg (patient representative) who contributed to study design and helped review the website, the student volunteers who helped to test the website, and Dr Jin Zhang and the core LifeGuide team who provided technical support for programming the webpage.

Conflicts of Interest

None declared.

References

1. Medicines and Healthcare Products Regulatory Agency (MHRA). Good Clinical Practice Guide. Norwich: The Stationery Office; 2012.
2. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310:2191-2194. [doi: 10.1001/jama.2013.281053] [Medline: 24141714]
3. Bishop FL, Adams AEM, Kaptchuk TJ, Lewith GT. Informed consent and placebo effects: a content analysis of information leaflets to identify what clinical trial participants are told about placebos. PLoS One 2012;7:e39661 [FREE Full text] [doi: 10.1371/journal.pone.0039661] [Medline: 22761859]
4. Finniss DG, Kaptchuk TJ, Miller F, Benedetti F. Biological, clinical, and ethical advances of placebo effects. Lancet 2010;375:686-695 [FREE Full text] [doi: 10.1016/S0140-6736(09)61706-2] [Medline: 20171404]
5. Kaptchuk TJ, Friedlander E, Kelley JM, Sanchez MN, Kokkotou E, Singer JP, et al. Placebos without deception: a randomized controlled trial in irritable bowel syndrome. PLoS One 2010;5:e15591 [FREE Full text] [doi: 10.1371/journal.pone.0015591] [Medline: 21203519]
6. Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: recent advances and current thought. Annu Rev Psychol 2008;59:565-590. [doi: 10.1146/annurev.psych.59.113006.095941] [Medline: 17550344]

7. Benedetti F, Amanzio M. The placebo response: how words and rituals change the patient's brain. Patient Educ Couns 2011;84:413-419. [doi: 10.1016/j.pec.2011.04.034] [Medline: 21621366]
8. Huston P. What does the public think of placebo use? The Canadian experience. Sci Eng Ethics 2004;10:103-117. [Medline: 14986777]
9. Pope JE, Tingey DP, Arnold JMO, Hong P, Ouimet JM, Krizova A. Are subjects satisfied with the informed consent process? A survey of research participants. J Rheumatol 2003;30:815-824. [Medline: 12672205]
10. Criscione LG, Sugarman J, Sanders L, Pisetsky DS, St Clair EW. Informed consent in a clinical trial of a novel treatment for rheumatoid arthritis. Arthritis Rheum 2003;49:361-367 [FREE Full text] [doi: 10.1002/art.11057] [Medline: 12794792]
11. Bishop FL, Jacobson EE, Shaw JR, Kaptchuk TJ. Scientific tools, fake treatments, or triggers for psychological healing: how clinical trial participants conceptualise placebos. Soc Sci Med 2012;74:767-774 [FREE Full text] [doi: 10.1016/j.socscimed.2011.11.020] [Medline: 22285289]
12. Kaptchuk TJ, Shaw J, Kerr CE, Conboy LA, Kelley JM, Csordas TJ, et al. "Maybe I made up the whole thing": placebos and patients' experiences in a randomized controlled trial. Cult Med Psychiatry 2009;33:382-411 [FREE Full text] [doi: 10.1007/s11013-009-9141-7] [Medline: 19597976]
13. White P, Bishop FL, Prescott P, Scott C, Little P, Lewith G. Practice, practitioner, or placebo? A multifactorial, mixed-methods randomized controlled trial of acupuncture. Pain 2012;153:455-462. [doi: 10.1016/j.pain.2011.11.007] [Medline: 22169359]
14. Welton AJ, Vickers MR, Cooper JA, Meade TW, Marteau TM. Is recruitment more difficult with a placebo arm in randomised controlled trials? A quasirandomised, interview based study. BMJ 1999;318:1114-1117 [FREE Full text] [Medline: 10213724]
15. Bishop FL, Jacobson EE, Shaw J, Kaptchuk TJ. Participants' experiences of being debriefed to placebo allocation in a clinical trial. Qual Health Res 2012;22:1138-1149 [FREE Full text] [doi: 10.1177/1049732312448544] [Medline: 22673094]
16. Di BZ, Crawford F, Bradley C, Kleijnen J. Reactions to treatment debriefing among the participants of a placebo controlled trial. BMC Health Serv Res 2005;5:30 [FREE Full text] [doi: 10.1186/1472-6963-5-30] [Medline: 15847683]
17. Moreland J, French TL, Cumming GP. The prevalence of online health information seeking among patients in Scotland: a cross-sectional exploratory study. JMIR Res Protoc 2015;4:e85 [FREE Full text] [doi: 10.2196/resprot.4010] [Medline: 26177562]
18. Powell J, Inglis N, Ronnie J, Large S. The characteristics and motivations of online health information seekers: cross-sectional survey and qualitative interview study. J Med Internet Res 2011;13:e20 [FREE Full text] [doi: 10.2196/jmir.1600] [Medline: 21345783]
19. Santana S, Lausen B, Bujnowska-Fedak M, Chronaki CE, Prokosch H, Wynn R. Informed citizen and empowered citizen in health: results from an European survey. BMC Fam Pract 2011;12:20 [FREE Full text] [doi: 10.1186/1471-2296-12-20] [Medline: 21496309]
20. Atkinson NL, Saperstein SL, Pleis J. Using the internet for health-related activities: findings from a national probability sample. J Med Internet Res 2009;11:e4 [FREE Full text] [doi: 10.2196/jmir.1035] [Medline: 19275980]
21. Cline RJ, Haynes KM. Consumer health information seeking on the Internet: the state of the art. Health Educ Res 2001;16:671-692 [FREE Full text] [Medline: 11780707]
22. Cook DA, Dupras DM. A practical guide to developing effective web-based learning. J Gen Intern Med 2004;19:698-707 [FREE Full text] [doi: 10.1111/j.1525-1497.2004.30029.x] [Medline: 15209610]
23. Office for National Statistics. Statistical Bulletin: Internet Access - Households and Individuals. 2015. URL: http://www.ons.gov.uk/peoplepopulationandcommunity/householdcharacteristics/homeinternetandsocialmediausage/bulletins/internetaccesshouseholdsandindividuals/2015-08-06 [accessed 2015-03-15] [WebCite Cache ID 6g1la5vII]
24. Benedetti F. Mechanisms of placebo and placebo-related effects across diseases and treatments. Annu Rev Pharmacol Toxicol 2008;48:33-60. [doi: 10.1146/annurev.pharmtox.48.113006.094711] [Medline: 17666008]
25. Hróbjartsson A, Gøtzsche PC. Placebo interventions for all clinical conditions. Cochrane Database Syst Rev 2010;1:CD003974. [doi: 10.1002/14651858.CD003974.pub3] [Medline: 20091554]
26. Mistiaen P, van OM, van VL, Howick J, Bishop FL, Di BZ, et al. The effect of patient-practitioner communication on pain: a systematic review. Eur J Pain 2015;20:675-688. [doi: 10.1002/ejp.797] [Medline: 26492629]
27. Zhang W, Robertson J, Jones AC, Dieppe PA, Doherty M. The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials. Ann Rheum Dis 2008;67:1716-1723. [doi: 10.1136/ard.2008.092015] [Medline: 18541604]
28. Michie S, Abraham C. Interventions to change health behaviours: evidence-based or evidence-inspired? Psychol Health 2004;19:29-49. [doi: 10.1080/0887044031000141199]
29. Michie S, Johnston M. Theories and techniques of behaviour change: developing a cumulative science of behaviour change. Health Psychology Review 2012;6:1-6. [doi: 10.1080/17437199.2012.654964]
30. Yardley L, Morrison L, Bradbury K, Muller I. The person-based approach to intervention development: application to digital health-related behavior change interventions. J Med Internet Res 2015;17:e30. [doi: 10.2196/jmir.4055] [Medline: 25639757]
31. Marteau TM, Dormandy E, Michie S. A measure of informed choice. Health Expect 2001;4:99-108. [Medline: 11359540]

32. Dormandy E, Hooper R, Michie S, Marteau TM. Informed choice to undergo prenatal screening: a comparison of two hospitals conducting testing either as part of a routine visit or requiring a separate visit. J Med Screen 2002;9:109-114. [doi: 10.1136/jms.9.3.109]
33. Michie S, Dormandy E, Marteau TM. The multi-dimensional measure of informed choice: a validation study. Patient Educ Couns 2002;48:87-91. [Medline: 12220754]
34. Ajzen I. The theory of planned behavior. Organ Behav Hum Decis Process 1991 Dec;50:179-211. [doi: 10.1016/0749-5978(91)90020-T]
35. Ellis PM, Butow PN. Focus group interviews examining attitudes to randomised trials among breast cancer patients and the general community. Aust N Z J Public Health 1998;22:528-531. [Medline: 9744203]
36. Asai A, Ohnishi M, Nishigaki E, Sekimoto M, Fukuhara S, Fukui T. Focus group interviews examining attitudes towards medical research among the Japanese: a qualitative study. Bioethics 2004;18:448-470. [doi: 10.1111/j.1467-8519.2004.00409.x]
37. Barlow F, Scott C, Coghlan B, Lee P, White P, Lewith GT, et al. How the psychosocial context of clinical trials differs from usual care: a qualitative study of acupuncture patients. BMC Med Res Methodol 2011;11:79 [FREE Full text] [doi: 10.1186/1471-2288-11-79] [Medline: 21612644]
38. Amanzio M, Corazzini LL, Vase L, Benedetti F. A systematic review of adverse events in placebo groups of anti-migraine clinical trials. Pain 2009;146:261-269. [doi: 10.1016/j.pain.2009.07.010] [Medline: 19781854]
39. Colloca L, Finniss D. Nocebo effects, patient-clinician communication, and therapeutic outcomes. JAMA 2012;307:567-568. [doi: 10.1001/jama.2012.115] [Medline: 22318275]
40. Benedetti F, Mayberg HS, Wager TD, Stohler CS, Zubieta J. Neurobiological mechanisms of the placebo effect. J Neurosci 2005;25:10390-10402 [FREE Full text] [doi: 10.1523/JNEUROSCI.3458-05.2005] [Medline: 16280578]
41. Kirsch I. Response expectancy theory and application: a decennial review. Appl Prev Psychol 1997;6:69-79. [doi: 10.1016/S0962-1849(05)80012-5]
42. Colloca L, Tinazzi M, Recchia S, Le Pera D, Fiaschi A, Benedetti F, et al. Learning potentiates neurophysiological and behavioral placebo analgesic responses. Pain 2008;139:306-314. [doi: 10.1016/j.pain.2008.04.021] [Medline: 18538928]
43. Moerman DE, Jonas WB. Deconstructing the placebo effect and finding the meaning response. Ann Intern Med 2002;136:471-476. [Medline: 11900500]
44. Kaptchuk TJ, Kelley JM, Conboy LA, Davis RB, Kerr CE, Jacobson EE, et al. Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. BMJ 2008;336:999-1003 [FREE Full text] [doi: 10.1136/bmj.39524.439618.25] [Medline: 18390493]
45. Ryan RM, Deci EL. An overview of self-determination theory. In: Deci EL, Ryan RM, editors. The Handbook of Self-Determination Research. Rochester, NY: University of Rochester Press; 2002:3-33.
46. Biggs J, Tang C. Teaching for Quality Learning at University (Society for Research Into Higher Education). Maidenhead: Open University Press; 2011.
47. Prince M. Does active learning work? A review of the research. J Eng Educ 2004;93:223-231. [doi: 10.1002/j.2168-9830.2004.tb00809.x]
48. Roediger HL, Karpicke JD. Test-enhanced learning: taking memory tests improves long-term retention. Psychol Sci 2006;17:249-255. [doi: 10.1111/j.1467-9280.2006.01693.x] [Medline: 16507066]
49. Bandura A. Social Foundations of Thought and Action: A Social Cognitive Theory. Englewood Cliffs: Prentice-Hall; 1986.
50. Schunk DH. Vicarious influences on self-efficacy for cognitive skill learning. J Soc Clin Psychol 1986;4:316-327. [doi: 10.1521/jscp.1986.4.3.316]
51. Schunk DH. Peer models and children's behavioral change. Rev Educ Res 1987;57:149-174. [doi: 10.3102/00346543057002149]
52. Gilbert DT, Fiske ST, Lindzey G. Attitude change: multiple roles for persuasion variables. In: The Handbook of Social Psychology. Boston: McGraw-Hill; 1998:323-390.
53. Petty R, Cacioppo J. Communication and persuasion: central and peripheral routes to attitude change. New York: Springer-Verlag; 1986.
54. Chaiken S. Heuristic versus systematic information processing and the use of source versus message cues in persuasion. J Pers Soc Psychol 1980;39:752-766. [doi: 10.1037/0022-3514.39.5.752]
55. Chaiken S. The heuristic model of persuasion. In: Zanna MP, Olson JM, Herman CP, editors. Social influence: The Ontario Symposium. Hillsdale, NJ: Erlbaum; 1987:3-39.
56. Coulter A, Ellins J. Patient-Focused Interventions: A Review of the Evidence. London: The Health Foundation; 2006.
57. Williams S, Yardley L, Wills GB. A qualitative case study of LifeGuide: users' experiences of software for developing Internet-based behaviour change interventions. Health Informatics J 2013;19:61-75. [doi: 10.1177/1460458212458915] [Medline: 23486826]
58. Kuomi J. Guidelines for Pedagogic Video Production. 2010. URL: http://jackkoumi.co.uk/gfp-video-production.pdf [accessed 2016-02-09] [WebCite Cache ID 6fAVph3A6]
59. Cowan N. The magical number 4 in short-term memory: a reconsideration of mental storage capacity. Behav Brain Sci 2001;24:87-114; discussion 114. [Medline: 11515286]

60. Korakidou V, Charitos D. Creating and perceiving abstract animation. 2006 Presented at: The 8th Conference on on "Consciousness Reframed: Art & Consciousness in the Post-Biological Era"; 21-23 July 2006; Planetary Collegium, University of Plymouth.
61. Allen J. The BBC News Styleguide. London: BBC; 2003. URL: http://www2.media.uoa.gr/lectures/linguistic_archives/academic_papers0506/notes/stylesheets_3.pdf [accessed 2016-02-09] [WebCite Cache ID 6fAWrKwZn]
62. Loftus EF, Fries JF. The potential perils of informed consent. Mcgill J Med 2008;11:217-218 [FREE Full text] [Medline: 19148326]
63. Diener HC, Dowson AJ, Ferrari M, Nappi G, Tfelt-Hansen P. Unbalanced randomization influences placebo response: scientific versus ethical issues around the use of placebo in migraine trials. Cephalalgia 1999;19:699-700. [Medline: 10570722]
64. Kirsch I, Weixel LJ. Double-blind versus deceptive administration of a placebo. Behav Neurosci 1988;102:319-323. [Medline: 3365327]
65. Kaptchuk TJ. The double-blind, randomized, placebo-controlled trial: gold standard or golden calf? J Clin Epidemiol 2001;54:541-549. [Medline: 11377113]
66. Paterson C, Dieppe P. Characteristic and incidental (placebo) effects in complex interventions such as acupuncture. BMJ 2005;330:1202-1205 [FREE Full text] [doi: 10.1136/bmj.330.7501.1202] [Medline: 15905259]

Edited by G Eysenbach; submitted 09.02.16; peer-reviewed by J Hughes, Q Wang; comments to author 10.03.16; revised version received 23.03.16; accepted 30.03.16; published 10.06.16.

Please cite as:
Greville-Harris M, Bostock J, Din A, Graham CA, Lewith G, Liossi C, O'Riordan T, White P, Yardley L, Bishop FL
Informing Patients About Placebo Effects: Using Evidence, Theory, and Qualitative Methods to Develop a New Website
JMIR Res Protoc 2016;5(2):e106
URL: http://www.researchprotocols.org/2016/2/e106/
doi:10.2196/resprot.5627
PMID:27288271

Original Paper

Evaluating a Web-Based Self-Management Intervention in Heart Failure Patients: A Pilot Study

Nazli Bashi[1], RN, MAppSc (Research); Carol Windsor[1], RN, PhD; Clint Douglas[1], RN, PhD

School of Nursing, Faculty of Health, Queensland University of Technology, Brisbane, Australia

Corresponding Author:
Nazli Bashi, RN, MAppSc (Research)
School of Nursing
Faculty of Health
Queensland University of Technology
Victoria Park Road, Kelvin Grove
Brisbane, 4059
Australia
Phone: 61 7 3253 3611
Fax: 61 7 3253 3611
Email: nazli.bashi@csiro.au

Abstract

Background: Web-based interventions may have the potential to support self-care in patients with chronic disease, yet little is known about the feasibility of Web-based interventions in patients with heart failure (HF).

Objective: The objective of our study was to develop and pilot a Web-based self-care intervention for patients with HF.

Methods: Following development and pretesting, we pilot tested a Web-based self-care intervention using a randomized controlled design. A total of 28 participants completed validated measures of HF knowledge, self-care, and self-efficacy at baseline and 1-month follow-up.

Results: Change scores and effect size estimates showed that the mean differences in HF knowledge (d=0.06), self-care (d=0.32), and self-efficacy (d=0.37) were small. Despite email reminders, 7 of 14 participants (50%) of the sample accessed the site daily and 4 of 14 (28%) had no record of access.

Conclusions: Larger randomized controlled trials are needed that attend to all sources of self-efficacy and include more comprehensive educational tools to improve patient outcomes.

(JMIR Res Protoc 2016;5(2):e116) doi:10.2196/resprot.5093

KEYWORDS

heart failure; knowledge; patient education; self-care; self-efficacy; self-management; web-based intervention

Introduction

Despite improvements in treatment and prevention, chronic heart failure (HF) remains a serious health burden and carries a poor prognosis [1]. Given the complex and progressive nature of HF, interventions are needed that slow disease progression and prevent hospital admissions [2]. One strategy to improve health outcomes in patients with HF is to enhance self-care behavior related to physical activity, nutrition, fluid management, and treatment adherence [3]. Self-care is defined as "a process of maintaining physiological stability by monitoring symptoms, adhering to the treatment regimen (self-care maintenance), and promptly identifying and responding to symptoms (self-care management)" [4]. Self-care education is a critical strategy in empowering HF patients to be informed and actively engaged in monitoring their condition and adjusting treatment accordingly [5].

Although findings are mixed, previous research suggests that Web-based interventions may have the potential to improve clinical outcomes and reduce hospitalizations in patients with chronic diseases including HF [6,7]. Using a Web-based app as a cost-effective intervention might facilitate access to education and improve self-care skills [8]. Yet there are very few clearly conceptualized studies that have evaluated Web-based interventions for HF patients. Two descriptive studies reported high levels of patient satisfaction with educational websites providing information [9] and a daily communication method between HF patients and health care

providers [10]. Findings indicated that older HF patients with limited computer skills were willing to engage with Web-based education if provided adequate resources and instruction [9].

Only two controlled studies could be identified that examined the effectiveness of a Web-based HF self-care program. Westlake et al [11] tested a Web-based HF and symptom management education progam specifically designed for older HF patients (≥60 years). In addition to educational modules, patients were encouraged to use the website at home to email a clinical nurse specialist for support, link to video-based Web content, and monitor personal clinical data. A total of 40 patients attending an outpatient HF clinic were recruited to the 12-week Web-based intervention and were compared with 40 age- and sex-matched historical controls who received HF care as usual. Groups were similar at baseline, and results showed a modest benefit for perceived control over health status and mental health quality of life, but not for physical health quality of life.

Another study [12] also tested a Web-based HF self-care program. In addition to usual care, 16 HF patients randomly assigned to the treatment group received a computer with Internet access, as well as basic computer training. The website provided self-care information and videos, access to record and monitor vital signs, health behavior, and HF symptoms daily, and emails from health professionals for feedback on progress and emotional support as needed. It was found that at both 6- and 12-month follow-ups, only the treatment group showed significantly improved HF knowledge, amount of exercise, and quality of life, as well as reduced HF symptoms, blood pressure, and health care utilization [12].

The preliminary findings of the HF studies above, combined with systematic reviews [13,14], suggest that Web-based educational interventions may have a role in supporting HF patients in the community. In this study, we pilot tested a Web-based self-care intervention that provided education and self-monitoring tools for ambulatory HF patients. Our primary aim was to evaluate the feasibility of a Web-based intervention in improving HF patients' knowledge, self-care, and self-efficacy.

Methods

Design

The website development phase involved seeking expert feedback and pretesting the user friendliness and appropriateness of the intervention and outcome measures with HF patients. We recruited an expert panel comprising two cardiologists, four cardiac nurse researchers, and one HF nurse practitioner to advise on the development and content of the website. The software was developed by an information technology team that also provided feedback on the design. We recruited a group of 10 patients with chronic HF visiting a community outpatient HF service to pretest the intervention. During face-to-face meetings, patients provided their feedback and recommendations on the Web-based app content, ease of navigation, and user friendliness. To examine the feasibility of the Web-based HF self-care intervention, we then piloted the intervention using a randomized controlled design over a 1-month period.

Participants

The pilot sample comprised 29 patients consecutively recruited from a tertiary hospital HF service and a university health clinic located in Brisbane, Australia, between December 2013 and May 2014. Patients were eligible if they were English-speaking adults, had cardiologist- diagnosed class I–III HF according to the New York Heart Association (NYHA) classification and had a left ventricle ejection fraction <40%. Participants were required to have home or mobile Internet access. Exclusion criteria included nursing home residents, severe cognitive impairment, and critical illness.

Procedure

After providing informed consent at an introductory face-to-face session, participants completed a baseline questionnaire and were randomly assigned to the intervention or control group. Participants in the intervention group were assigned a username and password and were provided basic training on how to use each component of the website. They could then access the website educational modules each day, and record and monitor personal data such as HF-specific symptoms. The intervention group also received a weekly personalized email to improve engagement with the intervention. Both intervention and control groups received usual care from the HF service or clinic, which included comprehensive educational information consisting of topics such as medication, nutrition, exercise, and psychosocial issues. Individual patients were referred to the programs for a duration of 12 weeks and were followed up by HF nurses, and physical and occupational therapists. At 1-month follow-up, all participants completed the same questionnaire as at baseline. Due to the scope of the study, the primary researcher collected all data, as blinding was not possible. All study procedures were approved by the relevant hospital and university human research ethics committees. The intervention was also made available to the control group after completion of the research.

Intervention

The pedagogical principals underpinning the Web-based app were based on two key elements of self-efficacy theory [15,16]: role modelling and mastery experience. Helping adults to improve their self-efficacy is a powerful and central factor in increasing chronic disease self-care [5,17]. Patients with greater self-efficacy have been found to be more willing to learn and commit to achieving goals, whereas low self-efficacy has been associated with task avoidance [18]. We anticipated that the use of informational sources such as role modelling and mastery experience would help patients to increase their self-efficacy. Role modelling can take the form of observing the actions of others [18]. As such, we created female and male avatars to resemble role models and to help users engage with educational materials on the website. We encouraged mastery experience by asking participants to monitor and record their signs and symptoms related to HF fluid overload. The daily weight measurements and HF symptoms were able to be recorded to show trends over time. We used a further source of self-efficacy, verbal persuasion, through weekly emails to each participant.

We developed the Web-based app based on feedback from three groups: HF experts, an information technology team, and HF

patients. The role of the HF expert panel was to ensure integrity of the content according to evidence-based guidelines, applicability of study instruments, appropriate language and images, and appropriate user interfaces. HF patients provided their feedback and recommendations on the content, ease of navigation, and user friendliness. We developed the Web-based educational materials based on the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand chronic HF guidelines [3]. The website was password protected, and both HF patients and their health care professionals had access to content including interactive HF teaching tools, self-care tools, a chart for recording daily measures, and self-care questionnaires.

Teaching Tools

This section consisted of educational topics including an explanantion of HF (with animations), HF signs and symptoms, daily weighings (related to fat and fluid differentiation), suggestions for healthy eating and being active, methods to avoid salty foods and tips for reading food lables, and taking appropriate action when symptoms were exacerbated.

Self-Care Tools

To reinforce self-monitoring, patients could enter daily clinical data including daily weight and any signs of fluid retention such as tight shoes or socks.

My Chart

This tool allowed patients to visually monitor their daily weight and severity of HF symptoms through simple graphs. In addition, health care professionals were able to monitor their patients' self-reported data by accessing their charts.

Self-Care Questionnaires

The final section was designed to help patients assess their knowledge and self-care skills over time. It included questionnaires such as the Self-Care of Heart Failure Index (SCHFI) and the Dutch Heart Failure Knowledge Scale (DHFK).

Outcome Measures

In addition to baseline demographics, questionnaires assessed the primary outcomes including HF knowledge, self-care, and self-efficacy. The DHFK [19] consists of 15 multiple-choice items concerning HF in general (4 items), HF treatment (6 items on diet, fluid restriction, and activity), and HF symptoms and symptom recognition (5 items). The scale has a minimum score of 0 (no knowledge) and a maximum score of 15 points (optimal knowledge). It is a frequently used measure of HF knowledge and has been validated in previous research evaluating educational intervention [1].

We measured self-care skills using the SCHFI version 6.2 [20,21]. This tool has 21 items, which are scored as three subscales: maintenance (symptom monitoring and adherence behaviors performed to prevent HF exacerbation), management (patients' abilities to recognize symptoms when they occur, treatment implementation in response to symptoms, and treatment evaluation), and confidence (measures task-specific self-efficacy behaviors to manage the process of self-care) [5]. The management subscale was answered only if the patient reported having trouble breathing or ankle swelling in the past 4 weeks. Each standardized subscale score ranged from 0–100, with a score of ≥70 or more indicating adequate self-care [21].

We also used the 6-item Self-Efficacy for Managing Chronic Disease Scale (SEMCD) [22] as a general measure of chronic disease self-efficacy. It covers several domains relevant to chronic disease self-care, including symptom control, role-function, emotional functioning, and communicating with physicians. Each item is rated on a 10-point scale ranging from "not at all confident" (1) to "totally confident" (10). A mean score is calculated, with higher scores indicating higher perceived self-efficacy.

Data Analysis

We analyzed data using IBM SPSS Statistics version 21 (IBM). We compared baseline characteristics using Fisher exact and *t* tests. Descriptive statistics were examined for all variables, and pre-post change scores were calculated for outcome measures. Given the small sample size and nonnormal distribution of outcome variables and to analyze between-group differences over time, we compared change scores using Mann-Whitney *U* tests. We considered $P<.05$ to be significant and report effect sizes where possible.

Results

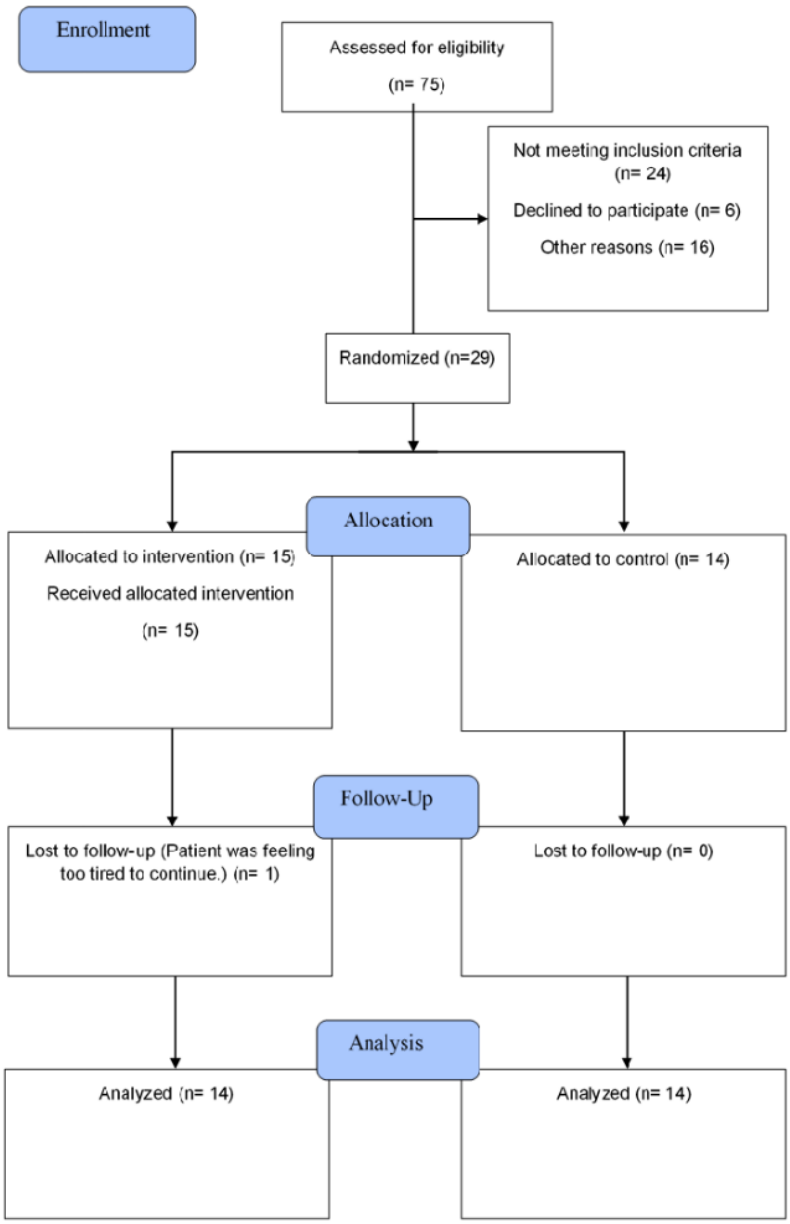
Study Recruitment and Baseline Characteristics

Of 75 HF patients who were assessed for eligibility, 29 agreed to participate and were enrolled into the study (see Figure 1). Table 1 shows the baseline demographic and clinical characteristics of the 28 patients who participated in the pilot study. One participant dropped out. Of the total sample, the majority were men (n=22, 79%) and the mean age was 60.8 (SD 11.9) years. The mean self-reported disease duration was 4.0 (SD 6.9) years. Most participants were asymptomatic (class I, n=14, 50%) or had mild HF (class II, n=12, 43%) according to the NYHA functional classification. Comparisons showed no significant differences between the intervention and control groups at baseline.

Table 1. Baseline characteristics of participants in a pilot study of a Web-based self-management intervention for chronic heart failure.

Characteristic	Control (n=14)	Intervention (n=14)
Age in years, mean (SD)	60.0 (14.0)	61.7 (9.9)
Sex, n (%)		
Male	11 (79)	11 (79)
Female	3 (21)	3 (21)
Marital status, n (%)		
Married	8 (57)	9 (64)
Widowed, divorced, or never married	6 (43)	5 (36)
Living arrangement, n (%)		
Live alone	6 (46)	5 (36)
Live with others	7 (54)	9 (64)
Level of education, n (%)		
<12 years or high school diploma	7 (50)	8 (57)
Some college/associate degree, bachelor's degree, or postgraduate degree	7 (50)	6 (43)
Total household income, n (%)		
≤A$40,000/year	4 (29)	9 (64)
≥A$70,000/year, or do not know, or refused	10 (71)	5 (36)
Overall perceived health, n (%)		
Excellent, very good, or good	7 (50)	7 (50)
Fair or poor	7 (50)	7 (50)
Medication treatment		
Angiotensin-converting enzyme inhibitor	10 (71)	10 (71)
Angiotensin II receptor blocker	4 (29)	2 (14)
Beta-blocker	14 (100)	11 (79)
New York Heart Association classification		
Class I	8 (57)	6 (43)
Class II	6 (43)	6 (43)
Class III	0 (0)	2 (14)
Ejection fraction, mean (SD)	33.7 (8.9)	33.4 (8.51)
Duration of heart failure in years, mean (SD)	3.0 (4.8)	4.9 (8.5)

Figure 1. Consort study flow chart.



Heart Failure Knowledge

Table 2 compares the change in knowledge scores for the intervention and control groups. As the maximum possible knowledge score is 15, the baseline mean scores of 12.5 (SD 1.1) for the intervention group and 12.2 (SD 2.4) for the control group indicated that participants had relatively high levels of HF knowledge at the outset. While change scores at 1 month showed slight improvement in HF knowledge, there was no significant difference between the intervention and control groups (U=91.5, P=.75), with a negligible effect size (d=0.06).

Table 2. Change score analysis: change in scores from baseline preintervention (pre) to post intervention (post).

Scale	Intervention group (n=14)		Pre-post difference, mean (95% CI)	Control group (n=14)		Pre-post difference, mean (95% CI)	Mann-Whitney *U* test	*P* value	Effect size (*d*)
	Pre, mean (SD)	Post, mean (SD)		Pre, mean (SD)	Post, mean (SD)				
DHFK[a]	12.5 (1.1)	12.9 (1.3)	0.35 (–0.67 to 1.3)	12.2 (2.4)	12.8 (1.7)	0.57 (–0.05 to 1.2)	91.5	.75	0.06
SCHFI[b] (maintenance)	61.9 (20.9)	71.9 (15.1)	9.9 (–3.6 to –23.6)	70.2 (17.4)	66.6 (17.7)	–3.5 (–10.3 to 1.3)	59.5	.07	0.32
SCHFI (confidence)	67.1 (20.3)	73.0 (18.0)	3.8 (–4.3 to 12.0)	65.5 (21.4)	69.9 (19.2)	3.8 (–4.3 to 12.0)	89.5	.94	0.16
SEMCD[c]	7.3 (1.6)	8.0 (1.7)	0.70 (–0.54 to 1.9)	7.1 (1.4)	7.4 (1.5)	0.35 (–0.21 to 0.92)	87.0	.61	0.37

[a]DHFK: Dutch Heart Failure Knowledge Scale.

[b]SCHFI: Self-Care of Heart Failure Index.

[c]SEMCD: Self-Efficacy for Managing Chronic Disease Scale.

Self-Care

As presented in Table 2, change scores showed an improvement in the SCHFI maintenance subscale in the intervention group to above the minimum level of self-care adequacy (mean difference 9.9, 95% CI –3.6 to –23.6), whereas the control group scores decreased over time (mean difference –3.5, 95% CI –10.3 to 1.3). While the effect size suggests an important trend (d=0.32), given the small sample size it did not reach statistical significance (U=59.9, P=.07). In addition, while we observed small improvements in the SCHFI confidence subscale, we found no significant between-group differences (U=89.5, P=.94). As answers to the management subscale were indicated by only 5 patients, we did not compare this subscale.

Self-Efficacy

Table 2 shows that both groups also reported high levels of self-efficacy at baseline. Change scores indicated an improvement among the intervention group (mean difference 0.70, 95% CI –0.54 to 1.9, d=0.37), although this was not statistically significant (U=87.0, P=.61).

Use of the Intervention

The intervention group accessed the website on average 16.8 times during the 1-month intervention period. Of the 14 participants, 7 (50%) accessed the intervention site every day, 4 (28%) had no record of access, 11 (78%) accessed the website from home and 3 (22%) through a mobile phone. The most reviewed section of the website was “How do I learn to read food labels?” followed by “How do I reduce salt in my daily meal?,” “What is the difference between fat and fluid weight gain?,” and “How do I become more physically active?” Based on personal data recorded, 7 participants entered their data every day, 1 participant on 25 days, 1 on 12 days, and 1 on 4 days; 4 participants did not enter any data.

To explore a possible dose-response relationship, we ran correlations between participants’ change scores and frequency of usage of the website. Within the intervention group, Spearman correlations between frequency of usage of the intervention and outcome change scores suggested greater use was associated with higher knowledge (ρ=.34), SCHFI subscales (ρ range .40–.43), and self-efficacy scores (ρ=.45).

Discussion

Principal Findings

In this pilot study, we developed and investigated the feasibility of a Web-based self-care intervention for HF outpatients. Overall, results showed that the intervention did not improve patients’ outcomes at 4 weeks’ follow-up. While there was a trend toward improved self-care and self-efficacy in the intervention group for behaviors such as symptom monitoring and strategies to prevent HF exacerbation, given the small sample size, the results were not statistically significant. In contrast to previous studies [10,11] we also found that a Web-based educational intervention was challenging for older HF patients, and usage was low. Despite face-to-face training and email reminders, only 50% of the sample accessed the site daily and 28% had no record of access.

Comparison With Prior Work

This study differed in important ways from previous intervention studies of Web-based HF self-care [11,12], which may account for the negative findings. Our cohort had shorter disease duration and less severe HF according to the NYHA classification than in previous studies [11,12]. The follow-up period was relatively short to examine changes in patient outcomes, and we acknowledge that a minimum of 6 months’ follow-up is recommended in the literature [12,23]. There were also differences in the scope of the intervention. The educational content of the website was at a basic level and focused on self-care skills. The standard face-to-face patient education received by both groups in the HF clinic, therefore, may not have been comprehensive enough to diminish the effect of the Web-based intervention. Our primary outcome measures of self-care skills and self-efficacy differed from previous studies, which focused on HF knowledge, symptoms, and quality of life [11,12]. Nonetheless, using validated measures was a strength of this study. Yet, because most of the participants in the sample were asymptomatic, we did not compare the management

subscale of the SCHFI. In addition, as the maximum score for the DHFK questionnaire was 15 and a score >10 indicated adequate knowledge [19], the high knowledge scores of participants at baseline (mean 12.5, SD 1.1) likely created a ceiling effect.

Notwithstanding the above limitations, our study findings are consistent with a body of literature that points to mixed evidence of the effectiveness of Web-based self-care interventions for chronic disease [13,24]. Despite the development of a plethora of Internet-based interventions over recent decades, systematic reviews have not shown any benefit of Web-based self-care interventions for chronic disease [25,26]. Moreover, meta-analyses have not demonstrated a significant benefit in the use of Web-based interventions when combining samples [27,28]. This is attributed, in the first instance, to issues of methodology and variability in research design [13,29-31]. There are significant differences in configuration (eg, educational materials, asynchronous discussion, live conferencing), instructional methods (eg, practice exercise, cognitive interactivity), and presentation [13]. These also extend to types of assessments, study populations, the etiology of symptoms, and times of intervention [27,32]. A further and related issue is a lack of appropriate theoretical frameworks [33,34]. Many studies are missing the theoretical rationale for multiple assessments and how these informed the development of the Web-based interventions. The authors of a previous study [33] reported that a limited number of interventions applied evidence-based theory and, more recently, a meta-analysis of research on reducing blood pressure with Internet-based interventions [34] emphasized that a priority for future research is to design and evaluate interventions according to theoretically grounded hypotheses.

In contrast to other kinds of educational intervention studies in HF patients [1], the role of theory in developing Internet-based interventions has been largely disregarded. While precise measures of key constructs and outcomes and well-defined associations improve research precision, theory is needed to inform the choice of study design and to enhance an understanding of causal relationships [35]. Robust theory is also critical in identifying the effectiveness of the specific components of the interventions and optimizing their intensity [35-37]. Key theoretical constructs and associations should therefore be applied in efficacy trials, tests of effectiveness, and adoption and sustainability studies. There is some evidence for the use of Bandura's self-efficacy theory as the most important element in developing self-care interventions [7].

Implications for Future Research

This pilot study presented a fundamental phase of the development of a Web-based self-care intervention for patients with HF that can be used to inform future research. To examine the effectiveness of the proposed Web-based intervention, a larger, adequately powered randomized controlled trial is needed. Longer follow-up periods at 3, 6, and 12 months are required to examine clinically meaningful change over time. In addition, we recommend that researchers actively support older HF patients to engage with Web-based interventions through face-to-face education sessions for basic computer and Internet skills. Greater resources may improve adherence and resolve possible barriers or difficulties in using Web-based self-care tools.

Well-designed educational strategies grounded in theory and contemporary evidence are crucial in improving HF self-care and patient outcomes [38]. More comprehensive educational content is needed, including nutrition and diet, physical activity, effects of alcohol and smoking, medications and their side effects [5], as well as psychosocial and emotional issues [1,39]. Moreover, as Tomita et al [12] argued, interventions should target improved physical activity and provide practical advice about appropriate types and levels of exercise. This would include walking, breathing, stretching, range of motion, and upper and lower extremity strength training. For better outcomes and in order to encourage HF patients to maintain healthy lifestyles, interventions would also incorporate more information on recommended diet and nutrition [12].

To strengthen the efficacy of the Web-based intervention, we recommend drawing on the sources and mediators of self-efficacy theory. Feedback, goal setting, videos of peer storytelling, monitoring tools such as for blood pressure, daily weight, and physical activities, and diaries are some examples of self-efficacy information sources [40]. We strongly recommend using a combination of the four primary information sources in Bandura's work to promote a stronger sense of self-efficacy and a greater willingness to undergo behavioral change and thus produce optimal results [41]. There are examples [6,7] of previous studies that have used the four primary dimensions of self-efficacy to enhance self-care in adults with chronic diseases. The primary focus of these interventions was the provision of efficacy-based information sources, including the mastery of performance accomplishments, role modelling (vicarious learning), social persuasion (verbal encouragement), and the interpretation of physiological and emotional responses [7].

Limitations

Recruitment was slow in part due to HF patients' lack of interest in the intervention, Internet access, or computer skills. Among the HF patients who were invited to participate in the study, 26 were not eligible based on the study inclusion and exclusion criteria. This exploratory pilot study was confined to an HF management program provided at a single-hospital HF service and university health clinic. To participate, it was essential that HF patients had access to the Internet at home or workplace or via a mobile phone. Although a large proportion of the HF population did have access to the Internet, a significant minority (22 participants) did not. As a result, our study was based on a small sample size, which limited statistical power. Finally, the study follow-up was relatively short for the examination of the Web-based intervention on patient knowledge, self-care, and self-efficacy.

Conclusion

This study examined the feasibility of a Web-based self-care intervention in improving HF knowledge, self-care, and self-efficacy. Although preliminary, our findings are consistent with current literature that demonstrates negative to small effects

of Web-based self-care interventions in chronic disease. Larger, theoretically informed, and more comprehensive studies are needed to support or refute this proposition. Nonetheless, the challenges of this study and lessons learned give some support to the argument that Web-based programs, as discrete interventions, will not be the remedy for the cost and social burden of chronic illness.

Acknowledgments

Thanks to Associate Professor John Atherton, Mrs Linda Prentice, Mr Carlos Fernandez, and HF clinic staff and participating patients at the Royal Brisbane and Women's Hospital. Special thanks to Professor Robyn Clark from Flinders University and Mrs Chris Horton and Dr Johannes Moolman from Ipswich Community Health and Ipswich Hospital for their generous support during phase one of the study.

Conflicts of Interest

None declared.

References

1. Boyde M, Song S, Peters R, Turner C, Thompson DR, Stewart S. Pilot testing of a self-care education intervention for patients with heart failure. Eur J Cardiovasc Nurs 2013 Feb;12(1):39-46. [doi: 10.1177/1474515111430881] [Medline: 22357784]
2. Shively MJ, Gardetto NJ, Kodiath MF, Kelly A, Smith TL, Stepnowsky C, et al. Effect of patient activation on self-management in patients with heart failure. J Cardiovasc Nurs 2013;28(1):20-34. [doi: 10.1097/JCN.0b013e318239f9f9] [Medline: 22343209]
3. National Heart Foundation of Australia, Cardiac Society of Australia and New Zealand, Chronic Heart Failure Guidelines Expert Writing Panel. Guidelines for the Prevention, Detection and Management of Chronic Heart Failure in Australia. Sydney, Australia: CSANZ; 2011 Jul. URL: http://www.csanz.edu.au/wp-content/uploads/2014/12/2011_HF_CSANZ_Chronic_Heart_Failure.pdf [accessed 2016-05-26] [WebCite Cache ID 6hmcS3UGt]
4. Vellone E, Fida R, D'Agostino F, Mottola A, Juarez-Vela R, Alvaro R, et al. Self-care confidence may be the key: A cross-sectional study on the association between cognition and self-care behaviors in adults with heart failure. Int J Nurs Stud 2015 Nov;52(11):1705-1713. [doi: 10.1016/j.ijnurstu.2015.06.013] [Medline: 26169451]
5. Barnason S, Zimmerman L, Hertzog M, Schulz P. Pilot testing of a medication self-management transition intervention for heart failure patients. West J Nurs Res 2010 Nov;32(7):849-870. [doi: 10.1177/0193945910371216] [Medline: 20702679]
6. Lorig KR, Ritter PL, Laurent DD, Plant K. Internet-based chronic disease self-management: a randomized trial. Med Care 2006 Nov;44(11):964-971. [doi: 10.1097/01.mlr.0000233678.80203.c1] [Medline: 17063127]
7. Lorig K, Ritter PL, Plant K, Laurent DD, Kelly P, Rowe S. The South Australia health chronic disease self-management Internet trial. Health Educ Behav 2013 Feb;40(1):67-77. [doi: 10.1177/1090198112436969] [Medline: 22491008]
8. Griffiths F, Lindenmeyer A, Powell J, Lowe P, Thorogood M. Why are health care interventions delivered over the internet? A systematic review of the published literature. J Med Internet Res 2006;8(2):e10 [FREE Full text] [doi: 10.2196/jmir.8.2.e10] [Medline: 16867965]
9. Evangelista LS, Strömberg A, Westlake C, Ter-Galstanyan A, Anderson N, Dracup K. Developing a Web-based education and counseling program for heart failure patients. Prog Cardiovasc Nurs 2006;21(4):196-201. [Medline: 17170595]
10. Delgado DH, Costigan J, Wu R, Ross HJ. An interactive Internet site for the management of patients with congestive heart failure. Can J Cardiol 2003 Nov;19(12):1381-1385. [Medline: 14631472]
11. Westlake C, Evangelista LS, Strömberg A, Ter-Galstanyan A, Vazirani S, Dracup K. Evaluation of a Web-based education and counseling pilot program for older heart failure patients. Prog Cardiovasc Nurs 2007;22(1):20-26. [Medline: 17342002]
12. Tomita MR, Tsai B, Fisher NM, Kumar NA, Wilding G, Stanton K, et al. Effects of multidisciplinary Internet-based program on management of heart failure. J Multidiscip Healthc 2008 Dec 1;2009(2):13-21 [FREE Full text] [Medline: 20505786]
13. Kuijpers W, Groen WG, Aaronson NK, van Harten WH. A systematic review of web-based interventions for patient empowerment and physical activity in chronic diseases: relevance for cancer survivors. J Med Internet Res 2013;15(2):e37 [FREE Full text] [doi: 10.2196/jmir.2281] [Medline: 23425685]
14. Im E, Chang SJ. Web-based interventions in nursing. Comput Inform Nurs 2013 Feb;31(2):94-102. [doi: 10.1097/NXN.0b013e3182771868] [Medline: 23254365]
15. Bandura A. Self-efficacy: toward a unifying theory of behavioral change. Psychol Rev 1977 Mar;84(2):191-215. [Medline: 847061]
16. Bandura A. Guide for constructing self-efficacy scales. In: Urdan T, Pajares F, editors. Self-Efficacy Beliefs of Adolescents. Greenwich, CT: Information Age Publishing; 2006:307-337.
17. Lorig KR, Holman HR. Self-management education: history, definition, outcomes, and mechanisms. Ann Behav Med 2003 Aug;26(1):1-7. [doi: 10.1207/S15324796ABM2601_01]
18. Bandura A. Self-Efficacy: The Exercise of Control. New York, NY: Freeman; 1997.

19. van der Wal M, Jaarsma T, Moser DK, van Veldhuisen D. Development and testing of the Dutch Heart Failure Knowledge Scale. Eur J Cardiovasc Nurs 2005 Dec;4(4):273-277. [doi: 10.1016/j.ejcnurse.2005.07.003] [Medline: 16126459]
20. Riegel B, Carlson B, Glaser D. Development and testing of a clinical tool measuring self-management of heart failure. Heart Lung 2000;29(1):4-15. [Medline: 10636953]
21. Vellone E, Riegel B, Cocchieri A, Barbaranelli C, D'Agostino F, Antonetti G, et al. Psychometric testing of the Self-Care of Heart Failure Index Version 6.2. Res Nurs Health 2013 Oct;36(5):500-511. [doi: 10.1002/nur.21554] [Medline: 23832431]
22. Lorig KR, Sobel DS, Ritter PL, Laurent D, Hobbs M. Effect of a self-management program on patients with chronic disease. Eff Clin Pract 2001;4(6):256-262 [FREE Full text] [Medline: 11769298]
23. Ditewig JB, Blok H, Havers J, van Veenendaal H. Effectiveness of self-management interventions on mortality, hospital readmissions, chronic heart failure hospitalization rate and quality of life in patients with chronic heart failure: a systematic review. Patient Educ Couns 2010 Mar;78(3):297-315. [doi: 10.1016/j.pec.2010.01.016] [Medline: 20202778]
24. Eland-de KP, van Os-Medendorp H, Vergouwe-Meijer A, Bruijnzeel-Koomen C, Ros W. A systematic review of the effects of e-health on chronically ill patients. J Clin Nurs 2011 Nov;20(21-22):2997-3010. [doi: 10.1111/j.1365-2702.2011.03743.x] [Medline: 21707807]
25. Samoocha D, Bruinvels DJ, Elbers NA, Anema JR, van der Beek AJ. Effectiveness of web-based interventions on patient empowerment: a systematic review and meta-analysis. J Med Internet Res 2010;12(2):e23 [FREE Full text] [doi: 10.2196/jmir.1286] [Medline: 20581001]
26. Stellefson M, Chaney B, Barry AE, Chavarria E, Tennant B, Walsh-Childers K, et al. Web 2.0 chronic disease self-management for older adults: a systematic review. J Med Internet Res 2013 Feb;15(2):e35 [FREE Full text] [doi: 10.2196/jmir.2439] [Medline: 23410671]
27. Macea DD, Gajos K, Daglia Calil YA, Fregni F. The efficacy of Web-based cognitive behavioral interventions for chronic pain: a systematic review and meta-analysis. J Pain 2010 Oct;11(10):917-929. [doi: 10.1016/j.jpain.2010.06.005] [Medline: 20650691]
28. Bossen D, Veenhof C, Dekker J, de Bakker D. The effectiveness of self-guided web-based physical activity interventions among patients with a chronic disease: a systematic review. J Phys Act Health 2014 Mar;11(3):665-677. [doi: 10.1123/jpah.2012-0152] [Medline: 23493018]
29. Bewick BM, Trusler K, Barkham M, Hill AJ, Cahill J, Mulhern B. The effectiveness of web-based interventions designed to decrease alcohol consumption: a systematic review. Prev Med 2008 Jul;47(1):17-26. [doi: 10.1016/j.ypmed.2008.01.005] [Medline: 18302970]
30. Bond GE, Burr R, Wolf FM, Price M, McCurry SM, Teri L. The effects of a web-based intervention on the physical outcomes associated with diabetes among adults age 60 and older: a randomized trial. Diabetes Technol Ther 2007 Feb;9(1):52-59 [FREE Full text] [doi: 10.1089/dia.2006.0057] [Medline: 17316098]
31. Kerr AJ, Broad J, Wells S, Riddell T, Jackson R. Should the first priority in cardiovascular risk management be those with prior cardiovascular disease? Heart 2009 Feb;95(2):125-129. [doi: 10.1136/hrt.2007.140905] [Medline: 18381374]
32. García-Lizana F, Sarría-Santamera A. New technologies for chronic disease management and control: a systematic review. J Telemed Telecare 2007;13(2):62-68. [doi: 10.1258/135763307780096140] [Medline: 17359568]
33. Cotter AP, Durant N, Agne AA, Cherrington AL. Internet interventions to support lifestyle modification for diabetes management: a systematic review of the evidence. J Diabetes Complications 2014;28(2):243-251 [FREE Full text] [doi: 10.1016/j.jdiacomp.2013.07.003] [Medline: 24332469]
34. Liu S, Dunford SD, Leung YW, Brooks D, Thomas SG, Eysenbach G, et al. Reducing blood pressure with Internet-based interventions: a meta-analysis. Can J Cardiol 2013 May;29(5):613-621. [doi: 10.1016/j.cjca.2013.02.007] [Medline: 23618507]
35. Campbell-Voytal K. The role of theory in clinical prevention research. Fam Pract 2010 Aug;27(4):357-358 [FREE Full text] [doi: 10.1093/fampra/cmq054] [Medline: 20660471]
36. Neville LM, O'Hara B, Milat AJ. Computer-tailored dietary behaviour change interventions: a systematic review. Health Educ Res 2009 Aug;24(4):699-720 [FREE Full text] [doi: 10.1093/her/cyp006] [Medline: 19286893]
37. Phillips R, Kennedy G, McNaught C. The role of theory in learning technology evaluation research. Australas J Educ Technol 2012;28(7):1103-1118.
38. Boyde M, Peters R. Education material for heart failure patients: what works and what does not? Curr Heart Fail Rep 2014 Sep;11(3):314-320. [doi: 10.1007/s11897-014-0200-1] [Medline: 24797119]
39. Tung H, Lin C, Chen K, Chang C, Lin Y, Chou C. Self-management intervention to improve self-care and quality of life in heart failure patients. Congest Heart Fail 2013;19(4):E9-E16. [doi: 10.1111/chf.12014] [Medline: 23279120]
40. Yu CH, Parsons J, Mamdani M, Lebovic G, Shah BR, Bhattacharyya O, et al. Designing and evaluating a web-based self-management site for patients with type 2 diabetes: systematic website development and study protocol. BMC Med Inform Decis Mak 2012;12:57 [FREE Full text] [doi: 10.1186/1472-6947-12-57] [Medline: 22726578]
41. Chao Y, Scherer YK, Wu Y, Lucke KT, Montgomery CA. The feasibility of an intervention combining self-efficacy theory and Wii Fit exergames in assisted living residents: a pilot study. Geriatr Nurs 2013;34(5):377-382. [doi: 10.1016/j.gerinurse.2013.05.006] [Medline: 23764366]

Abbreviations

DHFK: Dutch Heart Failure Knowledge Scale
HF: heart failure
NYHA: New York Heart Association
SCHFI: Self-Care of Heart Failure Index
SEMCD: Self-Efficacy for Managing Chronic Disease Scale

Edited by G Eysenbach; submitted 01.09.15; peer-reviewed by F Fatehi, W Groen, E Vellone; comments to author 12.11.15; revised version received 02.12.15; accepted 04.01.16; published 20.06.16.

Please cite as:
Bashi N, Windsor C, Douglas C
Evaluating a Web-Based Self-Management Intervention in Heart Failure Patients: A Pilot Study
JMIR Res Protoc 2016;5(2):e116
URL: http://www.researchprotocols.org/2016/2/e116/
doi:10.2196/resprot.5093
PMID:27324213

Protocol

Supporting Tablet Configuration, Tracking, and Infection Control Practices in Digital Health Interventions: Study Protocol

Robert D Furberg[1], PhD, MBA; Alexa M Ortiz[1], MSN; Brittany A Zulkiewicz[1], BS; Jordan P Hudson[1], BA; Olivia M Taylor[1], MPH; Megan A Lewis[1], PhD

RTI International, Research Triangle Park, NC, United States

Corresponding Author:
Alexa M Ortiz, MSN
RTI International
3040 E. Cornwallis Road
Research Triangle Park, NC,
United States
Phone: 1 919 316 3344
Fax: 1 919 541 6621
Email: amortiz@rti.org

Abstract

Background: Tablet-based health care interventions have the potential to encourage patient care in a timelier manner, allow physicians convenient access to patient records, and provide an improved method for patient education. However, along with the continued adoption of tablet technologies, there is a concomitant need to develop protocols focusing on the configuration, management, and maintenance of these devices within the health care setting to support the conduct of clinical research.

Objective: Develop three protocols to support tablet configuration, tablet management, and tablet maintenance.

Methods: The Configurator software, Tile technology, and current infection control recommendations were employed to develop three distinct protocols for tablet-based digital health interventions. Configurator is a mobile device management software specifically for iPhone operating system (iOS) devices. The capabilities and current applications of Configurator were reviewed and used to develop the protocol to support device configuration. Tile is a tracking tag associated with a free mobile app available for iOS and Android devices. The features associated with Tile were evaluated and used to develop the Tile protocol to support tablet management. Furthermore, current recommendations on preventing health care–related infections were reviewed to develop the infection control protocol to support tablet maintenance.

Results: This article provides three protocols: the Configurator protocol, the Tile protocol, and the infection control protocol.

Conclusions: These protocols can help to ensure consistent implementation of tablet-based interventions, enhance fidelity when employing tablets for research purposes, and serve as a guide for tablet deployments within clinical settings.

(JMIR Res Protoc 2016;5(2):e136) doi:10.2196/resprot.5400

KEYWORDS

tablet computers; mHealth; infection control; clinical research protocol; mobile device management

Introduction

The proliferation of tablet technologies has ushered in a new realm of connected health care and research-based interventions in the clinical setting. According to the Pew Research Center, 64% of American adults own a smartphone, and of those, 53% also own a tablet [1]. Advancements in policy, health information technology adoption by providers, mobile/social technology adoption by consumers, and development of health-focused mobile apps have created ideal conditions to enable the expansion of tablet-based interventions. According to the *2015 Healthcare Information and Management Systems Society Mobile Technology Survey*, 47% of responding organizations labeled mobile service implementation to access information as a top priority, and 57% indicated already having a mobile technology policy [2]. Further, as noted by the IMS Institute for Healthcare Informatics, more than 165,000 mobile health (mHealth) apps are currently available for consumer download through Google Play and the Mac App Store [3].

The use of electronic tools and services has created new opportunities for individuals to actively participate in monitoring and directing their health care through digital health

interventions. The body of evidence that supports the use of such strategies to improve health outcomes continues to expand [4]. However, insufficient guidance exists on deployment methods that could be used to support replication or subsequent scaling. To address this gap, we describe protocols relevant to three major phases of digital health intervention activities using tablets: initial device configuration, remote management of deployed technologies, and the ongoing maintenance of tablets deployed within clinical environments. The protocols are intended for use by three major audiences: (1) public health investigators responsible for the design of a digital health intervention, (2) research technologists seeking guidance on deployment methods, and (3) clinical staff responsible for monitoring tablets and carrying out infection control procedures in a health care setting.

There is scant literature describing the implementation of tablet-based public health interventions and the management of tablets. Tablet use takes place across multiple populations and settings including urban ambulatory care practices, grocery stores, pediatric practices, and primary care practices [5-8]. Several interventions describe the use of Web-based material optimized for delivery via tablets, whereas others used operating system–specific tablet-based interventions [7-13]. Irrespective of the mode of content delivery (eg, native app, hybrid app, or responsive Web application), proper configuration, management, and maintenance of the tablet computer is essential to ensure technical fidelity and control of participant exposure to intervention materials. To the best of our knowledge, no studies describe these procedures, and there are no predeveloped protocols surrounding the use of tablets in digital health interventions. We describe protocols to address the gap within the literature that can serve as a basic guide for configuration, management, and maintenance of tablet-based interventions.

Methods

Tablet Configuration

Characteristics of Configurator

The mobile device management software, known as Configurator, is a resource that may improve the reliability and enhance the reproducibility of digital health interventions. Configurator is a free utility available from the Mac App Store. It is designed to configure and deploy multiple iPhones, iPod Touches, iPads, or Apple TV devices [14]. Configurator users have the ability to push images, settings, apps, and security profiles across groups of iPhone operating system (iOS) devices [15]. These devices can be configured using an XML configuration file or by using the backup of a master iPad [16,17], which is configured by hand. The configuration can include all network and security settings as well as installs for the selected free or in-house apps. Once set, the master iPad is imaged using Configurator's backup function [16]. Remaining iPads are connected to the Mac OS device via universal serial bus (USB), and the image of the master iPad is restored to the remaining iPads. This can be done with up to 30 iPads [15]. Using Configurator to set up and maintain iOS devices gives administrative control over every aspect of the device, including wallpaper and lock screen settings, virtual private network and Wi-Fi (wireless local area network) settings, mail and calendar accounts, iOS version and upgrades, documents, and application access [16]. The end result is a number of identical, incrementally identified iOS devices. Subsequent alterations, including software updates, can only be made using Configurator by connecting the devices via USB to a Mac OS computer.

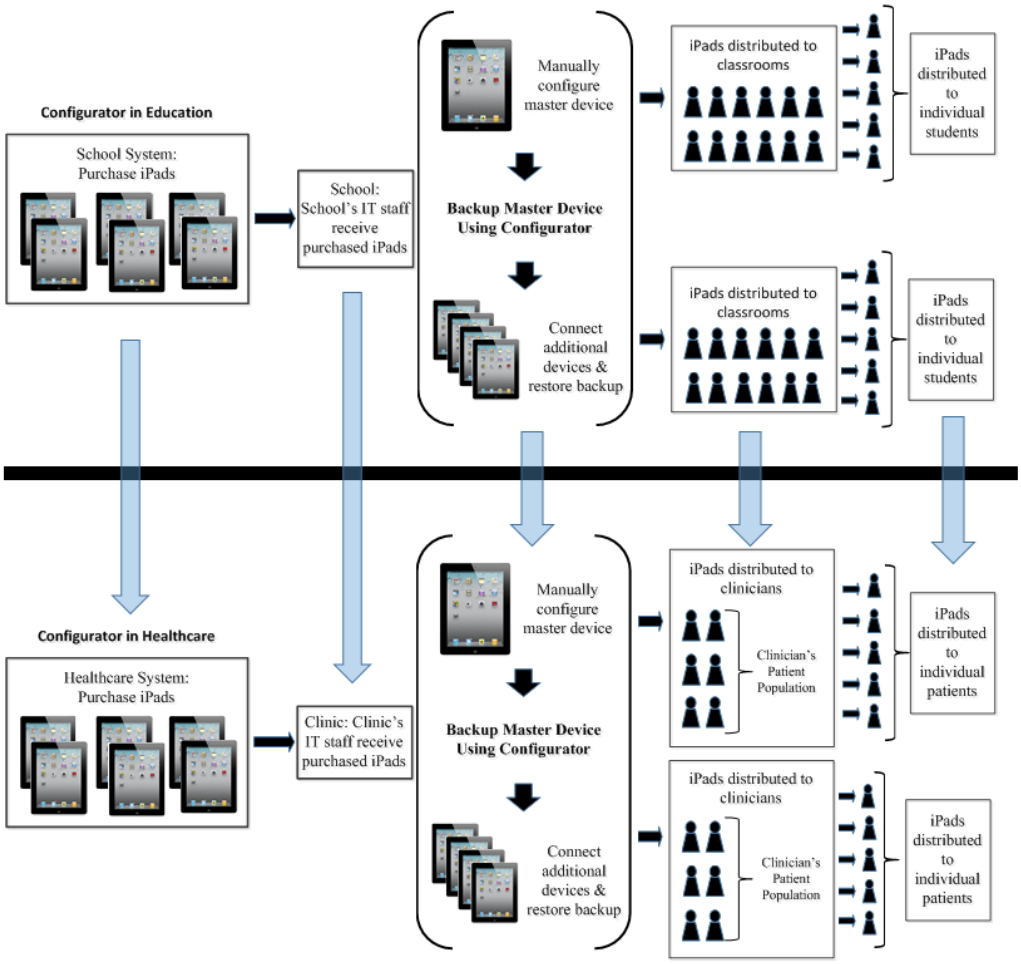
Applying Configurator to Tablet Deployment

Presently there is limited guidance available regarding tablet configuration for digital health interventions. However, with reported sales of more than 4.5 million iPads to educational institutions within the United States and almost twice that worldwide, Configurator is extensively used within the field of education [18,19]. Recommendations from Configurator's application in education can be applied to digital health interventions deployed for research or clinical purposes.

The Configurator application is widely used in education for configuring multiple iOS-based devices at scale, whether it be for a single classroom, school, or district. Consequently, a considerable amount of guidance is available about Configurator's setup and use in schools. Additionally, the Configurator education deployment model provides institutions with flexibility to manage multiple deployment scenarios, such as one-to-one, shared-use, and student-owned devices. Schools may choose to deploy iPads in one specific scenario or all three scenarios. However, Configurator is ideally used to set up one-to-one or shared-use devices, which gives educational IT staff the ability to customize and be flexible in addressing the school's specific needs.

The iOS education Configurator deployment model can easily be transposed to other domains, such as deployment within clinical settings or health research studies. The example provided in Figure 1 outlines how the educational infrastructure is similar to the health care infrastructure, as can be seen by changing the nomenclature from schools to clinics, teachers to clinicians, and students to patients.

Figure 1. Education and healthcare comparative configurator infrastructure.



Note: iPad image retrieved from www.flickr.com/photos/54450095@N05/6310585622, Apple iPad 2 Licensed under Creative Commons Attribution 2.0

Configurator Protocol

As the use of tablets continues to expand within clinical settings and tablets become more commonplace components in digital health interventions, a consistent method for configuring devices will become increasingly necessary. The protocol, as shown in Multimedia Appendix 1, provides a generic outline for iPad deployment using Configurator within research or clinical settings. The protocol reviews the requirements associated with Configurator's use and provides the steps for setting up an iPad using Configurator.

Tablet Management

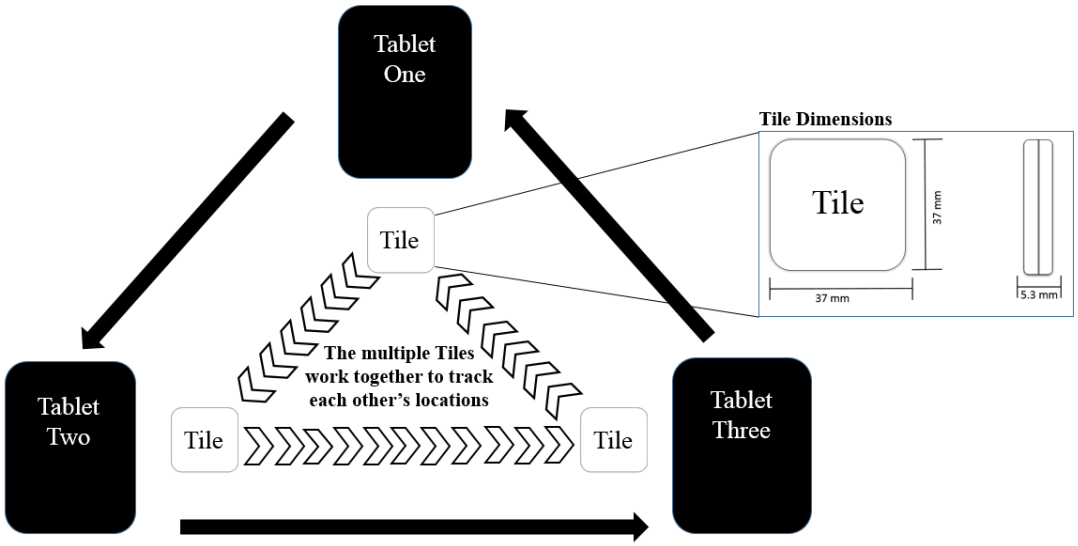
Characteristics of Tile

The ability to track tablets (or other mobile devices) is an investment in the retention of the digital health intervention. Tile is a small tracking tag (see Figure 2 for dimensions) associated with a free app compatible with iOS and the Android operating system [20-23]. The primary purpose of Tile is to assist users in locating lost items. While Tile was not designed for mobile device management, its capabilities and small size offer a unique method of tracking mobile devices in clinical settings to augment native management features, such as Find My iPhone, where a Global Positioning System (GPS) signal may not be available.

The Tile app is free and the cost of Tile's hardware is relatively low—usually less than $25 per device [24]. Tile locates items by using Bluetooth low energy (BLE) 4.0 [22,23]. BLE works optimally at a range of 30 feet but can extend to a maximum range of 100 feet [22,23]. If an item is lost but is in the range of the BLE, Tile can be triggered to play a short tune by selecting the *Find* option within the app to assist the user in locating the lost device [23,25]. If Tile is unable to track an item via BLE, the user can select the app's *Mark as Lost* option to report a missing Tile [23]. The app can also inform users about the last place their lost device was seen. As noted in the Tile informational material [23], "Tile maps the last place you had it."

Additionally, multiple Tiles can work together. While an individual Tile is only visible to its registered user, each Tile can be used in a *Community Find*, which allows any Tile to assist in communicating the location of a lost item to its registered owner [22,25,26]. Separate from the *Community Find* feature, the Tile app can share a Tile's location with another Tile app user [27]. The *Share* feature allows two different app users access to the same Tile [23,28].

Figure 2. Entity relationship diagram: option 1 and tile dimensions.

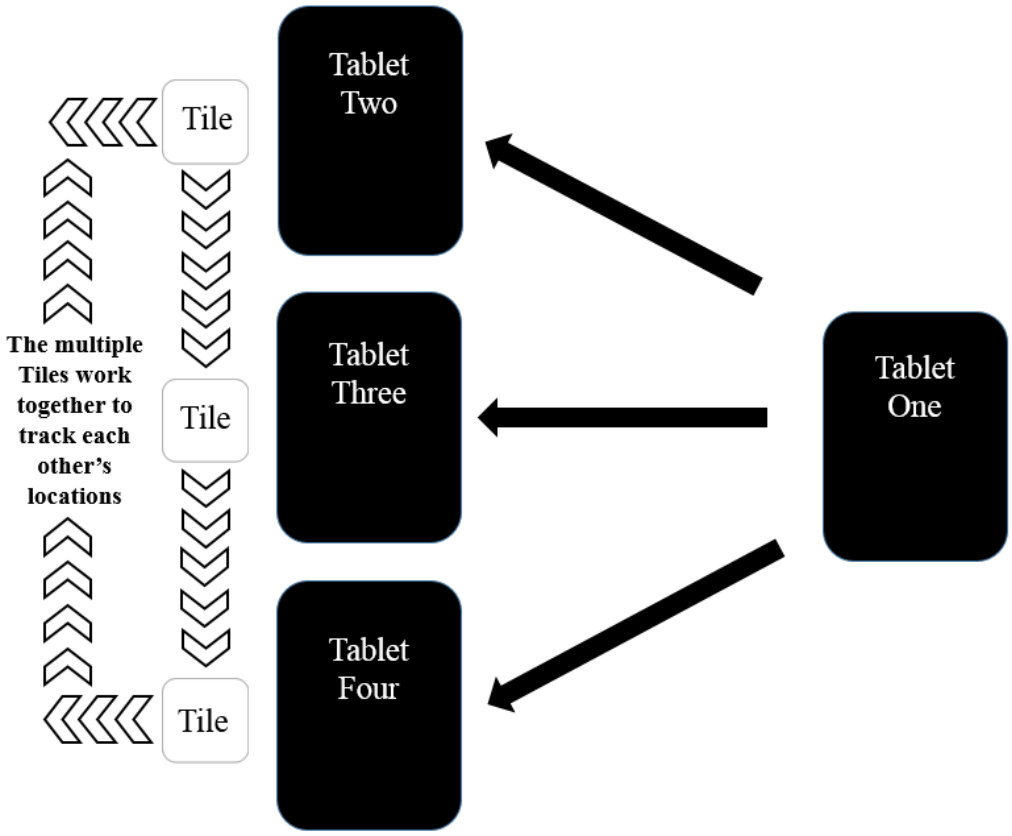


Applying Tile to Tablet Deployment

There are two approaches to applying Tile technology to tablet deployments. The first option, as outlined in Figure 2, displays three devices that each track one other device within the diagram. Since each Tile's BLE can only connect to one device at a time [27], each tablet is limited to tracking only one other tablet. That is, tablet 1 is used to track the location of tile 2 (attached to tablet 2); tablet 2 is used to track the location of tile 3 (attached to tablet 3); tablet 3 is used to track the location of tile 1 (attached to tablet 1).

The second option for applying Tile technology to tablet deployments is outlined in Figure 3, which displays four devices, three with Tiles attached and one device that is solely used for tracking the deployed Tiles. Because one Tile app can simultaneously track multiple individual Tiles, a single tablet can track the three deployed Tiles via BLE; that is, tablet 1 can track tablets 2, 3, and 4.

Figure 3. Entity relationship diagram: option 2.



Tile Protocol

Considering the compact nature of many tablets, the risk of theft, misplaced devices, or loss is a concern. Consequently, enhanced use of tablet technology in digital health interventions must be accompanied by innovative methods of device management. Multimedia Appendix 2 provides a protocol outlining the requirements for deployment as well as how to set up and use the various features offered by the Tile tracking device.

Tablet Maintenance

Characteristics of Infection Control

As tablets continue to proliferate the health care setting, the risk of device-based pathogen transmission increases [29]. In a 2009 study, the mobile phones of 200 intensive care and operating room health care workers were tested, and 94.5% showed some form of bacterial contamination [30]. Although the study does not discuss tablets, the same concerns of bacterial contamination and infection surrounding mobile phones are applicable to tablets.

Presently, Apple recommends using a soft, lint-free cloth for cleaning mobile devices, avoiding liquids, solvents, or spraying cleaners directly onto the device [31]. However, a plain cloth will not remove contagious pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant enterococcus (VRE) from a mobile device [29]. A study by Howell and colleagues [29] compared six different wipes (Sani-Cloth CHG 2%, Trigene, Clorox, Tristel, soap and water, and a plain cloth) and found that the Sani-Cloth CHG (chlorhexidine gluconate 2%/alcohol 70%) wipes were the most effective cleaning agent for tablets, with very low risk to the tablet's functional capabilities or accessories.

Infection Control Protocol

Proper disinfection is an important component to consider as tablets are increasingly integrated into both research studies and patient care. The infection control protocol is reviewed in Multimedia Appendix 3 and provides a list of the required supplies as well as an outline of the steps needed to disinfect tablet devices using CHG 2% wipes.

Results

This article provides three protocols within the multimedia appendices that can be applied to support the configuration, the management, and the maintenance of mobile devices employed in digital health interventions: the Configurator protocol, the Tile protocol, and the infection control protocol.

Discussion

This article addresses the literature gap on tablet protocols used in digital health interventions and describes three protocols supporting tablet configuration, management, and maintenance. The protocols discussed are furnished as generalized instructions or as a foundation for further enhancements, allowing for customization to further optimize tablet adoption. While these protocols can be used to support a single intervention, the resources may be used individually or bundled, at the discretion of investigators or clinicians, depending on the methodological requirements and deployment environment.

The availability and utilization of tablets is advancing the way researchers work, clinicians provide health care, and patients receive health care. However, along with the proliferation of tablets comes the need to advance tablet-focused protocols. The goal of this paper was not to test the effectiveness of Configurator, Tile, or the proposed infection protocol. Rather, we sought to review various options available to augment consistent tablet configuration, management, and maintenance. Further research is necessary to evaluate the feasibility and efficacy of the developed tablet-focused protocols.

Acknowledgments

Funding for this work was provided by the Centers for Disease Control and Prevention (CDC). The authors would like to acknowledge the contributions of Dr. Camilla Harshbarger and Carla Galindo, MPH. The content of this article is solely the responsibility of the authors and does not necessarily reflect the views of the CDC, the companies responsible for the production and distribution of Tile and Configurator, or the authors' employer, RTI International.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Configurator Protocol.

[PDF File (Adobe PDF File), 62KB - resprot_v5i2e136_app1.pdf]

Multimedia Appendix 2

Tile Protocol.

[PDF File (Adobe PDF File), 29KB - resprot_v5i2e136_app2.pdf]

Multimedia Appendix 3

Infection Control Protocol.

[PDF File (Adobe PDF File), 30KB - resprot_v5i2e136_app3.pdf]

References

1. Smith A. U.S. smartphone use in 2015. Chapter one: a portrait of smartphone ownership. Washington, DC: Pew Internet and American Life Project; 2015 Apr 01. URL: http://www.pewinternet.org/files/2015/03/PI_Smartphones_0401151.pdf [accessed 2016-06-12] [WebCite Cache ID 6d8l18Ykz]
2. 2015 HIMSS mobile technology survey: executive summary. Chicago, IL: Healthcare Information and Management Systems Society; 2015 Apr. URL: http://s3.amazonaws.com/rdcms-himss/files/production/public/FileDownloads/2015%20Mobile%20Technology%20Survey%20EXECUTIVE%20SUMMARY%20FINAL%20040215.pdf [accessed 2015-11-18] [WebCite Cache ID 6d8mbggUs]
3. Patient Adoption of mHealth. Danbury, CT: IMS Institute for Healthcare Informatics; 2015 Sep. URL: http://www.imshealth.com/da_DK/thought-leadership/ims-institute/reports/patient-adoption-of-mhealth [accessed 2016-06-12] [WebCite Cache ID 6iCgJZtLc]
4. Claborn KR, Fernandez A, Wray T, Ramsey S. Computer-based HIV adherence promotion interventions: A systematic review. Transl Behav Med 2015 Sep;5(3):294-306. [doi: 10.1007/s13142-015-0317-0] [Medline: 26327935]
5. Bickmore TW, Silliman RA, Nelson K, Cheng DM, Winter M, Henault L, et al. A randomized controlled trial of an automated exercise coach for older adults. J Am Geriatr Soc 2013 Oct;61(10):1676-1683. [doi: 10.1111/jgs.12449] [Medline: 24001030]
6. Kaplan CP, Livaudais-Toman J, Tice JA, Kerlikowske K, Gregorich SE, Pérez-Stable EJ, et al. A randomized, controlled trial to increase discussion of breast cancer in primary care. Cancer Epidemiol Biomarkers Prev 2014 Jul;23(7):1245-1253. [doi: 10.1158/1055-9965.EPI-13-1380] [Medline: 24762560]
7. Burckley E, Tincani M, Guld Fisher A. An iPad-based picture and video activity schedule increases community shopping skills of a young adult with autism spectrum disorder and intellectual disability. Dev Neurorehabil 2015 Apr;18(2):131-136. [doi: 10.3109/17518423.2014.945045] [Medline: 25084013]
8. Dempsey AF, Maertens J, Beaty BL, O'Leary ST. Understanding how different recruitment strategies impact parent engagement with an iPad-based intervention to provide personalized information about adolescent vaccines. J Adolesc Health 2015 May;56(5 Suppl):S7-S13. [doi: 10.1016/j.jadohealth.2014.11.022] [Medline: 25863557]
9. Levine J, Wolf RL, Chinn C, Edelstein BL. MySmileBuddy: an iPad-based interactive program to assess dietary risk for early childhood caries. J Acad Nutr Diet 2012 Oct;112(10):1539-1542. [doi: 10.1016/j.jand.2012.06.010] [Medline: 23017564]
10. Webster R, Gerressu M, Michie S, Estcourt C, Anderson J, Ang CS, MenSS Trial Group. Defining the content of an online sexual health intervention: The menSS website. JMIR Res Protoc 2015 Jul;4(3):e82 [FREE Full text] [doi: 10.2196/resprot.4316] [Medline: 26142304]
11. Breitenstein SM, Gross D. Web-based delivery of a preventive parent training intervention: A feasibility study. J Child Adolesc Psychiatr Nurs 2013 May;26(2):149-157. [doi: 10.1111/jcap.12031] [Medline: 23607827]
12. Farmer A, Toms C, Hardinge M, Williams V, Rutter H, Tarassenko L. Self-management support using an Internet-linked tablet computer (the EDGE platform)-based intervention in chronic obstructive pulmonary disease: Protocol for the EDGE-COPD randomised controlled trial. BMJ Open 2014 Jan;4(1):e004437. [doi: 10.1136/bmjopen-2013-004437] [Medline: 24401729]
13. Cook DJ, Moradkhani A, Douglas KS, Prinsen SK, Fischer EN, Schroeder DR. Patient education self-management during surgical recovery: Combining mobile (iPad) and a content management system. Telemed J E Health 2014 Apr;20(4):312-317. [doi: 10.1089/tmj.2013.0219] [Medline: 24443928]
14. Apple Configurator 2.: Mac App Store URL: https://itunes.apple.com/us/app/apple-configurator-2/id1037126344?mt=12 [accessed 2015-11-19] [WebCite Cache ID 6d9myVgh0]
15. Rivers K. ClassThink. 2013 May 27. What is Apple Configurator? URL: http://www.classthink.com/2013/05/27/apple-configurator-or-mdm/ [accessed 2015-11-23] [WebCite Cache ID 6dGN6T4bi]
16. iOS Deployment Reference. Cupertino, CA: Apple Inc; 2015. URL: https://manuals.info.apple.com/MANUALS/1000/MA1685/en_US/ios_deployment_reference.pdf [accessed 2015-11-19] [WebCite Cache ID 6d9n1Rufm]
17. iOS Education Deployment Overview. Cupertino, CA: Apple Inc; 2014 Sep. URL: http://www.apple.com/education/docs/EDU_deployment_overview_en_sept14.pdf [accessed 2015-11-19] [WebCite Cache ID 6d9n407Vz]
18. Paczkowski J. All Things D. 2013 Feb 28. Apple's iTunes U hits one billion downloads URL: http://allthingsd.com/20130228/apples-itunes-u-hits-1-billion-downloads/ [accessed 2015-11-19] [WebCite Cache ID 6d9nAr4rf]
19. Etherington D. TechCrunch. 2013 Feb 28. Apple has sold over 8M iPads direct to education worldwide, with more than 1B iTunes U downloads URL: http://techcrunch.com/2013/02/28/apple-has-sold-over-8m-ipads-direct-to-education-worldwide-with-more-than-1b-itunes-u-downloads/ [accessed 2015-11-19] [WebCite Cache ID 6d9opZ2Yy]

20. Tile: Dimensions. San Mateo, CA: Tile Inc; 2015. URL: https://support.thetileapp.com/hc/en-us/articles/200591648-Dimensions [accessed 2015-11-19] [WebCite Cache ID 6d9qad1O7]
21. Tile: device compatability. San Mateo, CA: Tile Inc; 2015. URL: https://www.thetileapp.com/compatibility [accessed 2015-11-19] [WebCite Cache ID 6d9qnV3e6]
22. Tile: Welcome to Tile. San Mateo, CA: Tile Inc; 2015. URL: https://www.thetileapp.com/got-my-tile [accessed 2015-11-19] [WebCite Cache ID 6d9r5CBEN]
23. Tile: Frequently Asked Questions. San Mateo, CA: Tile Inc; 2015. URL: https://www.thetileapp.com/faq [accessed 2015-11-19] [WebCite Cache ID 6d9r802ki]
24. The Tile App. San Mateo, CA: Tile Inc; 2015. URL: https://www.thetileapp.com/ [accessed 2015-11-19] [WebCite Cache ID 6d9rAtaxi]
25. Tile: How it Works. San Mateo, CA: Tile Inc; 2015. URL: https://www.thetileapp.com/how-it-works [accessed 2015-11-19] [WebCite Cache ID 6d9rDPrVc]
26. Tile: Community Find. We're All Looking Out for Each Other. San Mateo, CA: Tile Inc; 2015. URL: https://www.thetileapp.com/community-find [accessed 2015-11-19] [WebCite Cache ID 6d9rG3pb2]
27. Tile: Introducing Shared Tiles. San Mateo, CA: Tile Inc; 2015. URL: https://www.thetileapp.com/blog/shared-tiles-feature [accessed 2015-11-19] [WebCite Cache ID 6d9rmSdaP]
28. Tile: Sharing a Tile. San Mateo, CA: Tile Inc; 2015. URL: https://support.thetileapp.com/hc/en-us/articles/205332837-Sharing-a-Tile [accessed 2015-11-19] [WebCite Cache ID 6d9rdM6HQ]
29. Howell V, Thoppil A, Mariyaselvam M, Jones R, Young H, Sharma S, et al. Disinfecting the ipad: evaluating effective methods. J Hosp Infect 2014 Jun;87(2):77-83. [doi: 10.1016/j.jhin.2014.01.012] [Medline: 24746231]
30. Ulger F, Esen S, Dilek A, Yanik K, Gunaydin M, Leblebicioglu H. Are we aware how contaminated our mobile phones with nosocomial pathogens? Ann Clin Microbiol Antimicrob 2009 Mar;8(7). [doi: 10.1186/1476-0711-8-7] [Medline: 19267892]
31. Apple Support: How to Clean Apple Products. Cupertino, CA: Apple Inc; 2015. URL: https://support.apple.com/en-us/ht204172 [accessed 2015-11-18] [WebCite Cache ID 6d8ibEtNd]

Abbreviations

BLE: Bluetooth low energy
CDC: Centers for Disease Control and Prevention
CHG: chlorhexidine gluconate
GPS: Global Positioning System
iOS: iPhone operating system
mHealth: mobile health
MRSA: methicillin-resistant *Staphylococcus aureus*
OS: operating system
PPE: personal protective equipment
USB: universal serial bus
VRE: vancomycin-resistant enterococcus
Wi-Fi: wireless local area network technology

Edited by G Eysenbach; submitted 01.12.15; peer-reviewed by R Shaw, B Green; comments to author 30.01.16; revised version received 26.02.16; accepted 31.03.16; published 27.06.16.

Please cite as:
Furberg RD, Ortiz AM, Zulkiewicz BA, Hudson JP, Taylor OM, Lewis MA
Supporting Tablet Configuration, Tracking, and Infection Control Practices in Digital Health Interventions: Study Protocol
JMIR Res Protoc 2016;5(2):e136
URL: http://www.researchprotocols.org/2016/2/e136/
doi:10.2196/resprot.5400
PMID:27350013

Original Paper

A Cross-Sectional Study on Attitudes to and Understanding of Risk of Acquisition of HIV: Design, Methods and Participant Characteristics

Janey Sewell[1], BNurs; Andrew Speakman[1], PhD; Andrew N Phillips[1], PhD; Fiona C Lampe[1], PhD; Ada Miltz[1], MSc; Richard Gilson[1], MBBS; David Asboe[2], MBBS; Nneka Nwokolo[2], MBBS; Christopher Scott[2], MBBS; Sara Day[2], MBBS; Martin Fisher[3†], MBBS; Amanda Clarke[3], MBBS; Jane Anderson[4], MBBS; Rebecca O'Connell[5], MBBS; Vanessa Apea[5], MBBS; Rageshri Dhairyawan[6], MBBS; Mark Gompels[7], MBBS; Paymaneh Farazmand[8], MBBS; Sris Allan[9], MBBS; Susan Mann[10], MBBS; Jyoti Dhar[11], MBBS; Alan Tang[12], MBBS; S Tariq Sadiq[13], MBBS; Stephen Taylor[14], MBBS; Simon Collins[15]; Lorraine Sherr[1], PhD; Graham Hart[1], PhD; Anne M Johnson[1], MBBS; Alec Miners[16], PhD; Jonathan Elford[17], PhD; Alison Rodger[1], MBBS

[1]Institute of Epidemiology and Health Care, Research Department of Infection and Population Health, UCL, London, United Kingdom
[2]Chelsea and Westminster NHS Foundation Trust, London, United Kingdom
[3]Brighton and Sussex University Hospitals NHS Trust, Brighton, United Kingdom
[4]Homerton University Hospital NHS Foundation Trust, London, United Kingdom
[5]Barts Health NHS Trust, London, United Kingdom
[6]Barking, Havering and Redbridge University Hospitals NHS Trust, London, United Kingdom
[7]North Bristol NHS Trust, Bristol, United Kingdom
[8]Calderdale and Huddersfield NHS Foundation Trust, Huddersfield, United Kingdom
[9]Coventry and Warwickshire Partnership NHS Trust, Coventry, United Kingdom
[10]King's College Hospital NHS Foundation Trust, London, United Kingdom
[11]Staffordshire and Stoke on Trent Partnership NHS Trust, Leicester, United Kingdom
[12]Royal Berkshire NHS Foundation Trust, Reading, United Kingdom
[13]Institute for Infection and Immunity, St George's, University of London, London, United Kingdom
[14]Heart of England NHS Foundation Trust, Birmingham, United Kingdom
[15]HIV i-Base, London, United Kingdom
[16]London School of Hygiene and Tropical Medicine, London, United Kingdom
[17]City University London, London, United Kingdom
[†]deceased

Corresponding Author:
Janey Sewell, BNurs
Institute of Epidemiology and Health Care
Research Department of Infection and Population Health
UCL
Royal Free Hospital,
London, NW3 2PF
United Kingdom
Phone: 44 20 7794 0500
Fax: 44 20 3108 2079
Email: j.sewell@ucl.ac.uk

Abstract

Background: The annual number of new human immunodeficiency virus (HIV) infections in the United Kingdom among men who have sex with men (MSM) has risen, and remains high among heterosexuals. Increasing HIV transmission among MSM is consistent with evidence of ongoing sexual risk behavior in this group, and targeted prevention strategies are needed for those at risk of acquiring HIV.

Objective: The Attitudes to and Understanding of Risk of Acquisition of HIV (AURAH) study was designed to collect information on HIV negative adults at risk of HIV infection in the United Kingdom, based on the following parameters: physical and mental health, lifestyle, patterns of sexual behaviour, and attitudes to sexual risk.

Methods: Cross-sectional questionnaire study of HIV negative or undiagnosed sexual health clinic attendees in the United Kingdom from 2013-2014.

Results: Of 2630 participants in the AURAH study, 2064 (78%) were in the key subgroups of interest; 580 were black Africans (325 females and 255 males) and 1484 were MSM, with 27 participants belonging to both categories.

Conclusions: The results from AURAH will be a significant resource to understand the attitudes and sexual behaviour of those at risk of acquiring HIV within the United Kingdom. AURAH will inform future prevention efforts and targeted health promotion initiatives in the HIV negative population.

(JMIR Res Protoc 2016;5(2):e58) doi:10.2196/resprot.4873

KEYWORDS

HIV infection; HIV negative; HIV undiagnosed; HIV transmission; HIV testing; men who have sex with men; black Africans; sexual risk behaviour; health and wellbeing.

Introduction

Background

During 2013, 6000 people were newly diagnosed with human immunodeficiency virus (HIV) in the United Kingdom (UK), and the estimated number of people living with HIV in the United Kingdom was 107,800 by the end of that year [1]. Despite no reported rise in the annual number of new diagnoses since 2005 in the overall UK population, there is evidence that HIV incidence is increasing among men who have sex with men (MSM) [2], and in 2013 the number of new HIV diagnoses remained high in black African men and women, who constitute two thirds of all heterosexuals living with HIV in the United Kingdom [1].

An estimated 38,700 black Africans were living with HIV in the United Kingdom in 2013. Despite a decline in new diagnoses among people born in sub-Saharan Africa, black Africans form the second largest social group affected by HIV in the United Kingdom [1]. The combination of high prevalence of HIV in the black African community [1] and the high proportion of undiagnosed infection as a consequence of late presentation [3] means that the potential for onward transmission of HIV is high within this community. Although the proportion of late HIV diagnoses has declined overall in the last decade, late diagnosis was highest among black African men (69%) and women (57%) in 2013 [1]. Research into factors that affect attitudes towards HIV and access to HIV testing and services is important. The African Health and Sex survey in 2013-2014 demonstrated a low level of awareness on HIV prevalence within black African people living in the United Kingdom, and poor knowledge of HIV treatment and care availability [4], which may impact on access to HIV testing services and sexual risk behavior. Furthermore, previous research into late presentation among black Africans demonstrated that HIV awareness did not translate into individual perception of risk or use of services, and that major structural barriers such as stigma, confidentiality and migration issues inhibit the uptake of HIV testing and services [5].

Evidence of ongoing, and likely increasing, HIV transmission among MSM [1,2,6-8] is consistent with evidence of ongoing sexual risk behavior in this group and there is evidence that the prevalence of condomless sex among MSM in the United Kingdom may have changed over the last few decades. In the United Kingdom the extensive research carried out in community-venue and clinic based studies [6,8-15] has indicated an increase in the prevalence of condomless anal intercourse among MSM during the late 1990s and early 2000s, coincident with the widespread introduction and use of successful combination antiretroviral treatment (ART) for HIV in developed countries. Research from the United States [16,17] and Europe [18-21] also describes an increase in diagnoses of other sexually transmitted infections (STI) over this time. It has been suggested that the increase in condomless sex that occurred in the late 1990s in the Western world may now have plateaued [9], and recent data from NATSAL-3 (a large representative survey of sexual behavior in the UK general population from September 2010 to August 2012) described no change in prevalence of condomless sex or risk perception in MSM over the last decade [22]. However, the incidence of HIV in MSM in the United Kingdom appears to have increased [2]. This increase cannot be explained by changes in HIV testing alone [23], but would be compatible with a modest ongoing increase in condomless sex among MSM [2].

Sexual transmission risk arises as a result of perceptions and behaviors which may differ depending on the HIV serostatus of individuals. Strategies aimed at reduction of HIV transmission need to address differences in both HIV positive and negative individuals' perceptions, choices, and behaviors [24]. As increasing evidence shows that a suppressed HIV viral load (VL) greatly reduces the risk of onward transmission of HIV to sexual partners [25,26], it is important to consider how this research might have reached and influenced HIV negative persons in different ways to those who are HIV positive. The PARTNER study recently presented transmission estimates of zero in heterosexuals and MSM for condomless sex where the positive partner was on suppressive ART, albeit with a high upper confidence limit in MSM [27]. These data may also influence HIV negative persons in understanding and perception of HIV transmission risks. Research from the United States suggests that HIV negative MSM perceive a number of sexual practices with HIV positive MSM on ART as less risky than

with HIV positive MSM who are not on ART [24]. Furthermore, evidence from Australia has demonstrated that a behavioral response by MSM to the risk of HIV transmission has evolved considerably over time [28]. Risk reduction strategies such as using HIV VL to negotiate condom use [28], serosorting (using HIV status as a decision-making point in choosing a sexual partner [29,30]), strategic positioning (choosing a different sexual position or practice depending on the serostatus of a partner [31]), negotiated safety (choosing not to use condoms with a primary partner and establishing specific rules for sex outside of the primary relationship [32]), and withdrawal are now commonly used to reduce the risk of transmitting or acquiring HIV during condomless anal intercourse.

Current data from the United Kingdom that inform on these themes from the perspective of HIV negative MSM and black Africans are limited. In particular, information is needed on HIV testing behavior and preferences, patterns of sexual behavior, prevalence of specific types of condomless sex (to capture potential risk reduction strategies), attitudes to condomless sex with individuals of known and unknown HIV status, and associations with factors such as mental/general health, STI history, and alcohol and drug use. Data from the Attitudes to and Understanding of Risk of Acquisition of HIV (AURAH) study will contribute to an understanding of how knowledge of ART and detectable/undetectable VLs among HIV negative individuals may affect attitudes and perceptions which lead to condomless sex with partners of unknown and/or known HIV status in the United Kingdom.

Uptake and frequency of HIV testing among MSM in the United Kingdom remains inadequate (an estimated 25% never tested [2]), as it does in black Africans (an estimated 40% never tested [33]). Therefore, improving efforts to expand testing outside sexual health clinics is a priority, and it is a key recommendation from Public Health England to reduce the burden of undiagnosed HIV in these two groups [1]. The first self-testing HIV kit featuring a Kitemark (a UK product and service quality certification) was released in the United Kingdom in April 2015 [34]. Although the majority of HIV tests are currently conducted in sexual health clinics, emerging evidence suggests that HIV self-testing is highly acceptable to both MSM and black Africans in low and high income settings [35,36]. HIV self-testing may remove some of the barriers around accessing sexual health services that are experienced by black Africans and MSM, and may help to improve access to HIV testing. However, there is a need to assess HIV testing preferences in HIV negative individuals, given the recent expansion of testing options to include HIV self-testing [34], and the need to increase HIV testing in the most at-risk populations in the United Kingdom. Results from the AURAH study will seek to inform on HIV testing preferences and acceptability of HIV testing outside of the traditional sexual health clinic setting.

The AURAH study will allow comparison of HIV negative or undiagnosed MSM and black Africans with HIV positive participants from the Antiretrovirals, Sexual Transmission Risk and Attitudes (ASTRA) study [37], a previous questionnaire study undertaken in 2011-2012 by the same group. The ASTRA study focused on patients with HIV under care within the United Kingdom, and asked many of the same questions as the AURAH about sexual behavior, attitudes, and health and lifestyle factors. The ASTRA study aimed to assess sexual risk behaviors, beliefs about HIV transmission risk, and attitudes towards the use of early ART in this population [37]. Previous studies have illustrated high prevalence rates of depression, anxiety, and drug and alcohol use in MSM [38], whilst black and minority ethnic groups in the UK's general population are also more likely to be diagnosed with mental health problems and experience poor outcomes from treatment than other ethnic groups [39,40]. There is some evidence that depression in MSM is associated with higher levels of condomless sex and higher risk behaviors [41] but there is limited data on mental health and wellbeing, and sexual behavior, among MSM or black Africans in the United Kingdom. Data from the AURAH study will allow insight into these issues. Furthermore, comparison between HIV positive and negative individuals in both MSM and black Africans will help to elucidate the specific effect of HIV and HIV treatments on health, wellbeing, and lifestyle among MSM and black Africans.

This paper describes key aspects underlying the AURAH study, including its rationale, design, methods and response rates. A description of the participant characteristics is also outlined. Details of both response rates and participant characteristics may be of use in the comparison to other studies set in sexual health clinics or outpatient settings, and inform future design and planning of subsequent studies. Further publications will address detailed research questions based on the data collected from the participants in the AURAH study.

Aims and Objectives

The primary aim of the AURAH study was to assess patterns of sexual behavior, and attitudes to sexual risk, among HIV negative adults at risk of HIV infection, and to investigate associations with demographic, socio-economic, health, and lifestyle factors.

Study Objectives

The detailed objectives of the AURAH study were to assess the following in HIV negative (not known to be HIV positive) sexual health clinic attendees:

1. Levels of recent condomless vaginal or anal sex according to demographic groups (sexuality, ethnicity).
2. Among those who have had condomless sex, the distribution of: number of sexual partners, type of partners, knowledge of HIV status of partners, number of times had condomless sex, type of condomless sex, and reasons for not using condom.
3. Among those having condomless sex with partners of positive or unknown HIV serostatus, the prevalence of risk-reduction measures such as seropositioning.
4. The prevalence of psychological and physical symptoms (ie, depression, anxiety) and lifestyle factors (ie, drug and alcohol use), and whether demographic/social factors, psychological and physical symptoms, quality of life, and lifestyle factors are associated with condomless sex.
5. Beliefs regarding the effect of ART in HIV positive individuals, and undetectable VL, on HIV transmission risk

(transmission risk beliefs) and the association of such beliefs with sexual behavior.

6. History of any HIV testing and attitudes to HIV and HIV medications, including awareness of, and any history of, taking post-exposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP).
7. Attitudes towards testing for HIV in different settings (ie, sexual health clinic, general practitioner, community based testing), type of testing (ie, self-sampling, self-testing) and preferred sample type for HIV self-testing (ie, saliva based or finger-prick sample of blood).

Methods

Study Design

AURAH was a cross-sectional self-administered questionnaire study in individuals attending 20 sexual health (Genito-Urinary Medicine) clinics, in 15 clinical centers (National Health Service trusts), across the United Kingdom. The recruitment period was 17 months, commencing June 2013.

Population and Setting

AURAH was conducted among individuals attending sexual health clinics for routine STI and/or HIV testing. The inclusion criteria were as follows: HIV negative (or undiagnosed) subjects aged 18 years or over, attending for routine STI or HIV testing in sexual health clinics. Individuals not known to be HIV positive at the time of recruitment to AURAH, but testing positive on that (or a subsequent) clinic visit were retained in the AURAH sample.

The 20 clinical centers were situated across England, and details of the locations and clinics are listed in the Acknowledgements section. The sites were selected on the understanding that they could provide access to large numbers of HIV negative patients attending clinics for STI screening and HIV testing, including the key demographic *at risk* subgroups in the United Kingdom (MSM and black Africans). Most clinics were able to provide a mixed demographic of study participants but a few clinics recruited large numbers of one type only. For example, the 56 Dean Street clinic and the Mortimer Market Center recruited a large number of MSM to the study. Similarly, there were other centers that provided a larger number of black African male and female participants for the study, including the Greenway Center, City of Coventry Healthcare Center, and the Sydenham Center, Barking, London.

Sample Size

The AURAH study adopted a recruitment target of 2000 total sample size, of which 1000 would be MSM, and 1000 heterosexuals, of whom 600 would be black African. After calculations the study would have sufficient power to:

1. Ascertain the proportion of individuals who report that they have had condomless sex in the past 3 months with a partner of unknown or positive HIV status and that one of the reasons for this was "*I knew there was a risk of acquiring HIV but I am not so concerned about having the disease that it made me want to have sex using a condom*." This would be calculated as a proportion of all study participants and as a proportion of all participants reporting condomless sex.
2. Ascertain the proportion of individuals who report that they have had condomless sex in the past 3 months with a positive partner who gave a reason as "*I thought the risks of catching HIV were low because my partner was taking anti-retroviral therapy.*"
3. Compare the prevalence of depression on the Patient Health Questionnaire (PHQ-9) scale [42] between HIV positive and HIV negative individuals, separately for HIV negative MSM, heterosexual men and women, and black African men and women.

For objectives (1) and (2), the planned sample size of 1000 MSM would allow estimation of a 5% prevalence (95% CI 3.65-6.35), a 10% prevalence (95% CI 8.65-11.35), and a 20% prevalence (95% CI 17.52-22.48). For the planned sample size of approximately 300 black African men (or women), prevalences of 5% (95% CI 2.55-7.45), 10% (95% CI 6.60-13.4) and 20% (95% CI 15.47-24.53) would be estimated.

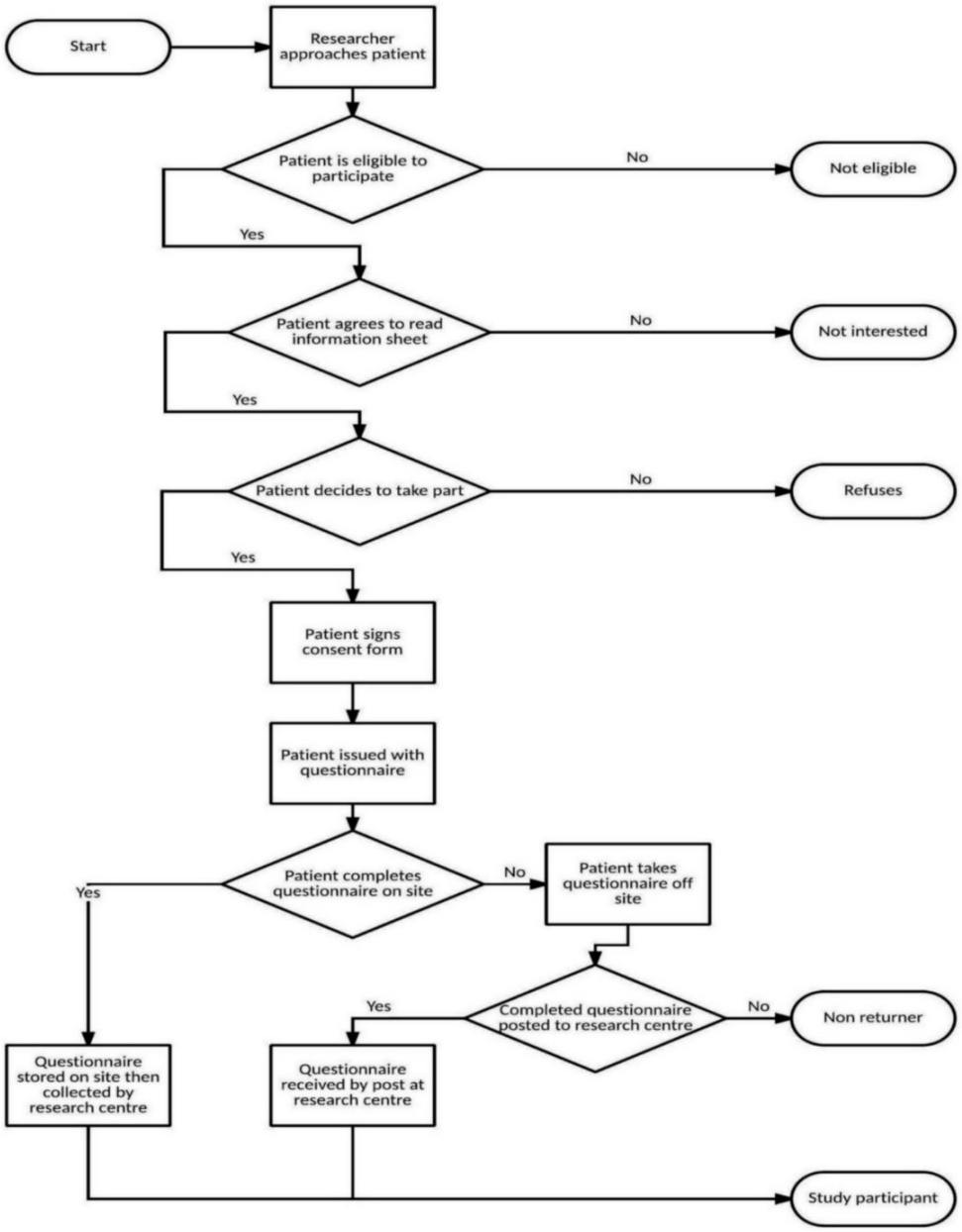
For objective (3), given approximately 2250 MSM, 200 black African men and 450 black African women in the ASTRA sample [37], and assuming a prevalence of depressive symptoms of 25% among each of these groups, the study would have 80% power (with 5% 2-sided significance level) and absolute difference in prevalence of 4.5% for MSM, 10.0% for black African men, and 8.5% for black African women.

Recruitment

Recruitment to the study took place between June 2013 and November 2014 during different periods at the 20 clinics. A flowchart of recruitment procedures for the study is included (see Figure 1).

Initial recruitment in the clinics was not restricted. Each site identified specific clinics each week, at which subjects were recruited, aiming to ensure a reasonably representative study population. Consecutive subjects attending each clinic were identified, approached, and invited to take part. It was more feasible to initially recruit in this unrestricted way, and the intent was to modify recruitment strategy as necessary to recruit a sufficient number of MSM and black Africans. After 6 months of unrestricted recruiting, targeted recruitment was implemented across all study sites, and clinic staff were asked to identify and recruit only MSM or those of black ethnicity. Once the recruitment target of 1000 MSM had been met (11 months into the study), 15 clinics were asked to concentrate on recruiting only those known to have specifically black African ethnicity before finishing recruitment, and the 5 sites that had recruited the largest number of MSM continued with sole recruitment of MSM to increase the power for some research questions.

Figure 1. Flowchart of AURAH clinic recruitment.



Consent

All subjects who were invited to participate were given an information sheet about the study. Those who agreed to complete the questionnaire were asked to sign a consent form. The form included an optional section for participants to provide details to allow contact regarding study reminders and, in the future, to invite participants to join future research studies. Participants were informed that consent to be contacted was optional but that those who provided contact details would be entered into a monthly draw offering a prize of £100 of shopping vouchers. Participants who agreed to be contacted were asked for their preferred contact details (email address and mobile phone number for short message service contact). The consent form noted that participants' contact details would only be used for these purposes and would be held securely at the study management center as part of the study records, but would be deleted after a period of two years. During the consent process, it was reiterated that the study was for HIV negative or undiagnosed individuals only. Participants were told that the questionnaire would take between 15 and 30 minutes to complete and were given an envelope to seal it in, so that their answers were not available to clinic staff. There was an option for participants to take the questionnaire off-site for completion, and postage paid envelopes were provided to return the questionnaire directly to the study management center if required. The option of taking the questionnaire off-site was aimed at including participants who did not have time to complete the questionnaire before they were called for their clinic appointment. Participants were encouraged to complete the questionnaire on-site if possible, to minimize non-return of questionnaires by consented participants.

Clinical Data

Participants were made aware that their participation included supplying information on the results of any STI or HIV tests that took place in the clinic on the day they were enrolled in to the study. The study log was used to record whether any HIV or STI tests were undertaken and to record the result of any HIV test (negative/positive) performed on the day of enrolment.

Data Processing

Completed questionnaires were collected in the clinic and transferred regularly to the study management center. Questionnaires were identified only by a unique study number. Participants were instructed not to write their name or clinic number on the questionnaire to maintain their anonymity.

Details of all clinic attendees approached for the study were collected in a study log maintained securely and updated daily at each clinical site. The study log contained study numbers, clinic identifiers and details of consent status for all patients invited to participate in the study, whether or not HIV and other STI tests had been done, and the result of any HIV test. Contact details of participants were also entered in the log if participants consented to being contacted about future research. Selected information from the study log at each clinical center was securely transferred on a regular basis to the study management center. At the study management center, contact details for future research were kept securely and separately from the questionnaire data.

Regular reports were sent from the study management center to each site during the recruitment period, detailing trends and overall progress in recruitment for each of the study sites. In addition, regular checks were made on the completeness and quality of the study log and its concordance with received questionnaires.

Questionnaires received at the management center were digitized by an external data processing contractor. Each paper questionnaire was checked for legibility, digitally scanned, and the resulting images were used as the source for two manual data entry rounds with subsequent quality checking. The completed data entry batches delivered by the contractor were checked for accuracy at the study management center by fully examining a 5% sample.

The original pseudonymized study datasets, including scanned images of the questionnaires, were stored at the study management center in encrypted digital form. They were preserved by being duplicated and stored on managed servers with regular backup and professional administration. The original paper questionnaires were stored securely in locked cabinets. The study datasets will be made freely and readily available to the research community after a suitable interval in a form that ensures that participant anonymity and confidentiality is maintained.

Study Questionnaire

The questionnaire was based on the design of the ASTRA study questionnaire, a cross sectional study that took place among HIV positive participants attending outpatient HIV clinics across the United Kingdom in 2011-2012 [37] that aimed to include a representative sample of outpatients attending for care at each center. The AURAH study questionnaire was adapted to capture relevant information from HIV negative participants. An initial questionnaire design was printed in A5 booklet format and piloted at one study site in June 2013, using the recruitment procedures described above. Following feedback from participants and research staff, minor revisions were made to the final questionnaire, the patient information sheet, the consent form, and an insert was designed to attain further information on preferences for HIV testing. These changes were submitted as amendments for ethical approval and were incorporated into the final version employed during the main recruitment period, which commenced in July 2013.

The final questionnaire consisted of a printed A5 booklet, with versions for men (24-page questionnaire) and women (20-page questionnaire). The pilot study indicated that the questionnaire took roughly 20-25 minutes to complete. The questionnaire sought detailed information on the following factors:

1. *Demographic and social factors*: including gender, age or year of birth, ethnicity, education, employment, housing, financial status, sexuality, relationship status (whether in long-term partnership and HIV-status of partner), country of birth, and number of children.
2. *Health and well-being*: including psychological and physical symptoms (modified version of Memorial Symptom Assessment Scale Short-Form [43,44]), depression (PHQ-9 [42]), anxiety (Generalized Anxiety Disorder 7 [45]), health-related quality of life (EuroQoL-3L [46]), and social support (modified version of the Duke-UNC Functional Social Support Questionnaire [47]).
3. *Health and relevant medical history*: including any major medical conditions, recently diagnosed STIs, symptoms of STIs, diagnosed hepatitis B and C, treatment for depression, treatment for other mental health problems, pregnancy status for women, and whether circumcised for men.
4. *HIV-related information*: including HIV status (participants reporting HIV positive status on the questionnaire were excluded from the study), history of any HIV tests, beliefs about transmission risk in relation to ART and undetectable VL, knowledge and history of use of PEP and PrEP, and attitudes towards HIV self-testing and clinic based tests.
5. *Lifestyle factors*: including cigarette smoking status, usual alcohol intake, evidence of alcohol dependency (the CAGE questionnaire [48]), recent use of recreational drugs (with details), and recent use of injecting drugs.
6. *Sexual lifestyle*: MSM participants were asked about disclosure of their sexuality to others and involvement in the gay social scene.
7. *Sexual activity*: sexual activity (vaginal or anal sex) during the previous 3 months was ascertained separately for (i) men having sex with women, (ii) men having sex with men, and (iii) women having sex with men. For those participants who reported condomless sex in the past 3 months, there were questions on number of partners, type of partners (long-term or other), attitudes to the risk of HIV infection, and knowledge of the HIV status of partners. There were additional questions on the number and type of partners if the participant reported condomless sex with people known

to be HIV positive. All participants were also asked about the use of the Internet to find sexual partners, different sex practices and group sex, attitudes towards disclosure of HIV status to sexual partners and negotiation of condom use, their total number of new sexual partners in the past year, and preferred information sources (if any) about safer sex.

8. *HIV testing preferences*: participants were asked to rank different ways of testing for HIV. Ranking from least liked to most appealing on a scale of 1-4, the options were (i) in a sexual health clinic, (ii) general practitioner, (iii) self-sampling, and (iv) self-testing. Participants were also asked to indicate a preference for saliva or blood based self-testing options.

Ethics Statement

The research protocol and all versions of the study documents for the AURAH study (information sheet, consent form, questionnaires and insert) were approved by the designated Research Ethics Committees (REC) (National Research Ethics Service committee London-Hampstead, ref: 13/LO/0246). Based on these documents, the study subsequently received permission for clinical research at all participating National Health Service (NHS) sites from local Research & Development (R&D). The REC (NRES committee London-Hampstead) further approved the protocol and study documents for the AURAH2 study in December 2014 (REC ref: 14/LO/1881) and subsequent permission by local R&D for clinical research at the three NHS clinic sites in March 2015.

Study Management

The study was managed on a day-to-day basis by a core group of five staff at the study management center: the HIV Epidemiology and Biostatistics Group, Research Department of Infection and Population Health, Royal Free Campus, University College London.

An advisory group was also established at the start of the study to provide guidance and support. The advisory group consisted of representatives from University College London, HIV i-Base, the London School of Hygiene and Tropical Medicine and City University London.

Results

Over the 17-month study period a total of 4393 eligible patients were approached and asked to participate in this study. Of those approached, 3340 (76.03%) gave consent to take part in the study. The number of completed questionnaires finally collected was 2630 and thus the response rate was 59.87% (2630/4393) of eligible patients approached, and 78.74% (2630/3340) of those who gave consent. The majority of respondents (1432/2630, 54.44%) agreed to provide their contact details for participation in future research.

Eighteen of the 20 participating clinics were able to provide estimates of the number of outpatients seen in all clinical sessions over the same period, and the numbers of these in the key groups (MSM and black Africans). More than 288,090 patients were found to have attended these 18 clinics at some point during the respective recruitment periods. Of the combined total attending the clinics, it was estimated that approximately 7.6% were black African and 13.6% were MSM. Table 1 shows the patient population (recruited to AURAH) and response rates for the 20 clinical centers.

Characteristics of Those Recruited

The mean age (of the 2630 participants who supplied details) at the time of questionnaire completion was 32 years (SD 10, range 18-80 years). Overall, 1954 (74.30%) participants were men and 676 (25.70%) were women. Of the 1939 male participants whose sexuality was known, 1484 (76.53%) self-classified as MSM and 455 (23.47%) as heterosexual. Of the 1484 MSM participants, 965 (65.03%) agreed to provide their contact details for participation in future research, whereas only 36.92% (168/455) of heterosexual males and 43.20% (292/676) of females agreed to provide these details.

In terms of ethnic origin, 1505 of the 2630 (57.22%) participants self-classified as white, 580 participants (22.05%) as black African ethnicity, 249 (9.47%) as other black ethnicity, 264 (10.04%) as other ethnicity, and ethnic status was missing for 32 (1.22%). Of 548 people of black African ethnicity, 323 (58.9%) were female and 225 (41.1%) were male. Of 250 men of black African ethnicity whose sexuality was known, 30 (12.0%) self-classified as MSM and 220 (88.0%) as heterosexual. Of the 580 participants of black African ethnicity, 213 (36.7%) agreed to provide contact details for participation in future research.

Overall, 2535 of the 3340 consenting participants (75.90%) took an HIV test on the day they were approached in clinic. Of those tested, 18 of 2535 (0.71%) received a positive result that they were unaware of at the time. Of these 18 participants, nine returned completed questionnaires (these are retained in the AURAH sample). All nine of these cases were male, of which five were MSM and four were black heterosexuals. Clinics reported that 2624 of the 3340 consenting (78.56%) also tested for STIs on the day, although information on the nature of each test and the results were not collected for this study.

The characteristics of those recruited at the 20 clinical centers in terms of gender, sexual orientation, relevant ethnic status and testing are detailed in Table 2.

Table 1. Recruitment results for the 20 AURAH study clinical centers, 2013-2014.

Site	Length of study period in days	Individual patients attending during recruitment period	Eligible patients approached	Patients consenting (as % of approached = consent rate)	Patients responding = completed questionnaires received (as % of approached = response rate)
Barking	335	3475	64	59 (92%)	34 (53%)
Barts	31	[a]	16	13 (81%)	11 (69%)
Birmingham	127	[a]	53	49 (92%)	33 (62%)
Brighton	482	13918[c]	243	240 (99%)	227 (93%)
Bristol	312	1021	59	58 (98%)	55 (93%)
Calderdale & Huddersfield	428	13662	92	82 (89%)	73 (79%)
Coventry	337	11218	269[b]	256 (95%)	246 (91%)
Dean Street	473	51882[d]	1384	895 (65%)	604 (44%)
Homerton	300	25312	159	149 (94%)	123 (77%)
John Hunter	450	20236[d]	235	131 (56%)	84 (36%)
Kings	283	15500	305	204 (67%)	168 (55%)
Leicester	84	5173	69	66 (96%)	48 (70%)
Mortimer Market	332	13652[e]	382	370 (97%)	313 (82%)
Newham	320	9203	168	119 (71%)	113 (67%)
Reading	405	14807	82	75 (91%)	75 (91%)
Royal Free	416	33216	137	126 (92%)	101 (74%)
St George's	333	17041	110	90 (82%)	81 (74%)
The London	247	13747	40	35 (88%)	33 (83%)
WLCSH	463	19094[d]	462	270 (58%)	164 (35%)
Whipps Cross	314	5933	64	53 (83%)	44 (69%)
TOTALS	-	288090	4393	3340 (76%)	2630 (60%)

[a]Clinic unable to supply data on total clinic attendance

[b]Clinic was unable to supply data about those declining to participate – value derived from 95% consent rate estimated by the clinic

[c]Covers 75% of the recruitment period only

[d]Covers 90% of the recruitment period only

[e]Covers 55% of the recruitment period only

Table 2.

Site label	Men (as % of questionnaires received)	MSM (as % of questionnaires received)	Black African men (as % of questionnaires received)	Women (as % of questionnaires received)	Black African women (as % of questionnaires received)	Tested for HIV on the day (as % of consenting)	STI test on the day (as % of consenting)
Barking	25 (74%)	8 (24%)	16 (47%)	9 (26%)	9 (26%)	43 (73%)	49 (83%)
Barts	11 (100%)	11 (100%)	0 (0%)	0 (0%)	0 (0%)	13 (100%)	13 (100%)
Birmingham	11 (33%)	7 (21%)	0 (0%)	22 (67%)	3 (9%)	40 (82%)	49 (100%)
Brighton	207 (91%)	197 (87%)	5 (2%)	20 (9%)	9 (4%)	170 (71%)	185 (77%)
Bristol	51 (93%)	44 (80%)	2 (4%)	4 (7%)	3 (5%)	55 (95%)	38 (66%)
Calderdale & Huddersfield	55 (75%)	47 (64%)	6 (8%)	18 (25%)	11 (15%)	69 (84%)	71 (87%)
Coventry	104 (42%)	34 (14%)	57 (23%)	142 (58%)	105 (43%)	124 (48%)	161 (63%)
Dean Street	585 (97%)	528 (87%)	14 (2%)	19 (3%)	7 (1%)	762 (85%)	618 (69%)
Homerton	70 (57%)	37 (30%)	8 (7%)	53 (43%)	19 (15%)	88 (59%)	122 (82%)
John Hunter	69 (82%)	49 (58%)	4 (5%)	15 (18%)	1 (1%)	94 (72%)	98 (75%)
Kings	65 (39%)	31 (18%)	13 (8%)	103 (61%)	25 (15%)	136 (67%)	164 (80%)
Leicester	14 (30%)	8 (17%)	2 (4%)	34 (71%)	11 (23%)	50 (76%)	54 (82%)
Mortimer Market	303 (97%)	266 (85%)	28 (9%)	10 (3%)	7 (2%)	323 (87%)	328 (89%)
Newham	61 (54%)	7 (6%)	50 (44%)	52 (46%)	41 (36%)	98 (82%)	113 (95%)
Reading	50 (67%)	35 (47%)	8 (11%)	25 (33%)	16 (21%)	64 (85%)	68 (91%)
Royal Free	41 (41%)	29 (29%)	6 (6%)	60 (59%)	16 (16%)	98 (78%)	116 (92%)
St George's	56 (69%)	36 (44%)	10 (12%)	25 (31%)	7 (9%)	65 (72%)	82 (91%)
The London	17 (52%)	10 (30%)	5 (15%)	16 (48%)	14 (42%)	26 (74%)	35 (100%)
WLCSH	134 (82%)	92 (56%)	7 (4%)	30 (18%)	3 (2%)	169 (63%)	210 (78%)
Whipps Cross	25 (57%)	8 (18%)	14 (32%)	19 (43%)	18 (41%)	48 (91%)	50 (94%)
TOTALS	1954 (74%)	1484 (56%)	255 (10%)	676 (26%)	325 (12%)	2535 (76%)	2624 (79%)

Discussion

The AURAH study recruited 2630 participants from 20 UK sexual health clinics during 2013-2014. The initial rate for consent (2630/3340, 78.74%) was relatively high in this study, and the overall response rate (questionnaires received) was 59.87% (2630/4393) of eligible patients approached. However, there was considerable variation between the clinics in the response rate achieved (ranging from 35% to 93%). The difference in response rates between the clinics could be due to a number of reasons. When researchers at the sites with low response rates were asked about potential barriers to participation they noted education and literacy levels, level of English fluency, and the perceived amount of time that the study questionnaire would take to complete, among clinic attendees at their sites. It was felt that the monthly prize draw had not had a significant effect as an incentive to participate but potentially a smaller cash sum might have, however the study did not seek ethical approval for this due to time restraints.

The intention of this study was also to recruit large numbers within the key demographic sub-groups most affected by HIV in the United Kingdom, namely MSM and black African men and women. The study succeeded in this aim, and there were 2034 individuals in these groups of interest: 1484 MSM participants and 580 black African participants, with 30 individuals (1.47%) falling into both of these categories.

It is difficult to compare the overall study response rate with other studies of HIV negative MSM, as many Internet or venue-based studies have no records of numbers not agreeing to participate, and therefore response rate cannot be calculated. Our response rate is comparable with other surveys taking place outside the clinical context that have investigated sexual behavior (70% [49]; 65% [50]), and with the previous ASTRA study on HIV positive patients whose response rate was 64% [37]. Many of the 1746 non-responding eligible patients were those who directly refused to participate (1036/1746, 59.34%). However, the remaining 710 were consenting participants who took a questionnaire away but did not return it (710/1746, 40.66% of non-responders). Although the option of taking a questionnaire off-site for completion was intended to maximize participation, some of the non-response in this study can be attributed to factors impacting upon questionnaire completion and postage after the questionnaires had been taken away from the study site. For example, lack of time or continued motivation

to complete and post the questionnaire. However, overall the consent rate was slightly lower than in the comparable ASTRA study and this may reflect the differences between the respective clinic populations in terms of potential ongoing engagement with care, and familiarity with the clinic research staff among those attending HIV and general sexual health clinics.

The average age of AURAH study participants was 32 years and, as expected, this was much younger than the average (45 years) of the ASTRA (HIV diagnosed) study participants [37]. The lower mean age for AURAH is consistent with the study's intention to sample from large numbers of currently HIV negative but *at risk* individuals, who could be expected to be younger than the HIV positive population.

The study population was not a random sample of those attending the clinics, as targeted recruitment was implemented after 6 months of recruitment. It should be noted that the target number for MSM recruitment (1000) was exceeded and that the target was reached early in the study. Recruitment was continued because it was desirable to increase power for some research questions. The number of black Africans recruited was 548, however this took a long time to achieve and required selective recruitment in 15 centers. A similar pattern of relative difficulty of recruitment in these two respective populations was observed in the ASTRA study (on HIV diagnosed individuals) [37] where it was found that MSM were over-represented in its sample in relation to the national HIV positive population, and conversely black Africans were under-represented. However, the relative difficulty of recruitment in AURAH may also be a reflection of the different proportions within the populations attending the sexual health clinics, with the overall proportion of MSM (13.6%) being almost double the proportion of black Africans (7.6%).

The number of study participants diagnosed as HIV positive in-clinic during this study was 18 (0.71%, 95% CI 0.38-1.04, of 2535 consenting and tested). The selective nature of our sampling means this is not a meaningful prevalence estimate but, as might be expected in those attending sexual health clinics, this is very much higher than the general UK population HIV estimate for undiagnosed HIV of 0.07% [1]. However, it should be noted that in those identifying as MSM, there were 5 HIV positive cases out of 1484 (0.34%, 95% CI 0.04-0.63) in this study, which is a relatively low value when compared with the estimated 0.94% for the prevalence of undiagnosed HIV in the UK MSM population as a whole [1]. This could reflect the fact that MSM who regularly attend STI clinics are likely to test more frequently for HIV than MSM in the United Kingdom overall.

Conclusions

In summary, the AURAH study includes a substantive but selective sample of those considered to be at risk of being infected with HIV in the United Kingdom. AURAH will give insights into the relationships between socio-demographic factors, physical and psychological symptoms, lifestyle factors, health-related quality of life, and sexual behavior in this population.

The results of the AURAH study will be relevant for understanding the process of HIV transmission within the United Kingdom, and for targeting of national prevention efforts. The data from AURAH will contribute to understanding the social, psychological and health-related factors that are linked to high risk sexual and HIV-testing behaviors, and therefore to ongoing transmission of HIV in the two most *at risk* groups of people in the United Kingdom.

Acknowledgments

We would like to thank all the study participants for their time and effort. We gratefully acknowledge the 20 participating sites and the contributions and efforts of the following at each site: *Barking* - Sydenham Center, Barking, Havering and Redbridge University Hospitals NHS Trust, London (Dr Sharmin Obeyesekera); *Barts* - Barts Sexual Health Center, Barts Health NHS Trust, London (John Saunders); *Birmingham* - Birmingham Heartlands Hospital, Heart of England NHS Foundation Trust (Gerry Gilleran, Cathy Stretton); *Brighton* - Claude Nicol Center, Brighton and Sussex University Hospitals NHS Trust (Nicky Perry, Elaney Youssef, Celia Richardson, Louise Kerr, Mark Roche, David Stacey, Sarah Kirk); *Bristol* - Brecon Unit, North Bristol NHS Trust (Louise Jennings, Caroline Holder, Katie-Anne Baker); *Calderdale & Huddersfield* - Princess Royal Community Health Center, Calderdale and Huddersfield NHS Foundation Trust (Matthew Robinson, Dr Emma Street); *Coventry* - City of Coventry Healthcare Center, Coventry and Warwickshire Partnership NHS Trust (Abayomi Shomoye); *Dean Street* - 56 Dean Street, Chelsea and Westminster Hospital NHS Foundation Trust, London (Ali Ogilvy); *Homerton* - Clifden Center, Homerton University Hospital NHS Foundation Trust, London (Sfiso Mguni, Rebecca Clark, Cynthia Sajani, Veronica Espa); *John Hunter* - John Hunter Clinic, Chelsea and Westminster Hospital NHS Foundation Trust, London (Ali Ogilvy, Sarah Ladd); *Kings* - King's College Hospital NHS Foundation Trust, London (Jonathan Syred, Lisa Hamza, Lucy Campbell, Emily Wandolo, Janagan Alagarajah); *Leicester* - Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust (Linda Mashonganyika, Sally Batham); *Mortimer Market* - The Mortimer Market Center, Central and North West London NHS Foundation Trust, London (Rita Trombin, Ana Milinkovic, Clare Oakland); *Newham* - Greenway Center, Newham Hospital, Barts Health NHS Trust, London (Nyasha Makoka); *Reading* - Florey Unit, Royal Berkshire NHS Foundation Trust, Reading (Ruth Wilson, Elizabeth Green, Sheila O'Connor, Sarah Kempster, Katie Keating-Fedders); *Royal Free* - Marlborough Clinic, Royal Free Hospital NHS Foundation Trust, London (Nicola Tyrrell, Jemima Rogers, Silvia Belmondo, Manjit Sohal); *St George's* - Courtyard Clinic, St George's Healthcare NHS Trust, London (Wendy Majewska, Anne Patterson, Olanike Okolo, David Cox, Mariam Tarik, Charlotte Jackson, Jeanette Honigsbaum, Clare Boggon, Simone Ghosh, Bernard Kelly, Renee Aroney); *The London* - Ambrose King Center, The London Hospital, Barts Health NHS Trust, London (James Hand, Nyasha Makoka); *WLCSH* - West London Center

for Sexual Health, Chelsea and Westminster Hospital NHS Foundation Trust, London (Ali Ogilvy); *Whipps Cross* - Whipps Cross Hospital, Barts Health NHS Trust, London (Monica Lascar, Nyasha Makoka, Elias Phiri, Zandile Maseko); the CAPRA grant Advisory Board: Nick Partridge; Kay Orton; Anthony Nardone; Ann Sullivan.

Authors' Contributions

Design and data collection: JS, AS, AP, FL, RG, DA, NN, CS, SD, MF, AC, JA, R O'C, ML, VA, RD, MG, PF, SA, SM, JD, AT, DI, TS, ST, LS, GH, SC, AJ, AM, JE, AR. Analysis and interpretation: JS, AS, AP, FL, AR. Drafting the manuscript: JS, AS, AP, FL, AR.

Conflicts of Interest

AJ is the Governor of the Wellcome Trust.

Funding and support: The AURAH study presents independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research funding scheme (PGfAR RP-PG-0608-10142). The AURAH Study Group acknowledges the support of the NIHR, through the Comprehensive Clinical Research Network. The views expressed in this presentation are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

References

1. Public Health England. Gov.UK. London; 2015. HIV in the United Kingdom: 2014 report URL: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/401662/2014_PHE_HIV_annual_report_draft_Final_07-01-2015.pdf http://www.webcitation.org/6ZZkdjDWT [accessed 2015-02-01] [WebCite Cache ID 6ZZkdjDWT]
2. Phillips AN, Cambiano V, Nakagawa F, Brown AE, Lampe F, Rodger A, et al. Increased HIV incidence in men who have sex with men despite high levels of ART-induced viral suppression: analysis of an extensively documented epidemic. PLoS One 2013;8(2):e55312 [FREE Full text] [doi: 10.1371/journal.pone.0055312] [Medline: 23457467]
3. Burns FM, Fakoya AO, Copas AJ, French PD. Africans in London continue to present with advanced HIV disease in the era of highly active antiretroviral therapy. AIDS 2001 Dec 7;15(18):2453-2455. [Medline: 11774832]
4. Bourne A, Reid D, Weatherburn P. Sigma Research. London: Sigma Research, London School of Hygiene & Tropical Medicine; 2014. African health & sex survey 2013-2014 URL: http://www.sigmaresearch.org.uk/files/report2014c.pdf http://www.webcitation.org/6cE6LaqUz [accessed 2015-10-12] [WebCite Cache ID 6cE6LaqUz]
5. Burns FM, Imrie JY, Nazroo J, Johnson AM, Fenton KA. Why the(y) wait? Key informant understandings of factors contributing to late presentation and poor utilization of HIV health and social care services by African migrants in Britain. AIDS Care 2007 Jan;19(1):102-108. [doi: 10.1080/09540120600908440] [Medline: 17129864]
6. Fisher M, Pao D, Brown AE, Sudarshi D, Gill ON, Cane P, et al. Determinants of HIV-1 transmission in men who have sex with men: a combined clinical, epidemiological and phylogenetic approach. AIDS 2010 Jul 17;24(11):1739-1747. [doi: 10.1097/QAD.0b013e32833ac9e6] [Medline: 20588173]
7. Likatavicius G, Klavs I, Devaux I, Alix J, Nardone A. An increase in newly diagnosed HIV cases reported among men who have sex with men in Europe, 2000-6: implications for a European public health strategy. Sex Transm Infect 2008 Nov;84(6):499-505. [doi: 10.1136/sti.2008.031419] [Medline: 19028955]
8. Mercer CH, Fenton KA, Copas AJ, Wellings K, Erens B, McManus S, et al. Increasing prevalence of male homosexual partnerships and practices in Britain 1990-2000: evidence from national probability surveys. AIDS 2004 Jul 2;18(10):1453-1458. [Medline: 15199322]
9. Elford J, Bolding G, Davis M, Sherr L, Hart G. Trends in sexual behaviour among London homosexual men 1998-2003: implications for HIV prevention and sexual health promotion. Sex Transm Infect 2004 Dec;80(6):451-454 [FREE Full text] [doi: 10.1136/sti.2004.010785] [Medline: 15572612]
10. Dodds JP, Mercey DE, Parry JV, Johnson AM. Increasing risk behaviour and high levels of undiagnosed HIV infection in a community sample of homosexual men. Sex Transm Infect 2004 Jun;80(3):236-240 [FREE Full text] [Medline: 15170012]
11. Hart GJ, Williamson LM. Increase in HIV sexual risk behaviour in homosexual men in Scotland, 1996-2002: prevention failure? Sex Transm Infect 2005 Oct;81(5):367-372 [FREE Full text] [doi: 10.1136/sti.2004.013995] [Medline: 16199733]
12. Elford J. Changing patterns of sexual behaviour in the era of highly active antiretroviral therapy. Curr Opin Infect Dis 2006 Feb;19(1):26-32. [Medline: 16374214]
13. Dodds JP, Johnson AM, Parry JV, Mercey DE. A tale of three cities: persisting high HIV prevalence, risk behaviour and undiagnosed infection in community samples of men who have sex with men. Sex Transm Infect 2007 Aug;83(5):392-396 [FREE Full text] [doi: 10.1136/sti.2006.021782] [Medline: 17472978]
14. Hart GJ, Elford J. Sexual risk behaviour of men who have sex with men: emerging patterns and new challenges. Curr Opin Infect Dis 2010 Feb;23(1):39-44. [doi: 10.1097/QCO.0b013e328334feb1] [Medline: 19949328]
15. Savage EJ, Marsh K, Duffell S, Ison CA, Zaman A, Hughes G. Rapid increase in gonorrhoea and syphilis diagnoses in England in 2011. Euro Surveill 2012;17(29) [FREE Full text] [Medline: 22835469]

16. Chen SY, Gibson S, Katz MH, Klausner JD, Dilley JW, Schwarcz SK, et al. Continuing increases in sexual risk behavior and sexually transmitted diseases among men who have sex with men: San Francisco, Calif, 1999-2001, USA. Am J Public Health 2002 Sep;92(9):1387-1388. [Medline: 12197957]
17. Crepaz N, Marks G, Liau A, Mullins MM, Aupont LW, Marshall KJ, HIV/AIDS Prevention Research Synthesis (PRS) Team. Prevalence of unprotected anal intercourse among HIV-diagnosed MSM in the United States: a meta-analysis. AIDS 2009 Aug 24;23(13):1617-1629. [doi: 10.1097/QAD.0b013e32832effae] [Medline: 19584704]
18. Stolte IG, Dukers NH, Geskus RB, Coutinho RA, de Wit JB. Homosexual men change to risky sex when perceiving less threat of HIV/AIDS since availability of highly active antiretroviral therapy: a longitudinal study. AIDS 2004 Jan 23;18(2):303-309. [Medline: 15075549]
19. Bezemer D, de Wolf F, Boerlijst MC, van Sighem A, Hollingsworth TD, Prins M, et al. A resurgent HIV-1 epidemic among men who have sex with men in the era of potent antiretroviral therapy. AIDS 2008 May 31;22(9):1071-1077. [doi: 10.1097/QAD.0b013e3282fd167c] [Medline: 18520351]
20. Stolte IG, Dukers NH, de Wit JB, Fennema JS, Coutinho RA. Increase in sexually transmitted infections among homosexual men in Amsterdam in relation to HAART. Sex Transm Infect 2001 Jun;77(3):184-186 [FREE Full text] [Medline: 11402225]
21. Urbanus AT, van de Laar TJ, Stolte IG, Schinkel J, Heijman T, Coutinho RA, et al. Hepatitis C virus infections among HIV-infected men who have sex with men: an expanding epidemic. AIDS 2009 Jul 31;23(12):F1-F7. [doi: 10.1097/QAD.0b013e32832e5631] [Medline: 19542864]
22. Mercer C, Prah P, Tanton C, Nardone A, Clifton S, Sonnenberg P, et al. How has sexual risk behaviour & perception changed among men-who-have-sex-with-men (MSM) in Britain since 2000? Evidence from national probability surveys. 2014 Presented at: Presentation Abstract from Public Health England Annual Conference; 2014; London URL: https://www.phe-events.org.uk/hpa/frontend/reg/absViewDocumentFE.csp%3FdocumentID%3D6954
23. Sullivan PS, Hamouda O, Delpech V, Geduld JE, Prejean J, Semaille C, Annecy MSM Epidemiology Study Group. Reemergence of the HIV epidemic among men who have sex with men in North America, Western Europe, and Australia, 1996-2005. Ann Epidemiol 2009 Jun;19(6):423-431. [doi: 10.1016/j.annepidem.2009.03.004] [Medline: 19460672]
24. Suarez T, Kauth MR. Assessing basic HIV transmission risks and the contextual factors associated with HIV risk behavior in men who have sex with men. J Clin Psychol 2001 May;57(5):655-669. [Medline: 11304705]
25. Vernazza P, Hirschel B, Bernasconi E, Flepp M. Les personnes séropositives ne souffrant d'aucune autre MST et suivant un traitment antirétroviral efficace ne transmettent pas le VIH par voie sexuelle. Bulletin des médecins suisses 2008;89(5):165-169.
26. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, HPTN 052 Study Team. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 2011 Aug 11;365(6):493-505 [FREE Full text] [doi: 10.1056/NEJMoa1105243] [Medline: 21767103]
27. Rodger A, Bruun T, Cambiano V, Vernazza P, Estrada V, Lunzen J, et al. HIV transmission risk through condomless sex if HIV+ partner on suppressive ART: PARTNER Study. 2014 Presented at: 21st CROI; 3-6 March 2014; Boston URL: http://www.croiwebcasts.org/console/player/22072,
28. Prestage G, Mao L, Kippax S, Jin F, Hurley M, Grulich A, et al. Use of viral load to negotiate condom use among gay men in Sydney, Australia. AIDS Behav 2009 Aug;13(4):645-651. [doi: 10.1007/s10461-009-9527-0] [Medline: 19199021]
29. Suarez TP, Kelly JA, Pinkerton SD, Stevenson YL, Hayat M, Smith MD, et al. Influence of a partner's HIV serostatus, use of highly active antiretroviral therapy, and viral load on perceptions of sexual risk behavior in a community sample of men who have sex with men. J Acquir Immune Defic Syndr 2001 Dec 15;28(5):471-477. [Medline: 11744837]
30. Jin F, Prestage GP, Templeton DJ, Poynten IM, Donovan B, Zablotska I, et al. The impact of HIV seroadaptive behaviors on sexually transmissible infections in HIV-negative homosexual men in Sydney, Australia. Sex Transm Dis 2012 Mar;39(3):191-194 [FREE Full text] [doi: 10.1097/OLQ.0b013e3182401a2f] [Medline: 22337105]
31. Van de Ven P, Kippax S, Crawford J, Rawstorne P, Prestage G, Grulich A, et al. In a minority of gay men, sexual risk practice indicates strategic positioning for perceived risk reduction rather than unbridled sex. AIDS Care 2002 Aug;14(4):471-480. [doi: 10.1080/09540120208629666] [Medline: 12204150]
32. Kippax S, Crawford J, Davis M, Rodden P, Dowsett G. Sustaining safe sex: a longitudinal study of a sample of homosexual men. AIDS 1993 Feb;7(2):257-263. [Medline: 8466689]
33. Hickson F, Owuor J, Weatherburn P, Reid D, Hammond G, Jessup J. Sigma Research. London: Sigma Research; 2009 Dec. Bass Line 2008-09: Assessing the sexual health needs of African people in England URL: http://www.sigmaresearch.org.uk/files/report2009h.pdf http://www.webcitation.org/6cENJS7g9 [accessed 2015-10-12] [WebCite Cache ID 6cENJS7g9]
34. Smitha M. BBC News. 2015. HIV home test kit goes on sale in UK URL: http://www.bbc.co.uk/news/health-3245319227 http://www.webcitation.org/6ZZgweQ01 [accessed 2015-05-15] [WebCite Cache ID 6ZZgweQ01]
35. Pant Pai N, Sharma J, Shivkumar S, Pillay S, Vadnais C, Joseph L, et al. Supervised and unsupervised self-testing for HIV in high- and low-risk populations: a systematic review. PLoS Med 2013;10(4):e1001414 [FREE Full text] [doi: 10.1371/journal.pmed.1001414] [Medline: 23565066]
36. Krause J, Subklew-Sehume F, Kenyon C, Colebunders R. Acceptability of HIV self-testing: a systematic literature review. BMC Public Health 2013;13:735 [FREE Full text] [doi: 10.1186/1471-2458-13-735] [Medline: 23924387]

37. Speakman A, Rodger A, Phillips AN, Gilson R, Johnson M, Fisher M, et al. The 'Antiretrovirals, Sexual Transmission Risk and Attitudes' (ASTRA) study. Design, methods and participant characteristics. PLoS One 2013;8(10):e77230 [FREE Full text] [doi: 10.1371/journal.pone.0077230] [Medline: 24143214]
38. Ostrow DG, Silverberg MJ, Cook RL, Chmiel JS, Johnson L, Li X, Multicenter AIDS cohort study. Prospective study of attitudinal and relationship predictors of sexual risk in the multicenter AIDS cohort study. AIDS Behav 2008 Jan;12(1):127-138. [doi: 10.1007/s10461-007-9223-x] [Medline: 17410419]
39. Mental Health Foundation. 2015. Black and Minority Ethnic Communities URL: http://www.mentalhealth.org.uk/help-information/mental-health-a-z/b/bme-communities/http://www.webcitation.org/6cE8zYr9P [accessed 2015-10-12] [WebCite Cache ID 6cE8zYr9P]
40. Sharpley M, Hutchinson G, McKenzie K, Murray RM. Understanding the excess of psychosis among the African-Caribbean population in England. Review of current hypotheses. Br J Psychiatry Suppl 2001 Apr;40:s60-s68. [Medline: 11315227]
41. Miltz A, Rodger A, Sewell J, Speakman A, Phillips P. Depression and sexual behaviour among MSM in the UK. 2015 Presented at: The British Association of Sexual Health and HIV (BASHH) conference; 1-3 June 2015; Glasgow.
42. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001 Sep;16(9):606-613 [FREE Full text] [Medline: 11556941]
43. Vogl D, Rosenfeld B, Breitbart W, Thaler H, Passik S, McDonald M, et al. Symptom prevalence, characteristics, and distress in AIDS outpatients. J Pain Symptom Manage 1999 Oct;18(4):253-262. [Medline: 10534965]
44. Chang VT, Hwang SS, Feuerman M, Kasimis BS, Thaler HT. The memorial symptom assessment scale short form (MSAS-SF). Cancer 2000 Sep 1;89(5):1162-1171. [Medline: 10964347]
45. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006 May 22;166(10):1092-1097. [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
46. EuroQol Group. EuroQol - a new facility for the measurement of health-related quality of life. Health Policy 1990 Dec;16(3):199-208. [Medline: 10109801]
47. Broadhead WE, Gehlbach SH, de Gruy FV, Kaplan BH. The Duke-UNC Functional Social Support Questionnaire. Measurement of social support in family medicine patients. Med Care 1988 Jul;26(7):709-723. [Medline: 3393031]
48. Ewing JA. Detecting alcoholism. The CAGE questionnaire. JAMA 1984 Oct 12;252(14):1905-1907. [Medline: 6471323]
49. Williamson LM, Dodds JP, Mercey DE, Hart GJ, Johnson AM. Sexual risk behaviour and knowledge of HIV status among community samples of gay men in the UK. AIDS 2008 May 31;22(9):1063-1070. [doi: 10.1097/QAD.0b013e3282f8af9b] [Medline: 18520350]
50. Johnson AM, Mercer CH, Erens B, Copas AJ, McManus S, Wellings K, et al. Sexual behaviour in Britain: partnerships, practices, and HIV risk behaviours. Lancet 2001 Dec 1;358(9296):1835-1842. [doi: 10.1016/S0140-6736(01)06883-0] [Medline: 11741621]

Abbreviations

ART: antiretroviral treatment
ASTRA: Antiretrovirals, Sexual Transmission Risk and Attitudes
AURAH: Attitudes to and Understanding of Risk of Acquisition of HIV
HIV: human immunodeficiency virus
MSM: men who have sex with men
NHS: National Health Service
NRES: National Research Ethics Service
PEP: post-exposure prophylaxis
PHQ: Patient Health Questionnaire
PrEP: pre-exposure prophylaxis
R&D: Research and Development
REC: Research Ethics Committee
STI: sexually transmitted infection
UK: United Kingdom
VL: viral load

Edited by G Eysenbach; submitted 28.06.15; peer-reviewed by C Aicken, J Loos; comments to author 09.10.15; revised version received 05.11.15; accepted 29.11.15; published 18.04.16.

Please cite as:
Sewell J, Speakman A, Phillips AN, Lampe FC, Miltz A, Gilson R, Asboe D, Nwokolo N, Scott C, Day S, Fisher M, Clarke A, Anderson J, O'Connell R, Apea V, Dhairyawan R, Gompels M, Farazmand P, Allan S, Mann S, Dhar J, Tang A, Sadiq ST, Taylor S, Collins S, Sherr L, Hart G, Johnson AM, Miners A, Elford J, Rodger A
A Cross-Sectional Study on Attitudes to and Understanding of Risk of Acquisition of HIV: Design, Methods and Participant Characteristics
JMIR Res Protoc 2016;5(2):e58
URL: http://www.researchprotocols.org/2016/2/e58/
doi:10.2196/resprot.4873
PMID:27091769

Protocol

Advancing Migrant Access to Health Services in Europe (AMASE): Protocol for a Cross-sectional Study

Ibidun Fakoya[1], BSc, MSc[‡]; Débora Álvarez-del Arco[2,3], BSc, PhD; Susana Monge[4], MSc, MPH, MD, PhD; Andrew J Copas[1], BA, MSc, PhD; Anne-Francoise Gennotte[5], MD; Alain Volny-Anne[6], BA; Siri Göpel[7], MD; Giota Touloumi[8], MSc, PhD; Maria Prins[9,10], MSc, PhD; Henrique Barros[11], MD, PhD; Cornelia Staehelin[12], MIH, MD; Julia del Amo[2], DTM&H, Dip GUM, MSc, MD, PhD; Fiona M Burns[1,13], MSc, MB ChB, PhD

[1]Centre for Sexual Health and HIV Research, Research Department of Infection and Population Health, University College London, London, United Kingdom

[2]National Centre of Epidemiology, Instituto de Salud Carlos III, Madrid, Spain

[3]Biomedical Research Network on Epidemiology and Public Health (CIBERESP), Faculty of Political Science and Sociology, Universidad Complutense de Madrid, Madrid, Spain

[4]Faculty of Medicine, University of Alcalá, Madrid, Spain

[5]Department of Infectious diseases, CHU Saint-Pierre, Brussels, Belgium

[6]European AIDS Treatment Group, Brussels, Belgium

[7]HIV Centre Frankfurt, Frankfurt, Germany

[8]Department of Hygiene, Epidemiology & Medical Statistics, Medical School, National and Kapodistrian University of Athens, Athens, Greece

[9]Department of Internal Medicine, Division of Infectious Diseases, Academic Medical Centre, Amsterdam, Netherlands

[10]Department of Infectious Diseases, Public Health Service of Amsterdam, Amsterdam, Netherlands

[11]University of Porto Medical School, Institute of Public Health, University of Porto, Porto, Portugal

[12]Department of Infectious Diseases, Bern University Hospital, University of Bern, Bern, Switzerland

[13]Royal Free London NHS Foundation Trust, London, United Kingdom

[‡]on behalf of the aMASE Study Group

Corresponding Author:
Ibidun Fakoya, BSc, MSc
Centre for Sexual Health and HIV Research
Research Department of Infection and Population Health
University College London
Mortimer Market Centre
off Capper Street
London, WC1E 6JB
United Kingdom
Phone: 44 02031082066
Email: Ibidun.fakoya@ucl.ac.uk

Abstract

Background: Migrants form a substantial proportion of the population affected by the human immunodeficiency virus (HIV) epidemic in Europe, yet HIV prevention for this population is hindered by poor understanding of access to care and of postmigration transmission dynamics.

Objective: We present the design and methods of the advancing Migrant Access to health Services in Europe (aMASE) study, the first European cross-cultural study focused on multiple migrant populations. It aims to identify the structural, cultural, and financial barriers to HIV prevention, diagnosis, and treatment and to determine the likely country of HIV acquisition in HIV-positive migrant populations.

Methods: We delivered 2 cross-sectional electronic surveys across 10 countries (Belgium, France, Germany, Greece, Italy, the Netherlands, Portugal, Spain, Switzerland, and United Kingdom). A clinic survey aimed to recruit up to 2000 HIV-positive patients from 57 HIV clinics in 9 countries. A unique study number linked anonymized questionnaire data to clinical records data (viral loads, CD4 cell counts, viral clades, etc). This questionnaire was developed by expert panel consensus and cognitively tested, and a pilot study was carried out in 2 countries. A Web-based community survey (n=1000) reached those living with HIV

but not currently accessing HIV clinics, as well as HIV-negative migrants. It was developed in close collaboration with a community advisory group (CAG) made up of representatives from community organizations in 9 of the participating countries. The CAG played a key role in data collection by promoting the survey to higher-risk migrant groups (sub-Saharan Africans, Latin Americans, men who have sex with men, and people who inject drugs). The questionnaires have considerable content overlap, allowing for comparison. Questions cover ethnicity, migration, immigration status, HIV testing and treatment, health-seeking behavior, sexual risk, and drug use. The electronic questionnaires, which were available in 15 languages, allowed for complex routing, preventing respondents from answering irrelevant questions.

Results: In total, we recruited 2249 participants from 57 HIV clinics as part of the clinic survey and retrieved 1637 complete responses as part of the community survey.

Conclusions: The findings will provide much-needed information for improving HIV prevention interventions and access to services for migrant communities.

(JMIR Res Protoc 2016;5(2):e74) doi:10.2196/resprot.5085

KEYWORDS

migrants; HIV; survey; community mobilization

Introduction

In 2014, with new human immunodeficiency virus (HIV) infections on the decline, the Joint United Nations Programme on HIV/AIDS (UNAIDS) announced the beginning of the end of the AIDS epidemic [1]. Although there are still approximately 35 million people living with HIV worldwide, UNAIDS has set a goal of ending the AIDS epidemic in "every region, every country, in every location, in every population and every community" by 2030 [1]. Reaching this ambitious goal is now possible because of vast improvements in the ability to provide widespread HIV testing and subsequent treatment with antiretroviral therapy. Within Europe, the end of AIDS is dependent on identifying, treating, and preventing onward transmission among an estimated 2.2 million people living with HIV [2], a substantial and disproportionate number of whom are people who were born in another country, that is, migrants. While 9.7% of the European Union (EU)/European Economic Area population were born outside the current borders of their country of residence [3], over a third (35.0 %) of those newly diagnosed with HIV in 2013 were migrants [4]. Approximately 15% of those were people who had migrated from a country with a generalized epidemic, notably sub-Saharan Africa (13%). Smaller proportions of newly diagnosed migrants were from Central and Eastern Europe (5.1%), Latin America and the Caribbean (4.9%), other Western European countries (3.9%), and South and Southeast Asia (2.2%) [4].

Despite the heavy burden of HIV among migrant communities, HIV prevention and treatment for these populations is hindered by a relatively sparse evidence base and the heterogeneity of the populations affected [5]. Migrants are more likely to be exposed to social determinants of ill health (such as poverty, social exclusion, and unemployment), which can result in poor health-seeking behaviors [6]. Other structural factors such as legal and administrative status, together with health care- and community-related barriers, can further prevent migrants from accessing health services, particularly HIV testing [7]. Yet little is known about migrant access to health services, particularly HIV testing, access to treatment, and safer sex practices [8]. Previously it had been assumed that most HIV diagnosed among migrants in Europe was acquired in the country of origin, particularly those born in sub-Saharan Africa. Yet it is unclear whether infections are acquired pre- or postmigration [5]. Although surveillance data show that people living outside their country of birth form a substantial proportion of the population affected by the HIV epidemic in Europe, limited data are available about migrant populations to inform policy and practice for these communities.

Understanding barriers to accessing HIV care and postmigration transmission dynamics will provide policy makers and program managers much-needed evidence for effectively planning HIV prevention programs for migrant communities. Several cross-sectional sexual health and HIV studies have sampled migrant populations, but these were often limited to migrants from 1 region (black Africans in Burns et al [9] or Central and Eastern Europeans in Evans et al [10]) or migrants in 1 country (Dray-Spira et al [11]), and there has not been a collaborative European study to address these research questions jointly. Within the European Network of HIV/AIDS Cohort Studies to Coordinate at European and International Level Clinical Research on HIV/AIDS (EuroCoord), we set up the advancing Migrant Access to health Services in Europe (aMASE) study whose overall aim is to provide the evidence to prevent HIV infection and improve diagnosis and prognosis of migrant populations living with HIV in Europe in order to support policy development at the European level. Specifically, aMASE aims to identify the structural, cultural, and financial barriers to HIV prevention, diagnosis, and treatment and to determine the likely country of HIV acquisition in HIV-positive migrant populations. In this paper, we present the design and methods of the 2 cross-sectional studies that form aMASE and the unique challenges associated with multisite, multidisciplinary, multinational research.

Methods

Study Design

aMASE is formed of 2 cross-sectional, electronic surveys of 2 populations: (1) migrant adults living with HIV and attending HIV services (the clinic survey), and (2) migrant adults living in Europe (the community survey). For the purposes of this study, we define migrants as foreign-born individuals intending

to live in their current country of residence for ≥6 months. Residency was not dependent on formal documentation, and immigration status, while captured within the survey, was not part of the inclusion or exclusion criteria. The clinic survey was delivered using a computer-assisted self-interview (CASI) or computer-assisted personal interview (CAPI) and augmented with clinical data from patient records. The community study was a Web-based survey designed to reach those living with HIV but not currently accessing HIV clinics, as well as HIV-negative migrants.

Clinic Survey

Study Setting and Time Period

The clinic survey was implemented in 57 clinics in 9 countries (Belgium, Germany, Greece, Italy, the Netherlands, Portugal, Spain, Switzerland, and the United Kingdom) between July 2013 and June 2015. Multimedia Appendix 1 lists the clinics' names.

Participants and Eligibility Criteria

Patients were eligible for inclusion in the study if they were (1) HIV-positive, (2) aged ≥18 years, (3) foreign-born and resident in the country of recruitment for ≥6 months, (4) diagnosed within 5 years of the study date, and (5) able to complete, either alone or supported, a CASI in any of the 15 languages available (Amharic, Arabic, Dutch, English, French, German, Greek, Italian, Polish, Portuguese, Russian, Turkish, Tigrinya, Spanish, and Somali). In Switzerland, local eligibility criteria applied (migrants from neighboring Austria, France, Germany, and Italy are excluded due to close linguistic and cultural ties).

Sample Size

The sample size calculation was based on precision and used the standard formula for standard error of a proportion: SE=Sqrt (p*(1–p)/n). In calculating the sample size, the primary outcome measures were health service use (registered with primary care physician) and the proportion of participants with a previous negative HIV test.

Initially we anticipated recruiting 4000 participants (2000 men and 2000 women) from 2 to 5 clinics in each of 7-9 EU countries (creating about 40 clusters). We considered the within-cluster correlation likely to be relatively weak (eg, 0.005), at least for regression analyses, as the average cluster size may potentially have been large (eg, 75-125). Assuming a design effect of 1.5 for the study, the overall effective sample size would have been ~2670. This sample size would have provided good precision for our estimates. Specifically, within each gender group, our outcomes could be estimated to within 3% across Europe and to within around 8% for each country. As recruitment was slower than anticipated, to a large extent due to the decrease in the number of new HIV-positive migrants in Europe [12], we revised this sample size in December 2014.

The revised target sample size calculation was 2000 participants (1000 men and 1000 women) from all clinics. We recruited participants from a minimum of 2 clinics in each of the 9 countries, with each clinic forming a discrete cluster. We estimated this within-cluster correlation also to be relatively weak (eg, 0.005), at least for regression analyses including patient and city characteristics as covariates. As the average cluster size was likely to be smaller than first estimates (eg, 40–60), we assumed a design effect of 1.25 for the study and, hence, an overall effective sample size of ~1600. This revised sample still provides good precision for estimates. Specifically, within each gender group, we will be able to estimate our outcomes to within 3.5% across Europe and to within 10% for each country.

Sampling Strategy

The main inclusion criteria for study sites were a sizable migrant clinic population (sufficient to recruit a minimum of 40 study participants in most sites) and the human resource capacity to conduct the study with minimal additional funding. Eligible patients attending participating clinics within the study period were approached by members of their clinical care team or a recruitment researcher to participate in the clinic survey.

Variables and Questionnaire Development

We formed a working group, made up of international experts and EuroCoord collaborators, to act as an expert panel tasked with reaching consensus on survey instrument development and provide overall supervision of the study. Where possible, we adapted questionnaire items from existing survey instruments. New questions were drafted by the core research team and expert panel members.

We validated the questionnaire using cognitive testing (cognitive aspects of survey methodology approach [13]). It was tested in Spanish (in Spain) and English (in the United Kingdom) on 7 black African and 3 Latin American migrants recruited from community-based HIV service organizations. The finalized patient questionnaire is divided into 3 sections: (1) detailed sociodemographic data and extensive migration history data, (2) sexual and HIV risk behavior, including drug use before and after migration, and (3) service use and experiences of living with HIV, including stigma and discrimination. Questions were tailored to reflect the different health care or ethical approval systems in different countries. For example, respondents completing the survey in Portugal were not asked questions about ethnicity or health care costs. There are 90-92 items included depending on current country of residence, although through skipping and filters some respondents answered as few as 43 questions. Most questions were closed and the survey completion time was between 15 and 50 minutes depending on the language selected. The survey was translated from English into 15 languages (see Participants and Eligibility Criteria above) by a professional translation company. These translations were then checked by a different translation company, who back-translated a portion of the questionnaire into English to ensure quality control.

Participating patients' questionnaires were matched to a clinical data form using a unique study number. The clinical data form contains 20 items, including CD4 cell count and viral load (at diagnosis, at antiretroviral therapy initiation, and the latest available); previous HIV-negative tests and viral clade; AIDS-defining illnesses and coinfections; and treatment initiation. Clinical data were completed electronically.

Ethics

Ethical approval for the aMASE studies was received separately in each participating country (see Table 1).

Pilot Study

We piloted the function and reliability of the CASI and the clinical data form in 3 clinics (2 in London, 1 in Madrid) with 115 patients. The pilot study also tested whether recruitment procedures, study implementation, and data collection, storage, and handling methods were feasible and appropriate. Following feedback about the function of the CASI software from recruitment researchers, we redesigned the survey using new CASI software. To facilitate recruitment, the selection criterion of HIV diagnosis in the previous 3 years was increased to 5 years. Based on the results of the pilot study, the survey questions remained essentially the same; however, we redesigned some items to produce a better user experience.

Study Implementation

The patient questionnaire was administered using tablets, computers, or laptops running Fluidware version 5.0 (SurveyMonkey Canada Inc, Ottawa, ON). Enrollment commenced in participating clinics in July 2013 and was completed in July 2015.

As of August 2015, there were 57 participating clinics in 9 countries: Belgium (n=4), Germany (n=2), Greece (n=8), Italy (n=2), the Netherlands (n=3), Portugal (n=7), Spain (n=18), Switzerland (n=6), and the United Kingdom (n=7).

A study coordinator at the Institute of Health, Carlos III, Spain, was responsible for the overall management of the fieldwork, but in each country a nominated country lead (usually a member of the expert panel) was responsible for collating data across clinics in his or her country. This coordinator actively engaged with all participating centers and country leads to ensure compliance with the study standards, and identified aspects that needed improvement throughout the study period. Where necessary, clinics were supplied with laptops and tablets preloaded with CASI software and instructions for use. Clinics were given a clinic study pack (developed during the pilot study), which detailed the general protocol and maintenance instructions for the CASI devices. Clinic recruiters were able to access an online Web resource with electronic versions of all the required documentation for the study. Incentives were not provided to participants, although some clinics supported travelling costs in the context of their research practices.

Recruitment procedures varied slightly across countries and between clinics, but in general recruitment and consent procedures were as follows.

Eligible patients were identified though clinic databases and their clinical records were flagged. Clinic numbers of eligible patients were noted next to precoded unique study numbers on an enrollment log. Eligible patients were then approached by either members of their clinical care team or a recruitment researcher and provided with a patient information sheet and the opportunity to ask questions. Patients who declined to participate had their age, ethnicity or nationality, and gender noted on the enrollment log. Those who agreed to participate were asked to complete the CASI/CAPI on site. In most countries, ethical approval for obtaining informed consent through a tick box in the questionnaire was given; however, in Belgium, Switzerland, Greece, and Germany local ethical approval standards required separate consent forms.

Enrollment logs were stored in a locked cabinet; electronic versions of the completed forms were returned to the study coordinator on a monthly basis. Survey data were either captured and then stored directly on a central secure database operated by FluidSurveys (online questionnaire) or stored on the device's hard drive until they were transferred to a secure network in Madrid (offline questionnaire).

Statistical Analysis

We will explore barriers to accessing health care by using the primary outcomes measures: access to a primary care physician and a previous negative HIV test.

Participating clinics are not necessarily representative of the number of clinics within countries or, indeed, the migrants living with HIV within those countries. For these reasons, the overall sample prevalence of our primary outcome measures, pooled across countries and clinics, may not be informative. We shall give it emphasis in our results only if the prevalence across countries is similar and otherwise focus on the prevalence in each country. We anticipate that associations with the primary outcomes, for example their association with age, will be broadly comparable across countries. However, if associations differ substantially between countries, then we shall investigate this heterogeneity and report an overall measure of association if we judge this to be meaningful. Furthermore, as men and women are expected to have different barriers to accessing care, we will analyze them separately. We will analyze individuals who identify as transsexual separately if numbers are sufficient. We will conduct analyses separately by region of birth if associations differ substantially by region, and we may conduct separate analyses for men who do and do not have sex with men if associations differ substantially between these 2 groups of participants.

Our interest is in associations between the primary outcome measures and each of the following factors: age, gender, region of birth, sexual orientation, immigration status, and age at migration or diagnosis. We will first describe these associations through cross-tabulations. To acknowledge the clustering of participants, we shall analyze associations using hierarchical random effects logistic regression, with a random effect for clinics nested within countries, analyzing factors individually and then jointly in a multiple regression model. We will report associations as odds ratios with 95% CIs.

Within EuroCoord, a group of experts has been established to develop and evaluate a reliable algorithm to determine probable country of infection. The algorithm will incorporate demographic (eg, gender, race or ethnicity, age) and clinical data (eg, CD4 counts, HIV RNA levels, clinical stage according to the US Centers for Disease Control and Prevention) and will be evaluated in simulation studies and in cohorts with well-estimated seroconversion dates. The algorithm will be further elaborated using data from the questionnaire (eg,

migration and HIV testing history, sexual partners pre- and postmigration). CD4 cell counts and viral loads for the study participants will be extracted from the clinical records. Methods for calculating a proxy date for seroconversion rely on clinical parameters with very little, if any, behavioral information informing the model [14]. Our analysis will draw on more detailed information than what is available in routinely collected surveillance data, thus allowing for a more nuanced approach in determining probable country of infection. We will use imputation methods to account for missing data in clinical records. Further details on the methodology used to develop, verify, and apply the algorithm will be published separately.

Response Rates

The age, nationality or ethnicity, and gender of all patients approached to participate in the study were noted on a clinic log. We will analyze these data to assess whether those who agreed to participate are significantly different from those who declined.

Community Survey

Study Setting and Time Period

We designed the aMASE community survey to complement the clinic survey and capture data on all migrants regardless of their HIV status. The community survey was available through Web browsers between April 2014 and July 2015.

Participants and Eligibility Criteria

All migrants living in the World Health Organization European area (52 countries) aged ≥18 years, irrespective of their HIV status or current country of residence, were eligible to participate in the aMASE community survey.

Sample Size

No sampling frame for migrants in Europe exists, so we used a convenience sampling strategy. The main outcome measures on which we based our sample size estimates were registration with a primary care physician and ever having tested for HIV. The community survey aimed to recruit 1000 migrants, which allows for estimates of outcomes by gender to within 5%. This sample size also provided 80% power to detect a difference of 6% in 1 of the key outcomes (assuming an overall outcome prevalence of 50%) compared with service users (in the clinic study), or smaller differences for less prevalent outcomes.

Sampling Strategy

We actively promoted the survey from June 2014 to May 2015 using social marketing and community participatory methods in 9 countries: Belgium, France, Germany, Greece, Italy, the Netherlands, Portugal, Spain, and the United Kingdom. We targeted some of these countries for active promotion because they were also involved in clinic recruitment. An ongoing survey with African migrants in Switzerland precluded active promotion in that country, and we selected France because it has a large migrant population. A community advisory group (CAG), a group of individuals working for local community-based organizations that provide services to migrant communities or oversee pan-European migrant or HIV networks, was integral to the sampling strategy. The aMASE expert panel selected CAG members with representation from all countries involved in active promotion of the survey. CAG members were contracted to deliver outreach meetings, with the aim of promoting the survey to other organizations within their country. In turn, these organizations promoted the survey to other organizations and their service users and cascaded the study promotion in a method similar to snowball sampling.

Variables and Questionnaire Development

We developed the community survey instrument using an iterative community participatory approach involving the CAG and the expert panel. The expert panel was responsible for the survey content and design and all technical aspects of administering the questionnaire. The CAG ensured that the survey content was relevant to migrant communities within Europe and provided a “real-world” critique of the survey items. The CAG was able to highlight culturally insensitive questions (eg, increasing the number of available gender categories from 2 to 6) or request items that will provide findings that can be quickly translated into policy and practice recommendations (eg, knowledge about access to free condoms). After 4 iterations of the survey development process, we tested the survey CASI for programming inconsistences. The survey was then translated into 14 languages (identical to the clinic survey with the exclusion of Tigrinya) by a professional translation company. These translations were then checked by members of the CAG or colleagues fluent in the available languages. Almost three-quarters (66/93) of the items in the clinic survey patient questionnaire are replicated in the community questionnaire to allow for comparison between the 2 samples. The remaining items include country-specific questions and topics of interest to the CAG and cover health service use in the country of origin or residence; home testing or sampling for HIV and other infections; mental health; and social determinants of health (eg, housing).

Table 1. Ethical approval for the advancing Migrant Access to health Services in Europe (aMASE) study in each country.

Country	Committee	Number
Belgium (Antwerp)	Institute of Tropical Medicine, Institutional Review Board	911/13
Belgium (Brussels)	Comité local d'éthique hospitalier, Centre Hospitalier Universitaire Saint-Pierre	B076201215754
Belgium (Gent)	Universitair Ziekenhuis Gent, Commissie voor Medische Ethiek	B076201215754
Belgium (Liège)	Comité local d'éthique Hospitalo-Facultaire Universitaire de Liège	B707201318791
Germany (Bonn)	Rheinische Friedrich-Wilhelms-Universität Bonn, Medizinische Fakultat Ethik-Kommission	008/14
Greece	National and Kapodistrian University of Athens Institutional Review Board	6/3/2013[a](# 6313)
Italy	Istituto Nazionale per le Malattie Infettive "Lazzoro Spallanzani"	22/02/2013[a]
The Netherlands	Universiteit van Amsterdam	2013_137#C20131038
Portugal	Centro Hospitalar de São João, EPE	28/8/2013[a]
Portugal	Hospital Prof. Doutor Fernando Fonseca, EPE	31/8/2013[a]
Portugal	Centro Hospitalar Lisboa Norte, EPE	9/10/2013[a]
Portugal	Centro Hospitalar Lisboa Central, EPE	11/7/2013[a]
Portugal	Centro Hospitalar de Setúbal, EPE	21/1/2015[a]
Portugal	Comissão Nacional de Proteção de Dados (Portuguese Data Protection Authority), EPE	14/10/2014[a]
Spain	Comité de Ética de la Investigación y del bienestar animal, Instituto de Salud Carlos III	CEI PI 01_2012-v2
Switzerland	Kantonale Ethikkommission Bern	024/13
United Kingdom	London-Bentham Research Ethics Committee	11/LO/1600

[a]Date of approval letter.

Ethics

Ethical approval was obtained from the London Bentham Research Ethics Committee (11/LO/1600). Additional approvals were obtained in all countries also undertaking the clinic survey.

Pilot Study

We carried out a short pilot study with CAG and expert panel members (38 respondents) who completed the survey in a language of their choice. The CASI was revised to improve the quality of translations and make them more suitable for our target population.

Study Implementation

EuroCoord's primary community partner, the European AIDS Treatment Group (a European network of nationally based volunteer activists), employed a project coordinator to assist the research team in community engagement and chair the CAG. CAG members were provided with a suite of promotional materials including posters, business cards, postcards, and electronic banner advertisements, which were available from the aMASE website. Over 18,000 small media items (3100 business cards; 15,600 postcards) were printed and disseminated to community-based organizations across Europe. The CAG also used additional promotional and recruiting strategies: for example, 12 organizations (in France, the Netherlands, Greece, and the United Kingdom) allowed participants to complete the survey on laptops or other devices on their premises.

We contacted a further 243 community-based organizations identified through a mapping exercise and asked them to promote the survey on their websites and social media pages (eg, Facebook, Twitter). Approximately 300 webpages and apps also carried banner advertisements or links for the community survey, including PlanetRomeo, Grindr, Poz Traveler, and EasyExpat.

All community survey promotional materials referenced the aMASE website, where potential participants were able to select 1 of the 14 survey languages on the initial landing page [15]. Participant information sheets about the community survey were available in all 14 survey languages. Further information with in-depth details about both cross-sectional surveys was available in Dutch, English, French, German, Italian, Portuguese, and Spanish. Individuals who wished to participate in the study clicked through to a separate website, where the survey is hosted by FluidSurveys. All participants provided within-survey tick box consent. Survey data were captured and then stored directly on a central secure database operated by FluidSurveys.

Statistical Analysis

Statistical analysis will follow similar methods to those outlined for the clinic survey. Direct comparisons between the clinic population and the community population in the primary outcome measures may identify additional barriers to accessing health care, especially HIV testing, treatment, and care. Secondary outcomes explored in the community survey include

chronic illness and infection other than HIV; access to condoms; access to needle exchange programs; and experiences of racism and homophobia.

Funding

The aMASE study is part of Work Package 14 of EuroCoord, which is funded by the EU's Seventh Framework Programme for research, technological development, and demonstration (under grant no. 260694). The community mobilization and engagement project was sponsored by Gilead Sciences Europe Ltd. Multimedia Appendix 2 lists other funding sources that contributed to the aMASE study.

Results

By the end of July 2015, recruitment for both clinic and community surveys had concluded. In total, we recruited 2249 participants from 57 HIV clinics as part of the clinic survey and we retrieved 1637 complete responses as part of the community survey. Following data cleaning and analysis, we submitted initial findings and results for peer review in April 2015.

Discussion

The aMASE study is the first multinational study to specifically sample migrants from across the globe living in Europe. The data gathered will provide not only valuable information about the barriers faced by migrants when trying to access HIV testing, prevention, treatment, and care, but also data about postmigration HIV acquisition. A literature review estimated that postmigration HIV acquisition among migrants from countries with a generalized epidemic range from 2% in Switzerland to 62% among migrant black Caribbean men who have sex with men in Europe [5]. The aMASE study will be the first to estimate postmigration HIV acquisition among European migrants living in Europe, as well as those from endemic regions. These data will provide policy makers and HIV program managers with a sound evidence base on which to develop HIV testing and prevention initiatives for these populations.

There were limitations to this study. Clinics from 9 countries were involved in data collection for the clinic study, and we recruited participants from 57 clinics. We selected these countries in part because they have large migrant populations (including those from Latin America and sub-Saharan Africa); in 2011, the United Kingdom, Germany, Spain, and Italy were the destination countries of 60.3% of all immigrants to EU member states [3]. The selected countries also contain the largest numbers of nonnationals (not including migrants who acquired citizenship in their current country of residence) living in the EU: Germany (7.7 million persons), Spain (5.1 million), Italy (4.4 million), the United Kingdom (4.9 million), and France (3.8 million) [3]. In Greece and Belgium, migrants make up a substantial proportion of the population (7.8% and 11.2%, respectively). Migrants living in France are a notable omission from our clinic sample; however, agreements are in place that will enable us to compare aMASE data with data from similar studies conducted in France.

Participating clinics were not chosen at random and may not be representative of clinics throughout their country of location. Nonetheless, the majority of sites are located in conurbations with large migrant populations, and the clinic sample is likely to be broadly representative of migrants accessing health care within each participating country. Our clinic (and community) sample is unlikely to be representative of the European migrant population as a whole in terms of such factors as country of residence, region of birth, gender, and sexual orientation. Consequently, a naive analysis of the overall data might underestimate or overestimate the strength of associations with our outcomes in the total population, but we believe our strategy of investigating heterogeneity of associations between countries and conducting analyses separately within subgroups determined by these factors, where necessary, will limit the bias in our findings.

Finally, the long recruitment period for both the clinic and the community surveys may present a challenge to interpreting the data. Migrant populations within Europe can fluctuate and change rapidly. Those recruited at the beginning of the study may represent a different migration cohort with differing barriers to accessing care from those recruited toward the end.

The aMASE clinic survey links self-reported data provided by participants with data from clinical records, which is vital for the accurate estimation of probable country of HIV acquisition. Furthermore, the clinical data will also allow us to estimate factors associated with late diagnosis, recent seroconversion, and hepatitis coinfection, thereby providing insight into the barriers and facilitators to earlier testing and access to care for study populations that have rarely been the sole focus of HIV research in Europe. The clinic survey will also augment the evidence base with regard to distal determinants of health such as poverty and hunger, as well as the sexual health needs of migrants living with HIV.

The aMASE Study as a whole also provides a useful model for community participatory methods in research. The community survey was developed using iterative methods with close communication between the research team, a panel of experienced epidemiologists, statisticians, and HIV clinicians, and an advisory group made up of community activists. Actively involving the CAG in survey development was time consuming and presented logistical challenges for the research team (eg, language barriers, inability to schedule some meetings during the working day). Those issues notwithstanding, the benefits in adopting this strategy were clear shortly after the 2014 European parliamentary elections, in which parties that campaigned on an anti-immigration platform performed successfully. Without the endorsement and support of the CAG, a study about the health of migrants in Europe may have been viewed with suspicion across the political spectrum. A careful balancing act between active promotion on migrant-friendly media and low-level promotion on mainstream media has enabled the CAG and the research team to promote the study without experiencing a significant backlash from anti-immigrant organizations.

Community stakeholders will be actively involved in guiding analysis and disseminating the results of both surveys. A detailed publication agreement has been drafted that gives community-based organizations access to community survey data relevant to their communities. In addition, CAG members

will assist in creating a policy advocacy information sheet based on the results of both surveys. This information sheet will provide community-based organizations with key local and pan-European health policy advocacy points designed to improve access to health care for people living with diagnosed HIV. Involving community stakeholders in this final stage of the study increases the likelihood that the findings from this study will be incorporated into policy and practice across Europe. The results of this study will improve the understanding of postmigration transmission dynamics and the barriers to health care for migrants in Europe.

Acknowledgments

This project has received funding from the European Union's Seventh Framework Programme for research, technological development, and demonstration under EuroCoord grant agreement no. 260694.

Ibidun Fakoya is funded by a Doctoral Research Fellowship from the National Institute for Health Research, United Kingdom. The views expressed in this paper are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health.

This study would not be possible without the entire Work Package 14 collaboration. The aMASE study team are: Aerssens A, Aguado M, Alimi B, Álvarez.D, Anagnostou O, Anderson J, Antoniadou A, Arando M, Barberà MJ, Barros H, Barthélemy A, Belda-Ibáñez J, Bertisch B, Bil J, Blanco JR, Block K, Boesecke C, Boura M, Burgos J, Burns FM, Cabo J, Calabuig E, Campbell L, Cardoso O, Claudia W, Clumeck N, Colucci A, Corrao S, Cuellar S, Cunha J, Daikos G, Darling K, del Amo J, del Romero J, Dellot P, Dixneuf M, Domingo P, Dronda F, Ebeling F, Engelhardt A, Engler B, Fakoya I, Farrell J, Fehr J, Feijó M, Fernández E, Fernández García E, Fernandez T, Fortes AL, Fox J, Garcia de Olalla P, García F, Gargalianos-Kakolyris P, Gennotte AF, Germano I, Gilleran G, Gilson R, Goepel S, Gogos HA, Gómez Sirvent JL, Gountas I, Gregg A, Gutiérrez F, Gutierrez MM, Hermans I, Iribarren JA, Knobel H, Koulai L, Kourkounti S, La Morté C, LeCompte T, Ledergerber B, Leonidou L, Ligero MC, Lindergard G, Lino S, Lopes MJ, Lopez Lirola A, Louhenapessy M, Lourida G, Luzi AM, Maltez F, Manirankunda L, Martín-Pérez A, Martins L, Masía M, Mateu MG, Meireles P, Mendes A, Metallidis S, Mguni S, Milinkovic A, Miró JM, Mohrmann K, Monge S, Montero M, Mouhebati T, Moutschen M, Müller M, Murphy C, Nöstlinger C, Ocaña I, Okumu-Fransche S, Onwuchekwa G, Ospina JE, Otiko D, Pacheco P, Palacios R, Paparizos V, Papastamopoulos V, Paredes V, Patel N, Pellicer T, Peña A, Petrosillo N, Pinheiro A, Poças J, Portillo A, Post F, Prestileo F, Prestileo T, Prins M, Prins P, Protopapas K, Psichogiou M, Pulido F, Rebollo J, Ribeirinho A, Río I, Robau M, Rockstroh JK, Rodrigues E, Rodríguez M, Sajani C, Salavert M, Salman R, Sanz N, Schuettfort G, Schüttfort G, Schwarze- Zander C, Serrão R, Silva D, Silva V, Silverio P, Skoutelis A, Staehelin C, Stephan C, Stretton C, Styles F, Sutre AF, Taylor S, Teixeira B, Thierfelder C, Touloumi G, Tsachouridou O, Tudor K, Valadas E, van Frankenhuijsen M, Vázquez M, Velasco Arribas M, Vera M, Vinciana P, Volny-Anne A, Voudouri N, Wasmuth JC, Wengenroth C, Wilkins E, Young L, Yurdakul S, Zafra Espinosa T, Zuilhof W, Zuure F

Authors' Contributions

IF, DAA, SM, JDA, and FB were the core research team who led the design and implementation of the study. IF wrote the initial draft of the manuscript and DAA, SM, JDA, and FB edited the manuscript. AJC provided the sample size calculations and statistical advice. AVA was our community partner and chair of our working group. FB, JDA, AFG, CW, GT, MP, CS, and HB were on the expert panel and oversaw data collection in their countries. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

aMASE Clinic Survey Sites.

[PDF File (Adobe PDF File), 33KB - resprot_v5i2e74_app1.pdf]

Multimedia Appendix 2

aMASE Funding Sources.

[PDF File (Adobe PDF File), 44KB - resprot_v5i2e74_app2.pdf]

References

1. Joint United Nations Programme on HIV/AIDS (UNAIDS). The Gap Report. Geneva: UNAIDS; 2014. URL: http://www.unaids.org/sites/default/files/en/media/unaids/contentassets/documents/unaidspublication/2014/UNAIDS_Gap_report_en.pdf [accessed 2016-04-01] [WebCite Cache ID 6gRt6S9Sc]

2. World Health Organization Regional Office for Europe. Data and Statistics. Copenhagen: WHO Regional Office for Europe; 2015. URL: http://www.euro.who.int/en/health-topics/communicable-diseases/hivaids/data-and-statistics [accessed 2015-11-02] [WebCite Cache ID 6cjwdjyU8]
3. Statistics Explained: Migration and Migrant Population Statistics. Luxembourg: Eurostat; 2015 Sep 02. URL: http://ec.europa.eu/eurostat/statistics-explained/index.php/Migration_and_migrant_population_statistics [accessed 2015-11-02] [WebCite Cache ID 6cjwQxuZ1]
4. European Centre for Disease Prevention and Control, WHO Regional Office for Europe. HIV/AIDS Surveillance in Europe 2013. Stockholm: ECDC; 2014. URL: http://ecdc.europa.eu/en/publications/Publications/hiv-aids-surveillance-report-Europe-2013.pdf [accessed 2015-11-02] [WebCite Cache ID 6cjv2Jgc9]
5. European Centre for Disease Prevention and Control. Migrant Health: Sexual Transmission of HIV Within Migrant Groups in the EU/EEA and Implications for Effective Interventions. Stockholm: ECDC; 2013. URL: http://ecdc.europa.eu/en/publications/Publications/Migrant-health-sexual-transmission.pdf [accessed 2015-09-03] [WebCite Cache ID 6fjSaV2oh]
6. Eurostat. Migrants in Europe: A Statistical Portrait of the First and Second Generation. Luxembourg: European Commission; 2011. URL: http://ec.europa.eu/eurostat/documents/3217494/5727749/KS-31-10-539-EN.PDF [accessed 2016-04-12] [WebCite Cache ID 6giQJiYoP]
7. Alvarez-del AD, Monge S, Azcoaga A, Rio I, Hernando V, Gonzalez C, et al. HIV testing and counselling for migrant populations living in high-income countries: a systematic review. Eur J Public Health 2013 Dec;23(6):1039-1045 [FREE Full text] [doi: 10.1093/eurpub/cks130] [Medline: 23002238]
8. Del AJ, Bröring G, Hamers FF, Infuso A, Fenton K. Monitoring HIV/AIDS in Europe's migrant communities and ethnic minorities. AIDS 2004 Sep 24;18(14):1867-1873. [Medline: 15353972]
9. Burns FM, Johnson AM, Nazroo J, Ainsworth J, Anderson J, Fakoya A, et al. Missed opportunities for earlier HIV diagnosis within primary and secondary healthcare settings in the UK. AIDS 2008 Jan 2;22(1):115-122. [doi: 10.1097/QAD.0b013e3282f1d4b6] [Medline: 18090399]
10. Evans AR, Parutis V, Hart G, Mercer CH, Gerry C, Mole R, et al. The sexual attitudes and lifestyles of London's Eastern Europeans (SALLEE Project): design and methods. BMC Public Health 2009;9:399 [FREE Full text] [doi: 10.1186/1471-2458-9-399] [Medline: 19878564]
11. Dray-Spira R, Spire B, Heard I, Lert F. Heterogeneous response to HAART across a diverse population of people living with HIV: results from the ANRS-EN12-VESPA Study. AIDS 2007 Jan;21 Suppl 1:S5-12. [doi: 10.1097/01.aids.0000255079.39352.9b] [Medline: 17159588]
12. Hernando V, Alvárez-del AD, Alejos B, Monge S, Amato-Gauci A, Noori T, et al. HIV Infection in Migrant Populations in the European Union and European Economic Area in 2007-2012: An Epidemic on the Move. J Acquir Immune Defic Syndr 2015 Oct 1;70(2):204-211. [doi: 10.1097/QAI.0000000000000717] [Medline: 26068723]
13. Willis GB. Cognitive Interviewing: A Tool for Improving Questionnaire Design. Thousand Oaks, CA: Sage Publications; 2005.
14. Rice B, Elford J, Yin Z, Delpech VC. A new method to assign country of HIV infection among heterosexuals born abroad and diagnosed with HIV. AIDS 2012 Sep 24;26(15):1961-1966. [doi: 10.1097/QAD.0b013e3283578b80] [Medline: 22781226]
15. aMASE: advancing Migrant Access to health Services in Europe. URL: http://www.amase.eu/wp/ [accessed 2015-11-02] [WebCite Cache ID 6cjtYVkct]

Abbreviations

aMASE: advancing Migrant Access to health Services in Europe
CAG: community advisory group
CAPI: computer-assisted personal interview
CASI: computer-assisted self-interview
EU: European Union
EuroCoord: European Network of HIV/AIDS Cohort Studies to Coordinate at European and International Level Clinical Research on HIV/AIDS
HIV: human immunodeficiency virus
UNAIDS: Joint United Nations Programme on HIV/AIDS

Edited by P Bamidis; submitted 04.09.15; peer-reviewed by C Noestlinger, A Nikolentzos; comments to author 28.09.15; revised version received 27.11.15; accepted 04.01.16; published 16.05.16.

Please cite as:
Fakoya I, Álvarez-del Arco D, Monge S, Copas AJ, Gennotte AF, Volny-Anne A, Göpel S, Touloumi G, Prins M, Barros H, Staehelin C, del Amo J, Burns FM
Advancing Migrant Access to Health Services in Europe (AMASE): Protocol for a Cross-sectional Study
JMIR Res Protoc 2016;5(2):e74
URL: http://www.researchprotocols.org/2016/2/e74/
doi:10.2196/resprot.5085
PMID:27185491

Protocol

Prevalence, Motivations, and Social, Mental Health and Health Consequences of Cyberbullying Among School-Aged Children and Youth: Protocol of a Longitudinal and Multi-Perspective Mixed Method Study

Faye Mishna[1], PhD; Lauren B McInroy[1], MSW; Ashley Lacombe-Duncan[1], MSW; Payal Bhole[1], MSW; Melissa Van Wert[1], PhD; Kaitlin Schwan[1], MA; Arija Birze[2], MA; Joanne Daciuk[1], BEd; Tanya Beran[8], PhD; Wendy Craig[3], PhD; Debra J Pepler[4], PhD; Judith Wiener[5], PhD; Mona Khoury-Kassabri[6], PhD; David Johnston[7], PhD

[1]University of Toronto, Factor-Inwentash Faculty of Social Work, Toronto, ON, Canada
[2]University of Toronto, Dalla Lana School of Public Health, Toronto, ON, Canada
[3]Queens University, Department of Psychology, Kingston, ON, Canada
[4]York University, Department of Psychology, Faculty of Health, Canada
[5]University of Toronto, Ontario Institute for Studies in Education, Toronto, ON, Canada
[6]The Hebrew University of Jerusalem Mount Scopus, School of Social Work & Social Welfare, Jerusalem, Israel
[7]Seneca College, Toronto, ON, Canada
[8]University of Calgary, Cumming School of Medicine, Calgary, AB, Canada

Corresponding Author:
Faye Mishna, PhD
University of Toronto
Factor-Inwentash Faculty of Social Work
246 Bloor Street West
Toronto, ON, M5S1V4
Canada
Phone: 1 416 978 3255
Fax: 1 416 978 7072
Email: f.mishna@utoronto.ca

Abstract

Background: While the online environment may promote important developmental and social benefits, it also enables the serious and rapidly growing issue of cyberbullying. Cyberbullying constitutes an increasing public health problem – victimized children and youth experience a range of health and mental health concerns, including emotional and psychosomatic problems, maladaptive behaviors, and increased suicidality. Perpetrators demonstrate a lack of empathy, and may also struggle with health and mental health issues.

Objective: This paper describes the protocols applied in a longitudinal and multi-perspective mixed-methods study with five objectives: (1) to explore children/youth's experiences, and children/youth's, parents', and teachers' conceptions, definitions, and understanding of cyberbullying; (2) to explore how children/youth view the underlying motivations for cyberbullying; (3) to document the shifting prevalence rates of cyberbullying victimization, witnessing, and perpetration; (4) to identify risk and protective factors for cyberbullying involvement; and (5) to explore social, mental health, and health consequences of cyberbullying.

Methods: Quantitative survey data were collected over three years (2012-2014) from a stratified random baseline sample of fourth (n=160), seventh (n=243), and tenth (n=267) grade children/youth, their parents (n=246), and their teachers (n=103). Quantitative data were collected from students and teachers during in-person school visits, and from parents via mail-in surveys. Student, parent, and teacher surveys included questions regarding: student experiences with bullying/cyberbullying; student health, mental health, and social and behavioral issues; socio-demographics; and information and communication technology use. In-depth semi-structured qualitative interviews were conducted twice with a sub-sample of students (n=57), purposively selected based on socio-demographics and cyberbullying experience, twice with their parents (n=50), and once with their teachers (n=30).

Results: Data collection for this study is complete. Planned analyses include transition probabilities and repeated measures analyses to determine involvement in cyberbullying. Repeated measures analyses, including between-subject factors (eg, socio-demographics), will be utilized to determine factors that protect or increase risk of involvement in cyberbullying. Qualitative analysis utilizing grounded theory is planned, to permit rich understanding of participant experiences and perspectives. Results will be reported in 2016 and 2017.

Conclusions: This study will offer insight into the contemporary phenomenon of cyberbullying while also informing interventions to curb cyberbullying and address its pervasive social, mental health, and health consequences. Knowledge mobilization strategies and implications for research and practice are discussed.

(JMIR Res Protoc 2016;5(2):e83) doi:10.2196/resprot.5292

KEYWORDS

cyberbullying; ICT; children; youth; parents; teachers; victimization; mental health; longitudinal; mixed methods

Introduction

Information and Communication Technology Use Among North American Youth

Information and communication technologies (ICTs) are pervasive among socio-demographically diverse populations of young people in North America. Use of these technologies is increasingly mobile (eg, cell phones, smartphones, tablets). In the United States in 2014, 92% of adolescents (13-17 years) were online daily (56% several times per day), while 91% of youth went online occasionally, at minimum, through a mobile device [1,2]. The recent advances in ICTs offer immense benefits for children and youth, including innumerable and unprecedented opportunities for education, growth, and development [3-7], as well as facilitating their health and mental health [8]. The ever-growing ubiquity of ICTs has, however, inevitably brought new challenges [9,10]. Despite their technical proficiency, children and youth do not typically possess the critical thinking and decision-making abilities required to use technology safely [11], and may be exposed to significant risks in ICT environments, including cyberbullying.

Cyberbullying: A Growing Public Health Problem

In the past few years, there has been an explosion in research on cyberbullying, documenting it as a serious, prevalent, and growing problem. Prevalence rates for cyberbullying vary due to definitional inconsistencies, the population studied, and the time frames and methodologies used [12,13,14]. It has been established, however, that between 10-40% of youth report being cyberbullied, while 50% know someone who has experienced cyberbullying [15]. Bullying is generally defined as a form of aggression that can be direct or indirect, and includes hostile physical, verbal, psychological, or relational behaviors. Bullying is characteristically intentional, commonly occurring in the context of a relationship, and comprising a power imbalance among those involved. The aggressive behavior is typically repeated over time, resulting in harm or negative consequences for the victimized child or youth [2]. Although consensus on the definition of cyberbullying has been difficult to establish, it may be generally defined as the use of ICTs to bully another person [15-21]. Young people may be involved in cyberbullying as victim, perpetrator, and/or witness. These roles appear to be more fluid and difficult to distinguish in the case of cyberbullying compared to traditional offline bullying [22]. Occurrence of bullying and cyberbullying are also highly correlated [14]. Research suggests that regardless of the role played in cyberbullying incidents, all children and youth can experience serious negative social, mental health, and health consequences as a result of involvement [19-25].

Cyberbullying constitutes a mounting public health problem, as both victimized youth and perpetrators may experience significant and prolonged distress [14,17], as well as an array of mental health concerns and problem behaviors. Victimized children and youth are at risk of developing depression, anxiety, poor self-esteem, eating disorders, sleep difficulties, emotional problems (eg, fear, sadness, loneliness), psychosomatic problems (eg, abdominal pains, headaches), and suicidal ideation and behavior [26-28]. Victimized youth may also be at increased risk of using substances, experiencing difficulties in school, participating in delinquent behavior, and engaging in unsafe sexual practices [29-31]. Youth who are perpetrators similarly experience increased risk of problems including depressive symptoms, substance use, aggression, and suicidal ideation, and may demonstrate less empathy and more conduct problems [23,32,33]. Students who are marginalized due to particular social markers (such as race/ethnicity, gender, religion, appearance, sexual orientation, socioeconomic status, or disability) may be disproportionately vulnerable to experiencing cyberbullying and associated negative social, mental health, and health consequences [34,35].

While research to date has illuminated a great deal about the nature and consequences of cyberbullying, several areas require further examination. Additionally, few studies have employed a longitudinal study design to assess trends in cyberbullying over time. The purpose of this paper is to describe the protocols implemented in a longitudinal and multi-perspective mixed-methods cohort study that contributes to the existing research by investigating several of these underdeveloped areas.

Study Objectives

This study had five objectives: (1) to explore children/youth's experiences, and children/youth's, their parents', and their teachers' conceptions, definitions, and understanding of cyberbullying; (2) to explore how children/youth view the underlying motivations for cyberbullying; (3) to document the shifting prevalence rates of cyberbullying victimization, witnessing, and perpetration; (4) to identify risk and protective factors for cyberbullying involvement; and (5) to explore social,

mental health, and health consequences of cyberbullying among children/youth. In this paper, the methods of the study are clearly outlined, and future quantitative and qualitative data analysis plans are discussed.

Methods

Sample

Three participant groups were included in the baseline study sample: (1) students in 4th (n=160), 7th (n=243), and 10th (n=267) grades; (2) their teachers (n=103); and (3) their parents (n=246). A stratified random sampling strategy was utilized to select participants. First, a random sample of 19 schools was drawn from one of the largest school boards in North America [36], situated in Toronto, Canada, which is a large metropolitan city. Schools were stratified into three categories of need (low, medium, and high) based on an index developed by the school board that ranked schools on external challenges to student achievement. The school board developed this index using census data associated with the postal code of students attending each school. Neighborhood-level census data used to develop the index included income and education levels, ratio of households receiving social assistance, and ratio of single parent families [37]. The stratification of the sample based on this index ensured representation of ethno-cultural and socioeconomic diversity - factors that potentially impact access to ICTs, experiences of cyberbullying, and the manifestation of negative outcomes [1,38,39]. In year three of the study, 10 additional schools were recruited for participation in order to follow those students transitioning from elementary/middle school to middle/secondary school. A total of 29 schools participated in the study. All students in the selected grades at the original participating schools were offered the opportunity to participate, as were their parents and teachers.

Participating students and their parents provided data in all three years of the study, while matching teachers provided data in year one only (as student participants' teachers changed each year). All three participant groups completed quantitative questionnaire packages, and a sub-sample of each group participated in qualitative interviews. Quantitative data were collected from students and parents in each year of the study, while qualitative data were collected only during years one and three, in order to allow for enough time to elapse for any changes in beliefs, perceptions, attitudes, and understanding of cyberbullying to emerge (Figure 1). Sub-samples of students, parents, and teachers were purposefully selected to participate in interviews based on level of school need, and were representative of gender, grade, and bullying/cyberbullying involvement.

Figure 1. Study timeline.

Data Collection		
Students		
Year One	**Year Two**	**Year Three**
Quantitative Questionnaire Package **Qualitative** In-Person Interviews	**Quantitative** Questionnaire Package **Qualitative** N/A	**Quantitative** Questionnaire Package **Qualitative** Phone Interviews
Parents		
Year One	**Year Two**	**Year Three**
Quantitative Questionnaire Package **Qualitative** In-Person Interviews	**Quantitative** Questionnaire Package **Qualitative** N/A	**Quantitative** Questionnaire Package **Qualitative** Phone Interviews
Teachers		
Year One	**Year Two**	**Year Three**
Quantitative Questionnaire Package **Qualitative** In-Person Interviews	N/A	N/A

Study Team and Training of Research Assistants

The research team consisted of a principal investigator and five co-investigators (responsible for general study oversight), one research manager responsible for data management (including entry and cleaning), and four research coordinators. The research coordinators worked in collaboration, but were responsible for separate aspects of the project: (1) survey administration and overall coordination, (2) consent and maintenance of administrative databases, (3) qualitative interview coordination, and (4) coordination of supports for students identified as experiencing distress. Coordinators managed a team of approximately 10-15 research assistants (RAs) who held diverse and often multiple roles, including: collecting survey data in the school setting, collecting interview data in the school setting or by phone, following up with students in distress, and assisting with administrative tasks. Most RAs were in progress towards (or held) a Master of Social Work degree, while several were from other related professional faculties, such as public health and education.

Prior to working on the project, all RAs participated in a two-hour general training on study methods and procedures. RAs were then trained for specific roles and duties depending on their educational background, clinical experience, and interests. Training was provided for administering quantitative surveys in the school setting, conducting qualitative interviews in person or on the phone, completing assessments to evaluate

whether a student was in distress, and accomplishing various administrative study tasks.

Ethics and Consent Process

Ethics approval was sought and received from the University of Toronto Research Ethics Board (Protocol #26753). The External Research Review Committee at the partnering school board also provided ethics approval for this project.

Consent to participate in the study was obtained actively in year one and, with approval of the school board, passively in years two and three. In year one, RAs visited each 4th, 7th, and 10th grade classroom from the 19 selected schools to explain the study and distribute consent forms. Parents/guardians were asked to sign the form if they agreed to allow their child to participate, if they were interested in participating themselves, and/or if they permitted the research team to ask their child's teacher to participate. After collection of the parent/student consent forms, teachers were asked if they would like to participate, and completed a consent form. In years two and three (passive consent), parents/guardians were mailed a letter reminding them that they had consented for their child and/or themselves to participate in the study, and that the next year of the study was ready to commence. The letter also provided detailed instructions on how to withdraw from the study if desired.

A $5 gift card was offered to all students, teachers, and parents who participated in the quantitative survey portion of the research in each of the three years. A $10 gift card was offered to all participants who took part in an interview (in person or by telephone) in years one and three.

In anticipation that some questions could lead to distress or disclosure of information of a potentially sensitive or distressing nature, a Research Ethics Board-approved protocol (agreed upon by both the University and school board) was established to identify and assist students categorized as being *in distress* through their questionnaire and/or qualitative interview responses. Student participants were classified as *in distress* if they met one (or more) of the following five criteria: (1) indicated on the Bullying & Cyberbullying: Perpetrators, Victims & Witnesses Survey (B&C:PVWS) that they needed help and would like to speak to a researcher; (2) endorsed item related to fire-setting on the Youth Self Report (YSR); (3) endorsed items related to self-harm/suicide on the YSR; (4) scored above the 85th percentile on the YSR, which is indicative of experiencing numerous behavioral problems; and/or (5) indicated during qualitative interviews that they were highly stressed and in need of support. All children and youth identified as *in distress* were individually interviewed in a private and confidential school setting by a clinically trained researcher, who was a Master of Social Work student or who possessed equivalent education and experience [40]. Children and youth were interviewed regardless of whether the nature of their distress was bullying related. Participants were then connected to appropriate services established within the school board. This attention to the distress of participants was particularly salient in the research context, as access to mental health services in Canada remains problematic [41].

Data Collection

Quantitative Data Collection Methods

In year one, students in 4thgrade (n=160), 7th grade (n=243), and 10th grade (n=267) completed a 45-60 minute survey in the school setting, while parents (n=246) completed a 30-45 minute survey by mail. This procedure changed somewhat for years two and three of the study, with some students completing questionnaire packages by mail due to changing schools. Questionnaires for teachers (n=103), which took approximately 45-60 minutes to complete, were administered in the participating schools. Teachers were given approximately two weeks to complete the questionnaires about their students participating in the study, which were then collected by the research team.

Quantitative Data Collection Measures

This study utilized a variety of quantitative measures, including both standardized measures as well as measures developed specifically for the study (Table 1). Student, parent, and teacher surveys collected information regarding experiences with bullying/cyberbullying, socio-demographics, ICT use, and student mental health, health, social, and behavioral issues.

Table 1. Measures completed by students, parents, and teachers.

			Students			Parents	Teachers
			Grade Level				
Area	**Measure**	**Captures**	**4**	**7**	**10**		
Experiences with Bullying/ Cyberbullying	*Bullying & Cyberbullying: Perpetrators, Victims & Witnesses Survey*(B&C:PVWS)	Experiences as victims, perpetrators, and/or witnesses of both bullying/cyberbullying; Experiences with bullying/cyberbullying types (eg, physical, verbal, social, sexual); Experiences with (and content of) bullying/cyberbullying specific to a variety of socio-demographic factors (eg, race, sexual orientation, gender, disability, appearance, religion); Responses to bullying/cyberbullying; Thoughts about potential interventions to address bullying/cyberbullying. *Measure used to identify distress.*	✓	✓	✓		
Mental Health, Health, Social, & Behavioral Issues	*Youth Self-report*(YSR) [42]	Youth's self-reported anxiety/depression, suicidal ideation, self-harm, somatic complaints, social, thought and attention problems, delinquent (eg setting fires) and aggressive (eg hurting others) behaviors; *Measure used to identify distress.*		✓	✓		
	Child Behavior Checklist(CBCL) [43]	Parent counterpart to YSR.				✓	
	Teacher Report Form(TRF) [44]	Educator counterpart to YSR.					✓
	Self-Perception Profile for Children(SPPC) [45]	Self-esteem.	✓	✓			
	Self-Perception Profile for Adolescents(SPPA) [46]	Self-concept.			✓		
	Social Support Scale for Children[47]	Children's perceived support and regard from parents, teachers, close friends, and classmates.	✓	✓			
	Social Support Behaviors Scale[48]	Youth's perceived support from family members and peers with subscales: emotional, socializing, practical assistance, financial, advice/guidance.			✓		
Socio-Demographics	Developed for the purpose of this study (Multiple Versions)	Gender, age, country of birth, country of parents' birth, main language spoken at home, race/ethnicity, sexual orientation, disability, family composition, grades, and other socio-demographic characteristics. Four versions: (1) 4^{th}Grade; (2) $7^{th}$and 10^{th}Grade; (3) Parents; (4) Teachers.	✓	✓	✓	✓	✓
Information & Communication Technology Use	Developed for the purpose of this study (Multiple Versions)	Access to ICTs at home, activities while using ICTs, frequency of activities, online friends and connections. Four versions: (1) 4^{th}Grade; (2) $7^{th}$and 10^{th}Grade; (3) Parents; (4) Teachers.	✓	✓	✓	✓	✓

Children/youth's experiences with bullying and cyberbullying were measured using the B&C:PVWS, which is a compilation of survey questions developed from the research team's previous studies. The bullying and cyberbullying literature was reviewed and feedback was sought from the participating school board in order to ensure age-appropriate language. Specific questions were adapted or removed based on the feedback from the school board (eg, questions regarding online sex). For the questions measuring experiences of being bullied and bullying others, the Cronbach alphas were .77 and .71, respectively, indicating good internal consistency.

Children/youth's mental health, health, social, and behavioral issues were captured for 4^{th}, 7^{th} and 10^{th} grade cohorts. We captured mental health, health, and behavioral issues using the YSR, intended for children aged eleven and older [42]. Parents completed the Child Behavior Checklist (CBCL), which is the parental counterpart to the students' YSR [43], while teachers completed the Teacher Report Form (TRF), which is the educator counterpart to the YSR and CBCL [44]. These surveys are widely used measures with excellent reported test-retest reliability [42-44]. We captured children/youth's social issues, including self-esteem, using subscales from the Self-Perception Profile for Children (SPPC) [45] and the Self-Perception Profile for Adolescents (SPPA) [46]. These scales have adequate

internal consistency, and both measures have a stable factor structure [45,46]. We measured social support for students in the 4th and 7th grade cohorts using the Social Support Scale for Children, a 24-item instrument which assesses children's perceived support and regard from parents, teachers, close friends, and classmates [47]. The internal consistencies of the four subscales range from .72 to .88 using Cronbach alphas [47]. Adolescents in the 10th grade cohort completed the Social Support Behaviors Scale to assess perceived support from family members and peers (emotional, social, practical assistance, financial, and advice/guidance) [48]. Strong internal consistency (Cronbach alpha exceeding .85) has been reported for this scale, which includes several college samples [48,49].

Socio-demographics were collected using two versions of the student demographic questionnaire, capturing characteristics such as age, gender, and country of birth, which were developed by the research team with feedback from the school board (one for the 4th grade cohort and one for 7th and 10th grade cohorts). The questionnaires included similar items for both age groups and were based on previous instruments administered by the school board, instruments developed by co-investigators for similar studies, and a review of the literature. The questionnaire for the older cohorts included items regarding sexuality, which were not included in the version for 4th grade students. Similar questionnaires (two versions) were developed for parents and teachers.

Lastly, we collected data on ICT use, using two versions of the student ICT usage questionnaire (one for the 4th grade cohort and one for 7th and 10th grade cohorts), developed by the research team. Again, both included similar questions, soliciting information on access to ICTs at home, activities while using ICTs, frequency of activities (6-point scale, ranging from *never to more than once a day*), and online friends and connections. The questionnaire for older cohorts included items related to taking and distributing intimate and/or sexual photos, which were not included in the 4th grade version. These questionnaires were adapted from two previous studies. Parents and teachers also completed ICT usage questionnaires (two versions) similar to those filled out by students.

Qualitative Data Collection Methods

Student participants from 4th grade (n=20), 7th grade (n=21), and 10th grade (n=16) in the qualitative sub-sample were purposefully selected from the larger quantitative sample for qualitative interviews based on diversity of gender, grade, school need level, and whether they reported bullying/cyberbullying victimization, perpetration, and/or witnessing. Subsequent to selecting student participants, their teachers (n=30), and their parents (n=50) were also invited to participate in in-depth interviews. Interviews lasted approximately one hour, ranging in length from thirty to ninety minutes. All year one interviews (with students, parents, and teachers) took place in the school setting, and utilized a semi-structured interview guide. Following preliminary analysis, this interview guide was expanded and refined for use in the year three follow-up phone interviews with the students and parents (Multimedia Appendix 1). Interviews provided nuance and context to the information obtained through the quantitative measures. Areas explored included views and understanding of cyberbullying and how it compares with traditional offline bullying, experiences of online aggression, and others' attitudes and responses to the issue. Questions were guided by existing literature and the research team's considerable experience. Parent and teacher interviews included questions about their awareness and understanding of cyberbullying, their child or student's involvement in cyberbullying, links between cyber and traditional bullying, supports, and their responses to cyberbullying.

Data Management

All participants were assigned a unique code to maintain anonymity. Participants' names do not appear anywhere in the quantitative survey packages or qualitative transcripts. Paper surveys were scanned using Cardiff Teleform software, and entered into a project-specific IBM SPSS Statistics 22 database. Entry and cleaning of quantitative data took place throughout the study, and all cases were cross-referenced by hand twice (during entry and after preliminary data sets were compiled) to ensure accuracy of entries. Qualitative data were transcribed verbatim, anonymized, and prepared for analysis. The same unique identifiers were used to identify the qualitative interviews and quantitative surveys, in order to facilitate matching these two data sources for individual participants.

Results

Data collection for this study is complete. Results of the proposed analyses, outlined below, will be reported in 2016 and 2017.

Proposed Quantitative Data Analyses

Descriptive analyses will be conducted to calculate frequencies for categorical variables, and means and standard deviations for continuous variables. We will summarize socio-demographic variables among participants in each grade level (4, 7, 10) and differences between grades will be assessed using Student t-tests for continuous variables, and $\chi 2$ analyses or Fisher's exact tests for categorical variables. Items for each outcome scale (eg, Social Support Scale for Children) will be summed to calculate total or subscale scores for each measure. Reliability of scaled measures will be described using Cronbach alphas. Advanced statistical analyses are also planned. An example of a more advanced analysis that will be conducted is transition probabilities, which will determine involvement in cyberbullying, consistent with our objective of documenting the shifting prevalence rates of cyberbullying victimization, witnessing, and perpetration. To meet our objective of identifying factors that protect against (or increase risk of) involvement in cyberbullying, between-subject factors will be included in a repeated measures analysis. These factors include demographic variables, CBCL scales, self-esteem, and social support to determine their individual and combined contribution to cyberbullying experiences. Considering participants are clustered in classrooms, independence of the data cannot be assumed, and the data are dependent to some degree. Thus, classroom will be included as a dummy variable in the regressions. Multilevel analysis will be used to assess the

contribution of school need level (low, high, and medium) on individual cyberbullying experience.

Proposed Qualitative Data Analyses

Using the systematic procedures of a rigorous grounded theory inquiry, a theory about children/youth's, parents', and teachers' conceptions of cyberbullying and underlying motivations will be generated. Using this approach, researchers concurrently collect, analyze, and theorize about data in a reciprocal process of constant comparison to inductively construct empirically corroborated, explanatory theories [50-53]. The iterative process permits the analytical and theoretical categories developed by previously collected data to inform, as well as refine and focus, subsequent collection of data [52,54,55]. This refining and focusing commenced during data collection for this study, particularly between the qualitative interview phases (years 1 and 3), and is ongoing. With future analyses, emergent themes among youth, parents, and teachers over time will continue to be identified, and children's and adults' views compared.

While the intent is to develop a theoretical model, grounded theory methods will simultaneously allow for further exploration of interpersonal processes and experiences in a process of reciprocal analysis. Line-by-line and open coding of transcripts were, and will continue to be, conducted to establish preliminary analytic focuses, and subsequently emerging categories will be built and expanded. Axial coding will promote connections both within and between categories and sub-categories, and facilitate synthesis and explanation [50,51,56]. Several measures have been employed to ensure trustworthiness and authenticity. The researchers' prolonged engagement through many years of research and practice in this area will guide development of the grounded theory. Theory development will continue until saturation occurs. Reflexive journaling, bracketing, an audit trail, and dense descriptions will further ensure trustworthiness and transferability [50,51,54].

Discussion

The study described in this paper provides one of the first assessments of the understanding and experiences of children and youth involved in cyberbullying as victims, perpetrators, and/or witnesses, and involved the investigation of their perceptions, as well as those of their parents and teachers. We followed a baseline sample of 4th (n=160), 7th (n=243), and 10th (n=267) grade children/youth and their parents (n=246), for three years (2012-2014), along with collecting baseline data from their teachers (n=103). This study's multi-perspective approach allows for triangulated analysis of cyberbullying issues, and the design was strengthened by tracking participants longitudinally, during a period in which ICT use has continued to expand rapidly [57]. Recruiting students across grades/ages/socio-economic status permits the comparison of experiences across diverse socio-demographic groups and allows for an examination of trends in primary, middle, and secondary schools. Data collection for this study is complete, with results of proposed analyses anticipated in 2016 and 2017.

This research will elucidate the complex dynamics of cyberbullying incidents and contributes to the growing body of literature on the rates of cyberbullying, as well as risk and protective factors of involvement. In addition, this study will explicate how children/youth understand cyberbullying and how they experience and judge the underlying motivations for involvement. This inquiry addresses the lack of research capturing children and youth's experiences, feelings, and conceptions of cyberbullying, and uniquely examines the congruence or incongruence of children and youth's views with those of significant adults in their lives. Identifying how children, youth, and adults conceptualize cyberbullying is critical to ensuring the understanding of its extent and impact, and developing effective prevention and intervention strategies [15]. Developing informed strategies relevant to contemporary young people's lives and contexts is especially salient, as increasing recognition of the negative consequences of cyberbullying "has lead parents, educators, and policymakers to embrace intervention efforts, and there is now substantial educational and clinical interest in programs that help to mitigate… harmful outcomes" [58]. For emerging findings based upon study objectives, please refer to Multimedia Appendix 2 .

Knowledge translation and exchange activities will be a priority in order to translate study findings for study participants, educators, helping/healthcare professionals, and the broader community. Presentations will be made to the partner school board and a report will be provided to schools, participants, and community members. Any requests by individual schools for presentations will be accommodated by a member of the research team. Findings will be disseminated within the academic community through refereed journals and presentations at juried Canadian and international conferences. We will publish in relevant academic journals, and results will be disseminated to policy makers and practitioners, and presentations will be made to professional organizations and to the community.

Most importantly, these findings can inform interventions to curb cyberbullying among young people in an effort to prevent the negative social, mental health, and health consequences. In keeping with the preliminary findings of this study, previous research has indicated that most children and youth do not disclose their experience with cyberbullying to parents, and are even less likely to disclose cyberbullying experiences to school-based adults (eg, teachers, administrators) [12]. Such lack of disclosure indicates a critical need to provide prevention and intervention efforts in school settings as a way to promote disclosure [12]. Further, little evidence for best practices in intervention efforts exists [13]. The study described in this paper can inform intervention efforts by offering insight into student perceptions of what is helpful or not helpful when experiencing, perpetrating, and/or witnessing cyberbullying, as well as the contexts in which prevention and intervention efforts may be most effective (including via ICTs) [12]. Results of our quantitative data analysis exploring the social, mental health, and health consequences of cyberbullying can inform the development of resources at the school-level. Moreover, future papers focusing on the research process of this study may glean important insights into the challenges of conducting longitudinal studies with children and youth in a school-based setting (ie, participant retention), and potential strategies to mitigate these

challenges (ie, the use of passive consent). Future research may also focus on mechanisms, beyond built-in research study protocols, to support students in distress.

The burgeoning body of literature on the phenomenon of cyberbullying is a relatively recent scholarly development, highlighting the crucial need to engage in discourse regarding this emerging field of research. This unique study offers insight into cyberbullying and provides a foundation for future research in this important and flourishing field. Importantly, as the frequency of ICT use is constantly growing, and with younger and younger children increasingly using ICTs, understanding the social, mental health, and health consequences of cyberbullying across grade levels may point to differing developmental impacts and inform targeted interventions.

Acknowledgments

This study was funded by a Social Sciences and Humanities Research Council Grant (Grant #410-2011-1001). We would like to acknowledge first and foremost the Toronto District School Board for their utmost commitment to participating in the study, as well as each school for their dedication to both data collection and ensuring the mental health needs of students identified through the study were addressed. Thank you to the students, parents, and teachers for sharing your experiences with us. Thank you to the research assistants, without whom we could not have completed this large study.

Authors' Contributions

FM, WC, TB, DJP, JW, and DJ, KS, JD conceived of the study and developed the initial study protocol. FM, ALD, LBM, KS, PB, and AB and MVW contributed to writing the protocol for publication and provided ongoing data collection oversight during the duration of the study. JD managed the data throughout the duration of the study and contributed to writing the protocol for publication. All authors read and approved the final protocol for publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Qualitative interview guide.

[PDF File (Adobe PDF File), 45KB - resprot_v5i2e83_app1.pdf]

Multimedia Appendix 2

Preliminary results.

[PDF File (Adobe PDF File), 43KB - resprot_v5i2e83_app2.pdf]

References

1. Lenhart A, Duggan M, Perrin A, Stepler R, Rainie L, Parker K. Pew Research Center. Washington, DC; 2015. Teens, social media & technology overview 2015 URL: http://www.pewinternet.org/files/2015/04/PI_TeensandTech_Update2015_0409151.pdf [accessed 2016-02-13] [WebCite Cache ID 6fH8k4Hz4]
2. Mishna F, Cook C, Gadalla T, Daciuk J, Solomon S. Cyber bullying behaviors among middle and high school students. Am J Orthopsychiatry 2010 Jul;80(3):362-374. [doi: 10.1111/j.1939-0025.2010.01040.x] [Medline: 20636942]
3. Blumenfeld W, Cooper R. LGBT and allied youth responses to cyberbullying: policy implications. IJCP 2010;31:114-133.
4. Craig S, McInroy L. You can form a part of yourself online: the influence of new media on identity development and coming out for LGBTQ youth. J Gay Lesbian Mental 2014;18:95-109.
5. Elwell L, Grogan S, Coulson N. Adolescents living with cancer: the role of computer-mediated support groups. J Health Psychol 2011 Mar;16(2):236-248. [doi: 10.1177/1359105310371398] [Medline: 20733012]
6. Johnson G, Puplampu K. Canadian Journal of Learning & Technology. 2008. Internet use during childhood and the ecological techno-subsystem URL: http://www.cjlt.ca/index.php/cjlt/article/view/172/168.Archived [accessed 2016-02-13] [WebCite Cache ID 6fH9DUzUN]
7. Strom P, Strom R. Growing up with social networks and online communities. The Education Digest 2012;78:48-51.
8. Ammerlaan JJ, Scholtus LW, Drossaert CH, van Os-Medendorp H, Prakken B, Kruize AA, et al. Feasibility of a website and a hospital-based online portal for young adults with juvenile idiopathic arthritis: views and experiences of patients. JMIR Res Protoc 2015;4(3):e102 [FREE Full text] [doi: 10.2196/resprot.3952] [Medline: 26276373]
9. Gasser U, Maclay C, Palfrey Jr JG. Berkman Center Research Publication. 2016 Jun 16. Working towards a deeper understanding of digital safety for children and young people in developing nations URL: http://dmlhub.net/wp-content/uploads/files/SSRN-id1628276.pdf [accessed 2016-02-13] [WebCite Cache ID 6fHC6NF3e]

10. Livingstone S, Haddon L. Risky experiences for children online: charting European research on children and the Internet. Child Soc 2008;22:314-323.
11. Burrow-Sanchez J, Call M, Zheng R, Drew C. How school counselors can help prevent online victimization. J Couns Dev 2011;89:3-10.
12. DePaolis K, Williford A. The nature and prevalence of cyber victimization among elementary school children. Child Youth Care Forum 2015;44(3):377.
13. Faucher C, Jackson M, Cassidy W. Cyberbullying among university students: gendered experiences, impacts, and perspectives. Educ Res Int 2014:1.
14. Modecki KL, Minchin J, Harbaugh AG, Guerra NG, Runions KC. Bullying prevalence across contexts: a meta-analysis measuring cyber and traditional bullying. J Adolesc Health 2014 Nov;55(5):602-611. [doi: 10.1016/j.jadohealth.2014.06.007] [Medline: 25168105]
15. Kowalski RM, Giumetti GW, Schroeder AN, Lattanner MR. Bullying in the digital age: a critical review and meta-analysis of cyberbullying research among youth. Psychol Bull 2014 Jul;140(4):1073-1137. [doi: 10.1037/a0035618] [Medline: 24512111]
16. Ahlfors R. Many sources, one theme: analysis of cyberbullying prevention and intervention websites. J Soc Sci 2010 Apr 01;6(4):515-522. [doi: 10.3844/jssp.2010.515.522]
17. Cassidy W, Faucher C, Jackson M. Cyberbullying among youth: a comprehensive review of current international research and its implications and application to policy and practice. Sch Psychol Int 2013;34:575-612.
18. Collier A. Living Internet: some context for the cyberbullying discussion. In: Patchin JW, Hinduja S, editors. Cyberbullying Prevention and Response: Expert Perspectives. New York: Routledge; 2012:1-12.
19. Hinduja S, Patchin J. Bullying beyond the schoolyard: preventing and responding to cyberbullying. 2nd ed. Thousand Oaks, CA: Sage Publications; 2009.
20. Mishna F, Van Wert M. Bullying in Canada. Toronto: Oxford University Press Canada; 2015.
21. Smith P, del Barrio C, Tokunaga R. Definitions of bullying and cyberbullying: how useful are the terms? In: Bauman S, Cross D, Walker J, editors. Principles of cyberbullying research: definition, methods, and measures. New York: Routledge; 2013:26-40.
22. Barlińska J, Szuster A, Winiewski M. Cyberbullying among adolescent bystanders: role of the communication medium, form of violence, and empathy. J Community Appl Soc Psychol 2013;23:37-51.
23. Ang RP, Goh DH. Cyberbullying among adolescents: the role of affective and cognitive empathy, and gender. Child Psychiatry Hum Dev 2010 Aug;41(4):387-397. [doi: 10.1007/s10578-010-0176-3] [Medline: 20238160]
24. Beran TN, Li Q. The relationship between cyberbullying and school bullying. J Stud Wellbeing 2007;1:16-33.
25. Beran T, Stanton L, Hetherington R, Mishna F, Shariff S. Development of the bullying and health experiences scale. Interact J Med Res 2012;1(2):e13 [FREE Full text] [doi: 10.2196/ijmr.1835] [Medline: 23612028]
26. Campbell M, Spears B, Slee P, Butler D, Kift S. Victims' perceptions of traditional and cyberbullying, and the psychosocial correlates of their victimisation. J Emot Behav Diff 2012;17:389-401.
27. Bonanno RA, Hymel S. Cyber bullying and internalizing difficulties: above and beyond the impact of traditional forms of bullying. J Youth Adolesc 2013 May;42(5):685-697. [doi: 10.1007/s10964-013-9937-1] [Medline: 23512485]
28. Dehue F, Bolman C, Völlink T. Cyberbullying: youngsters' experiences and parental perception. Cyberpsychol Behav 2008 Apr;11(2):217-223. [doi: 10.1089/cpb.2007.0008] [Medline: 18422417]
29. Litwiller BJ, Brausch AM. Cyber bullying and physical bullying in adolescent suicide: the role of violent behavior and substance use. J Youth Adolesc 2013 May;42(5):675-684. [doi: 10.1007/s10964-013-9925-5] [Medline: 23381779]
30. Mitchell KJ, Ybarra M, Finkelhor D. The relative importance of online victimization in understanding depression, delinquency, and substance use. Child Maltreat 2007 Nov;12(4):314-324. [doi: 10.1177/1077559507305996] [Medline: 17954938]
31. Ybarra ML, Diener-West M, Leaf PJ. Examining the overlap in internet harassment and school bullying: implications for school intervention. J Adolesc Health 2007 Dec;41(6 Suppl 1):S42-S50. [doi: 10.1016/j.jadohealth.2007.09.004] [Medline: 18047944]
32. Calvete E, Orue I, Estevez A, Villardon L, Padilla P. Cyberbullying in adolescents: modalities and aggressors' profile. Comput Human Behav 2010;26:1128-1135.
33. Ybarra ML, Mitchell KJ. Prevalence and frequency of Internet harassment instigation: implications for adolescent health. J Adolesc Health 2007 Aug;41(2):189-195. [doi: 10.1016/j.jadohealth.2007.03.005] [Medline: 17659224]
34. Cappadocia MC, Weiss JA, Pepler D. Bullying experiences among children and youth with autism spectrum disorders. J Autism Dev Disord 2012 Feb;42(2):266-277. [doi: 10.1007/s10803-011-1241-x] [Medline: 21499672]
35. Kosciw J, Bartkiewicz M, Greytak EA. Promising strategies for prevention of the bullying of lesbian, gay, bisexual, and transgender youth. Prev Res 2012;19:10-13.
36. Toronto District School Board. 2014. Quick facts URL: http://www.tdsb.on.ca/AboutUs/QuickFacts.aspx [accessed 2016-02-13] [WebCite Cache ID 6fH9PvbV6]
37. Toronto District School Board. 2014. The 2014 Learning opportunities index: questions and answers URL: http://www.tdsb.on.ca/Portals/0/AboutUs/Research/LOI2014.pdf [accessed 2016-02-13] [WebCite Cache ID 6fH9XXntM]
38. Roberts DF, Foehr UG. Trends in media use. Future Child 2008;18(1):11-37. [Medline: 21338004]

39. Steeves V. MediaSmarts. 2014. Young Canadians in a wired world, phase III URL: http://mediasmarts.ca/young-canadians-wired-world-phase-iii-0 [accessed 2016-02-13] [WebCite Cache ID 6fHCxA4pv]
40. Mishna F, Schwan K, Lefebvre R, Bhole P, Johnston D. Students in distress: unanticipated findings in a cyber bullying study. Child Youth Serv Rev 2014;44:341-348.
41. Ewen V, Mushquash AR, Bailey K, Haggarty JM, Dama S, Mushquash CJ. Same-day counseling: study protocol for the evaluation of a new mental health service. JMIR Res Protoc 2016;5(1):e22 [FREE Full text] [doi: 10.2196/resprot.5206] [Medline: 26842891]
42. Achenbach T. Achenbach System of Empirically Based Assessment (ASEBA). 2001. Youth self-report URL: http://www.aseba.org/forms/ysr.pdf [accessed 2016-04-25] [WebCite Cache ID 6h1Ks0uZm]
43. Achenbach T. Achenbach System of Empirically Based Assessment (ASEBA). 2001. The child behavior checklist URL: http://www.aseba.org/schoolage.html [accessed 2016-02-13] [WebCite Cache ID 6h1KvivYP]
44. Achenbach T. University of Vermont. 2001. Teacher report form URL: http://www.aseba.org/schoolage.html [accessed 2016-02-13] [WebCite Cache ID 6h1L1FhEh]
45. Harter S. University of Denver. 2012. The self-perception profile for children URL: https://portfolio.du.edu/SusanHarter/page/44210 [accessed 2016-02-13] [WebCite Cache ID 6fH9sAYGT]
46. Harter S. University of Denver. 2012. Manual for the self-perception profile for adolescents URL: https://portfolio.du.edu/SusanHarter/page/44210 [accessed 2016-02-13] [WebCite Cache ID 6fH9sAYGT]
47. Harter S. University of Denver. 2012. Manual for the social support scale for children URL: https://portfolio.du.edu/SusanHarter/page/44343 [accessed 2016-02-13] [WebCite Cache ID 6fH9yldNw]
48. Vaux A, Riedel S, Stewart D. Modes of social support: the social support behaviors (SS-B) scale. Am J Community Psychol 1987;15:209-237.
49. Hogan M, Parker J, Wiener J, Watters C, Wood L, Oke A. Academic success in adolescence: relationships among verbal IQ, social support and emotional intelligence. Aust J Psychol 2010;62:30-41.
50. Birks M, Mills J. Grounded theory: a practical guide. 1st Ed. Thousand Oaks, CA: Sage Publications Inc; 2011.
51. Corbin J, Strauss A. Basics of qualitative research: techniques and procedures for developing grounded theory. 3rd ed. Thousand Oaks, CA: Sage Publications Inc; 2008.
52. Patton M. Qualitative research and evaluation methods. 3rd ed. Thousand Oaks, CA: Sage Publications Inc; 2002.
53. Strauss A, Corbin J. Basics of qualitative research: techniques and procedures for developing grounded theory. 2nd ed. Thousand Oaks, CA: Sage Publications Inc; 1998.
54. Bowen G. Grounded theory and sensitizing concepts. Int J Qual Methods 2006;5:12-23.
55. Charmaz K. Constructing grounded theory: a practical guide through qualitative analysis. Thousand Oaks, CA: Sage Publications Inc; 2006.
56. Charmaz K. Grounded theory. In: Smith JA, editor. Qualitative psychology: a practical guide to research methods. Thousand Oaks, CA: Sage Publications Inc; 2008:81-110.
57. Pew Research Center. 2015. Device ownership over time URL: http://www.pewinternet.org/data-trend/mobile/device-ownership/ [accessed 2016-02-13] [WebCite Cache ID 6fHA64Fep]
58. Modecki KL, Barber BL, Vernon L. Mapping developmental precursors of cyber-aggression: trajectories of risk predict perpetration and victimization. J Youth Adolesc 2013 May;42(5):651-661. [doi: 10.1007/s10964-012-9887-z] [Medline: 23242509]

Abbreviations

B&C: PVWS: Bullying & Cyberbullying: Perpetrators, Victims & Witnesses Survey
CBCL: Child Behavior Checklist
ICT: Information and communication technology
RA: Research assistant
SPPA: Self-Perception Profile for Adolescents
SPPC: Self-Perception Profile for Children
TRF: Teacher Report Form
YSR: Youth Self-Report

Edited by G Eysenbach; submitted 28.10.15; peer-reviewed by M van Geel, H Na, M Campbell; comments to author 03.02.16; revised version received 15.02.16; accepted 20.02.16; published 24.05.16.

Please cite as:
Mishna F, McInroy LB, Lacombe-Duncan A, Bhole P, Van Wert M, Schwan K, Birze A, Daciuk J, Beran T, Craig W, Pepler DJ, Wiener J, Khoury-Kassabri M, Johnston D
Prevalence, Motivations, and Social, Mental Health and Health Consequences of Cyberbullying Among School-Aged Children and Youth: Protocol of a Longitudinal and Multi-Perspective Mixed Method Study
JMIR Res Protoc 2016;5(2):e83
URL: http://www.researchprotocols.org/2016/2/e83/
doi:10.2196/resprot.5292
PMID:27220556

Protocol

Predictive Factors for Anastomotic Leakage After Colorectal Surgery: Study Protocol for a Prospective Observational Study (REVEAL Study)

Audrey CHM Jongen[1,2], MD; Joanna WAM Bosmans[1,2], MD; Serdar Kartal[1], BSc; Tim Lubbers[3], MD, PhD; Meindert Sosef[4], MD, PhD; Gerrit D Slooter[3]; Jan H Stoot[5], MD, PhD; Frederik-Jan van Schooten[2], PhD; Nicole D Bouvy[1,2], MD, PhD; Joep PM Derikx[6], MD, PhD

[1]Department of General Surgery, Maastricht University Medical Centre, Maastricht, Netherlands

[2]NUTRIM School for Nutrition & Translational Research in Metabolism, Maastricht University, Maastricht, Netherlands

[3]Department of Surgery, Maxima Medical Centre, Veldhoven, Netherlands

[4]Department of Surgery, Zuyderland Medical Centre, Heerlen, Netherlands

[5]Department of Surgery, Zuyderland Medical Centre, Sittard, Netherlands

[6]Pediatric Surgical Centre Amsterdam, Emma Children's hospital, Amsterdam Medical Centre/Vrije Universiteit Medisch Centrum, Amsterdam, Netherlands

Corresponding Author:
Audrey CHM Jongen, MD
Department of General Surgery
Maastricht University Medical Centre
P.O. Box 5800
P. Debeyelaan 25
Maastricht, 6202 AZ
Netherlands
Phone: 31 651360560
Fax: 31 433884154
Email: a.jongen@maastrichtuniversity.nl

Abstract

Background: Anastomotic leakage (AL) remains the most important complication following colorectal surgery, and is associated with high morbidity and mortality rates. Previous research has focused on identifying risk factors and potential biomarkers for AL, but the sensitivity of these tests remains poor.

Objective: This prospective multicenter observational study aims at combining multiple parameters to establish a diagnostic algorithm for colorectal AL.

Methods: This study aims to include 588 patients undergoing surgery for colorectal carcinoma. Patients will be eligible for inclusion when surgery includes the construction of a colorectal anastomosis. Patient characteristics will be collected upon consented inclusion, and buccal swabs, breath, stool, and blood samples will be obtained prior to surgery. These samples will allow for the collection of information regarding patients' inflammatory status, genetic predisposition, and intestinal microbiota. Additionally, breath and blood samples will be taken postoperatively and patients will be strictly observed during their in-hospital stay, and the period shortly thereafter.

Results: This study has been open for inclusion since August 2015.

Conclusions: An estimated 8-10% of patients will develop AL following surgery, and they will be compared to non-leakage patients. The objectives of this study are twofold. The primary aim is to establish and validate a diagnostic algorithm for the pre-operative prediction of the risk of AL development using a combination of inflammatory, immune-related, and genetic parameters. Previously established risk factors and novel parameters will be incorporated into this algorithm, which will aid in the recognition of patients who are at risk for AL. Based on these results, recommendations can be made regarding the construction of an anastomosis or deviating stoma, and possible preventive strategies. Furthermore, we aim to develop a new algorithm for the post-operative diagnosis of AL at an earlier stage, which will positively reflect on short-term survival rates.

Trial Registration: Clinicaltrials.gov: NCT02347735; https://clinicaltrials.gov/ct2/show/NCT02347735 (archived by WebCite at http://www.webcitation.org/6hm6rxCsA)

(JMIR Res Protoc 2016;5(2):e90) doi:10.2196/resprot.5477

KEYWORDS

Anastomotic leakage; Colorectal surgery; Postoperative complications; Biomarkers; Personalized medicine

Introduction

Surgery remains the predominant curative treatment for patients with colorectal cancer (CRC), but can lead to severe post-operative complications, of which anastomotic leakage (AL) is the most feared. AL occurs in 8-15% of patients undergoing colorectal surgery and is associated with high morbidity and short-term mortality rates of up to 39% [1-4]. AL often requires one or more re-interventions, leading to a significant increase in length of hospital stay and subsequently to high health care costs [3]. Some authors even suggest that AL is associated with an impaired oncological prognosis [5-8]. Both decreased disease-specific survival (odds ratio [OR] 1.75) [9,10] and an increased local recurrence rate of CRC (OR 2.9) [10] have been reported.

In the past decades, important risk factors for AL such as male gender [4], neo-adjuvant chemotherapy [11], tumor size [12], malnutrition [13], smoking [14], steroid treatment [1,15], and the use of non-steroidal anti-inflammatory drugs (NSAIDs) [16] have been identified. Despite the determination of these risk factors for AL, surgeons' prediction of the risk to develop AL for the individual patient remains inaccurate [17]. Despite decades of extensive research on preventive methods, the introduction of innovative surgical techniques, and fast-track protocols, incidence rates of AL have remained stable [18].

A recently conducted study in one of the participating centers, that can be considered a pilot study, suggests that pre-operative levels of a certain plasma marker (intestinal fatty acid binding protein, I-FABP) can predict the development of AL in patients undergoing CRC surgery. I-FABP is present in mature enterocytes of the small and large intestine, and is released upon intestinal damage [19]. It is hypothesized that increased plasma levels of I-FABP are the result of an underlying clinical condition of the gastrointestinal tract, predisposing the patient to AL [20].

Cumulative evidence in the literature suggests that perioperative pain treatment with NSAIDs, commonly prescribed analgesics that inhibit cyclo-oxygenase 2 (COX-2) expression, increase the risk of AL [16,21,22]. COX-2 knockout mice have an increased risk of developing AL, and this risk can be reduced by the administration of prostaglandin E2, a product of COX-2 [23]. Another study conducted by our research group has demonstrated that decreased COX-2 expression, due to a polymorphism in the COX-2 gene, leads to an increased risk of the development of AL [23]. Furthermore, it has been shown that patients with different genotypes of mannose-binding lectin (MBL), an important complement factor of the immune system, respond differently to intestinal damage [24].

In the pilot study mentioned previously, it was shown that a combination of C-reactive protein (CRP) and calprotectin levels in plasma provides high diagnostic accuracy for AL during the post-operative period. Finally, we have shown that functional compromise (characterized by malnutrition, frailty, and sarcopenia) is associated with post-operative morbidity and mortality [25]. Malnutrition, as indicated by high Short Nutritional Assessment Questionnaire (SNAQ) scores, and sarcopenia were predictive for, or showed a trend towards, prediction of AL.

Based on previous literature and both our experimental and clinical data, we hypothesize that the occurrence of AL is partly due to patient-derived factors such as a compromised immune response, sarcopenia, genetic predisposition, and an aberrant intestinal microbiome composition, and that the post-operative course can be further influenced by surgical stress, ischemia, and a derailed systemic response. Our hypothesis is that, based on these parameters, individual risks for the development of AL can be assessed pre-operatively.

Besides the obvious improvements that can be made regarding pre-operative risk assessment, the post-operative recognition and management of AL has also proven to be challenging. The timing of AL diagnoses varies greatly, from post-operative day 3 to beyond 30 days, with a mean of 12.7 days post-operatively [26]. Abnormal vital signs and biochemical tests are quite common following the construction of a colorectal anastomosis, and can therefore not be used adequately in the diagnosis of AL. The presentation of AL can vary from abdominal pain and low-grade fever to peritonitis and severe sepsis. This nonspecific course of AL often delays radiologic imaging, and even if this test is undertaken, the diagnoses frequently remain uncertain. Previous research has presented false-negative rates varying from 17-52% for both contrast enemas and computerized tomography (CT) scans [27], resulting in a significant delay of re-intervention [28].

Since a delayed diagnosis of AL is associated with poor outcome [29] and premature re-intervention could lead to a high number of negative re-explorations, one should outweigh the risks of a delayed intervention and the morbidity of re-intervention. Physicians are armed with a restricted number of parameters contributing to risk analysis for the development of AL, with only limited specificity and sensitivity.

Study Objectives

The objectives of the Predictive Factors of Anastomotic Leakage after Colorectal Surgery (REVEAL) study are twofold. The primary aim of this study is to establish a risk assessment tool for the pre-operative prediction of the development of AL based on a combination of inflammatory, immune-related, and genetic parameters. This algorithm should enable surgeons to make an

adequate estimation for every individual patient's risk of AL, and will eventually aid in the decision-making process regarding the construction of anastomoses and deviating ostomies. In addition, this study aims to provide additional post-operative biomarkers for AL diagnosis at earlier stages, thereby reducing the clinical impact of this feared complication.

Methods

This is a study protocol for a multicenter, prospective observational study. This study is approved by the Medical Ethical Committee of the Maastricht University Medical Centre. A written informed consent is required from all participating patients and the trial will be conducted in compliance with the rules of *Good Clinical Practice*.

Study Population

All patients aged >18 years undergoing elective colorectal surgery for colorectal carcinoma, with the construction of an anastomosis, in one of the three participating centers are eligible for inclusion. Patients with large adenomas (large tubular, tubulovillous, or sessile) that cannot be resected radically by means of endoscopy will be included as well, provided that the adenoma is removed surgically with the construction of a colorectal anastomosis. Sample size analysis revealed that 588 consecutive patients have to be included at the outpatient department, prior to surgery. Patients undergoing colorectal surgery for benign conditions, those with permanent stomata without anastomosis, or patients that are unable to give informed consent will be excluded from participation in this study, as well as pregnant patients. If no anastomosis is constructed during surgery, the patient will be withdrawn from the study. Eligibility for inclusion will be determined during a visit at the outpatient department. Upon approval, the patient will receive oral and written information regarding the study, after which he/she will have ample time to reconsider participation. Informed consent will be signed in the presence of the surgeon or researcher.

Participating Centers

This study will be conducted at Maastricht University Medical Centre (MUMC+, Maastricht, The Netherlands), Zuyderland Medical Centre (Sittard-Geleen and Heerlen, The Netherlands), and Máxima Medical Centre (MMC, Veldhoven, The Netherlands).

Study Outline

Patients will be admitted to the ward one day prior to surgery, and perioperative care will be performed according to *Enhanced Recovery After Surgery* guidelines for elective colonic surgery [30]. Due to the compelling evidence regarding the detrimental effects of NSAIDs on intestinal wound healing, these drugs will not be administered in this patient population during the perioperative phase. Instead, adequate pain treatment will be provided by means of acetaminophen and opioids if necessary. A *Data Safety Monitoring Board* has been commissioned to evaluate the quality of data collection and monitor patient safety. A web-based system was constructed in order to facilitate the collection of standardized and coded patient data.

The primary end point of this study is post-operative AL, occurring during the first 30 days after surgery, either during hospital admission or following discharge. AL is defined as a communication between the intra- and extra-luminal compartments, resulting from a defect in the integrity of the intestinal wall. Leakage from the suture or staple line from a neorectal reservoir, as well as an abscess near the anastomosis, are also considered leaks [31]. The impact of AL on clinical management is recorded, together with the presence of subclinical (radiological) leaks.

Upon hospital admission, a buccal swab will be performed in order to collect DNA to screen for MBL and COX-2 polymorphisms. In addition, composition of volatile organic compounds (VOCs) in exhaled air will be measured both pre- and post-operatively. Various metabolic processes produce markers that are released into the circulation and, upon passage through the pulmonary system, can be identified as volatile products in exhaled air. The occurrence of (chronic) inflammation and/or oxidative stress can result in the excretion of volatile compounds that generate unique VOC patterns [32]. Furthermore, several baseline characteristics will be acquired prior to surgery, and stool will be collected on three occasions (pre-operatively, post-operatively and at the outpatient department during a control visit) in which the intestinal microbiome can be identified. It has been suggested that the microbiota play an important role in the pathogenesis of AL [33] and that the composition of the intestinal flora can be altered by surgical stress [34]. Plasma will be collected prior to surgery and on post-operative days 1, 3, and 5, in order to determine the concentration of markers for enterocyte damage (eg, I-FABP, citrullin, and calprotectin), transmural ischemia (eg, smooth muscle protein 22), and general inflammation markers (eg, CRP and leukocyte count).

In addition, SNAQ and Malnutrition Universal Screening Tool scores are obtained to assess the nutritional status of the patient, and CT-images are analyzed for total skeletal muscle cross-sectional area in order to distinguish sarcopenic patients from those in good nutritional health [25]. Generalized atherosclerosis will be assessed using abdominal CT-scans, as this is a proposed risk factor for AL [35,36]. Finally, a tissue sample will be obtained from the resected specimen, on which conventional and immunohistochemical staining will be performed.

Statistical Analyses

The sample size is calculated with a power analysis and is aimed at our main study outcome, AL. From literature, we know that approximately 10% of all colorectal patients receiving an anastomosis will develop AL [14,37]. The aim of the study is to detect significant and clinically relevant differences between the AL group and the non-AL group. Therefore, we used data from a previous study undertaken by our group to determine sample size [20]. We chose our least significant finding, to avoid the study being underpowered. Based on an effect size of 0.41 (calculated with mean calprotectin levels and SD on day 1), with a power of 0.80 and a 95% confidence interval, the total sample size will be 560, of whom an estimated 51 patients will

develop AL. Assuming a 5% dropout rate, the total number of patients that needs to be included in this study is 588.

After data collection, normality will be tested by the D'Agostino-Pearson test. Student's t-tests will be used for between-group comparisons for continuous data. Dichotomous variables will be compared using Pearson's chi-squared test. All data will be presented as mean and standard error of the mean. The area under the curve of receiver operating characteristic (ROC) curves will be used to calculate the diagnostic ability of the studied markers predicting AL. The area under the ROC curve is a summary measure of accuracy, lying in the range from 0.5 to 1, with 1 indicating perfect discrimination and 0.5 indicating no discrimination capacity. To determine the most ideal combination of markers, logistic regression analyses will be performed.

Results

This study has been open for inclusion since August 2015.

Discussion

Despite important improvements in peri-operative care for CRC surgeries and increased awareness of AL, incidence rates of this dreaded complication have remained stable for several decades. Most strikingly, leakage continues to occur in patients treated under the most expert care, without the presence of any known risk factors [38]. The lack of knowledge regarding the pathophysiological process of AL and the process of normal intestinal healing hampers the development of novel predictive and preventive methods. AL has significant impacts on morbidity and mortality, quality of life, and health care costs, and is suggested to negatively interfere with oncological prognoses [5,6,7,8]. Although large numbers of clinical trials have identified important patient-related and technical factors that aid in the prediction of AL [38,39], the search for a predictive biomarker for AL has hitherto remained unsuccessful. Almost all previously conducted studies reported a single risk factor for the development of AL in CRC patients undergoing surgery. The multi-modal design of the current study enables us to bypass the limitations encountered by previous studies.

In order to minimize the potentially life threatening clinical consequences of a leak, some surgeons opt to perform a deviating ostomy directly following the initial operation [41]. Although it is generally accepted that the presence of a colostoma or ileostoma reduces the sequelae of AL and the need for reoperation in case of a leak [42,43], a decrease in incidence of post-operative mortality has not yet been proven [42-46]. The presence of selection bias, in which an ostomy is performed in high-risk patients, should be considered when interpreting these results. Surgeons perform elective deviating ostomy in approximately 70% of cases of low rectal carcinoma, of which a significant percentage (19-40%) will never have their temporary ostomy reversed [47,48]. Possible benefits of a deviating stoma should be weighed against stoma-related morbidity, the impact on quality of life, and the mortality rates after stoma closure [49,50]. An adequate pre-operative risk analysis could aid surgeons and their patients in the decision-making process regarding the construction of temporary ostomies. The successful implementation of risk assessment tools would have a positive influence on morbidity and mortality rates, duration of hospital stays, and number of readmissions, re-interventions, and admissions to the ICU, leading to a significant increase in quality of life for the general patient population [38]. Anastomoses are also constructed in gastrointestinal surgery for other purposes than malignancies, such as inflammatory bowel disease or diverticulitis [51,52]. We have chosen to exclude these patients since their inflammatory status can be a confounding factor in the early detection and/or risk assessment of AL [53-55].

This study outline is based on the hypothesis that AL is partly due to patient-derived factors such as a derailed immune response, genetic predisposition, and a deficient microbiome composition, and that the clinical course can be further influenced by surgical stress, ischemia, and a compromised systemic response. This study aims at broadening our understanding of the pathophysiological process of AL by introducing novel biomarkers of intestinal damage and function, and to decrease the clinical burden of AL by both individual pre-operative risk assessment and early post-operative detection in the future.

Authors' Contributions

JD originated the study. AJ, JB, JD, TL and ND were involved in the study design. AJ and JB drafted the manuscript. AJ, SK, JB, TL, MS, GS and JS are local investigators at the participating centers. FS is head of the toxicology department and coordinates the VOC analyses. The study is supervised and coordinated by JD and NB. All authors provided essential feedback to the successive versions of the manuscript and approved the final version.

Conflicts of Interest

None declared.

References

1. Bertelsen CA, Andreasen AH, Jørgensen T, Harling H, Danish Colorectal Cancer Group. Anastomotic leakage after curative anterior resection for rectal cancer: short and long-term outcome. Colorectal Dis 2010 Jul;12(7 Online):e76-e81. [doi: 10.1111/j.1463-1318.2009.01935.x] [Medline: 19438879]
2. McArdle CS, McMillan DC, Hole DJ. Impact of anastomotic leakage on long-term survival of patients undergoing curative resection for colorectal cancer. Br J Surg 2005 Sep;92(9):1150-1154. [doi: 10.1002/bjs.5054] [Medline: 16035134]

3. Alves A, Panis Y, Trancart D, Regimbeau J, Pocard M, Valleur P. Factors associated with clinically significant anastomotic leakage after large bowel resection: multivariate analysis of 707 patients. World J Surg 2002 Apr;26(4):499-502. [doi: 10.1007/s00268-001-0256-4] [Medline: 11910487]
4. Lipska MA, Bissett IP, Parry BR, Merrie AE. Anastomotic leakage after lower gastrointestinal anastomosis: men are at a higher risk. ANZ J Surg 2006 Jul;76(7):579-585. [doi: 10.1111/j.1445-2197.2006.03780.x] [Medline: 16813622]
5. Branagan G, Finnis D, Wessex Colorectal Cancer Audit Working Group. Prognosis after anastomotic leakage in colorectal surgery. Dis Colon Rectum 2005 May;48(5):1021-1026. [doi: 10.1007/s10350-004-0869-4] [Medline: 15789125]
6. Walker KG, Bell SW, Rickard MJ, Mehanna D, Dent OF, Chapuis PH, et al. Anastomotic leakage is predictive of diminished survival after potentially curative resection for colorectal cancer. Ann Surg 2004 Aug;240(2):255-259. [Medline: 15273549]
7. Law WL, Choi HK, Lee YM, Ho JW, Seto CL. Anastomotic leakage is associated with poor long-term outcome in patients after curative colorectal resection for malignancy. J Gastrointest Surg 2007 Jan;11(1):8-15. [doi: 10.1007/s11605-006-0049-z] [Medline: 17390180]
8. Bell SW, Walker KG, Rickard MJ, Sinclair G, Dent OF, Chapuis PH, et al. Anastomotic leakage after curative anterior resection results in a higher prevalence of local recurrence. Br J Surg 2003 Oct;90(10):1261-1266. [doi: 10.1002/bjs.4219] [Medline: 14515297]
9. Kulu Y, Tarantio I, Warschkow R, Kny S, Schneider M, Schmied BM, et al. Anastomotic leakage is associated with impaired overall and disease-free survival after curative rectal cancer resection: a propensity score analysis. Ann Surg Oncol 2015 Oct;22(6):2059-2067. [doi: 10.1245/s10434-014-4187-3] [Medline: 25348782]
10. Mirnezami A, Mirnezami R, Chandrakumaran K, Sasapu K, Sagar P, Finan P. Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. Ann Surg 2011 May;253(5):890-899. [doi: 10.1097/SLA.0b013e3182128929] [Medline: 21394013]
11. Pommergaard HC, Gessler B, Burcharth J, Angenete E, Haglind E, Rosenberg J. Preoperative risk factors for anastomotic leakage after resection for colorectal cancer: a systematic review and meta-analysis. Colorectal Dis 2014 Sep;16(9):662-671. [doi: 10.1111/codi.12618] [Medline: 24655784]
12. Eberl T, Jagoditsch M, Klingler A, Tschmelitsch J. Risk factors for anastomotic leakage after resection for rectal cancer. Am J Surg 2008 Oct;196(4):592-598. [doi: 10.1016/j.amjsurg.2007.10.023] [Medline: 18571620]
13. Kang CY, Halabi WJ, Chaudhry OO, Nguyen V, Pigazzi A, Carmichael JC, et al. Risk factors for anastomotic leakage after anterior resection for rectal cancer. JAMA Surg 2013 Jan;148(1):65-71. [doi: 10.1001/2013.jamasurg.2] [Medline: 22986932]
14. Bertelsen CA, Andreasen AH, Jørgensen T, Harling H, Danish Colorectal Cancer Group. Anastomotic leakage after anterior resection for rectal cancer: risk factors. Colorectal Dis 2010 Jan;12(1):37-43. [doi: 10.1111/j.1463-1318.2008.01711.x] [Medline: 19175624]
15. Slieker JC, Komen N, Mannaerts GH, Karsten TM, Willemsen P, Murawska M, et al. Long-term and perioperative corticosteroids in anastomotic leakage: a prospective study of 259 left-sided colorectal anastomoses. Arch Surg 2012 May;147(5):447-452. [doi: 10.1001/archsurg.2011.1690] [Medline: 22249852]
16. Hakkarainen TW, Steele SR, Bastaworous A, Dellinger EP, Farrokhi E, Farjah F, et al. Nonsteroidal anti-inflammatory drugs and the risk for anastomotic failure: a report from Washington State's Surgical Care and Outcomes Assessment Program (SCOAP). JAMA Surg 2015 Mar 1;150(3):223-228. [doi: 10.1001/jamasurg.2014.2239] [Medline: 25607250]
17. Karliczek A, Harlaar NJ, Zeebregts CJ, Wiggers T, Baas PC, van Dam GM. Surgeons lack predictive accuracy for anastomotic leakage in gastrointestinal surgery. Int J Colorectal Dis 2009 May;24(5):569-576. [doi: 10.1007/s00384-009-0658-6] [Medline: 19221768]
18. Paun BC, Cassie S, MacLean AR, Dixon E, Buie WD. Postoperative complications following surgery for rectal cancer. Ann Surg 2010 May;251(5):807-818. [doi: 10.1097/SLA.0b013e3181dae4ed] [Medline: 20395841]
19. Schellekens DH, Grootjans J, Dello SA, van Bijnen AA, van Dam RM, Dejong CH, et al. Plasma intestinal fatty acid-binding protein levels correlate with morphologic epithelial intestinal damage in a human translational ischemia-reperfusion model. J Clin Gastroenterol 2014 Mar;48(3):253-260. [doi: 10.1097/MCG.0b013e3182a87e3e] [Medline: 24100750]
20. Reisinger KW, Poeze M, Hulsewé KW, van Acker BA, van Bijnen AA, Hoofwijk AG, et al. Accurate prediction of anastomotic leakage after colorectal surgery using plasma markers for intestinal damage and inflammation. J Am Coll Surg 2014 Oct;219(4):744-751. [doi: 10.1016/j.jamcollsurg.2014.06.011] [Medline: 25241234]
21. Rushfeldt CF, Sveinbjørnsson B, Søreide K, Vonen B. Risk of anastomotic leakage with use of NSAIDs after gastrointestinal surgery. Int J Colorectal Dis 2011 Dec;26(12):1501-1509. [doi: 10.1007/s00384-011-1285-6] [Medline: 21833507]
22. Subendran J, Siddiqui N, Victor JC, McLeod RS, Govindarajan A. NSAID use and anastomotic leaks following elective colorectal surgery: a matched case-control study. J Gastrointest Surg 2014 Aug;18(8):1391-1397. [doi: 10.1007/s11605-014-2563-8] [Medline: 24912916]
23. Reisinger KW, Schellekens DH, Bosmans JW, Boonen B, Hulsewé KW, Sastrowijoto P, et al. Cyclooxygenase-2 Is Essential for Colorectal Anastomotic Healing. Ann Surg 2016 Apr 8. [doi: 10.1097/SLA.0000000000001744] [Medline: 27070935]
24. Matthijsen RA, Derikx JP, Steffensen R, van Dam RM, Dejong CH, Buurman WA. Mannose-binding lectin null alleles are associated with preserved epithelial cell integrity following intestinal ischemia reperfusion in man. Mol Immunol 2009 Jul;46(11-12):2244-2248. [doi: 10.1016/j.molimm.2009.04.010] [Medline: 19477015]

25. Reisinger KW, van Vugt JL, Tegels JJ, Snijders C, Hulsewé KW, Hoofwijk AG, et al. Functional compromise reflected by sarcopenia, frailty, and nutritional depletion predicts adverse postoperative outcome after colorectal cancer surgery. Ann Surg 2015 Feb;261(2):345-352. [doi: 10.1097/SLA.0000000000000628] [Medline: 24651133]
26. Hyman N, Manchester TL, Osler T, Burns B, Cataldo PA. Anastomotic leaks after intestinal anastomosis: it's later than you think. Ann Surg 2007 Feb;245(2):254-258. [doi: 10.1097/01.sla.0000225083.27182.85] [Medline: 17245179]
27. Doeksen A, Tanis PJ, Wüst AF, Vrouenraets BC, van Lanschot JJ, van Tets WF. Radiological evaluation of colorectal anastomoses. Int J Colorectal Dis 2008 Sep;23(9):863-868 [FREE Full text] [doi: 10.1007/s00384-008-0487-z] [Medline: 18560844]
28. Doeksen A, Tanis PJ, Vrouenraets BC, Lanschot van JJ, Tets van WF. Factors determining delay in relaparotomy for anastomotic leakage after colorectal resection. World J Gastroenterol 2007 Jul 21;13(27):3721-3725 [FREE Full text] [Medline: 17659732]
29. Alves A, Panis Y, Pocard M, Regimbeau JM, Valleur P. Management of anastomotic leakage after nondiverted large bowel resection. J Am Coll Surg 1999 Dec;189(6):554-559. [Medline: 10589591]
30. Gustafsson UO, Scott MJ, Schwenk W, Demartines N, Roulin D, Francis N, Enhanced Recovery After Surgery Society. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS) Society recommendations. Clin Nutr 2012 Dec;31(6):783-800. [doi: 10.1016/j.clnu.2012.08.013] [Medline: 23099039]
31. Rahbari NN, Weitz J, Hohenberger W, Heald RJ, Moran B, Ulrich A, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. Surgery 2010 Mar;147(3):339-351. [doi: 10.1016/j.surg.2009.10.012] [Medline: 20004450]
32. Boots AW, van Berkel JJ, Dallinga JW, Smolinska A, Wouters EF, van Schooten FJ. The versatile use of exhaled volatile organic compounds in human health and disease. J Breath Res 2012 Jun;6(2):027108. [doi: 10.1088/1752-7155/6/2/027108] [Medline: 22621865]
33. Shogan BD, Belogortseva N, Luong PM, Zaborin A, Lax S, Bethel C, et al. Collagen degradation and MMP9 activation by Enterococcus faecalis contribute to intestinal anastomotic leak. Sci Transl Med 2015 May 6;7(286):286ra68. [doi: 10.1126/scitranslmed.3010658] [Medline: 25947163]
34. Shogan BD, Smith DP, Christley S, Gilbert JA, Zaborina O, Alverdy JC. Intestinal anastomotic injury alters spatially defined microbiome composition and function. Microbiome 2014;2:35 [FREE Full text] [doi: 10.1186/2049-2618-2-35] [Medline: 25250176]
35. Komen N, Klitsie P, Dijk JW, Slieker J, Hermans J, Havenga K, et al. Calcium score: a new risk factor for colorectal anastomotic leakage. Am J Surg 2011 Jun;201(6):759-765. [doi: 10.1016/j.amjsurg.2010.01.033] [Medline: 20870213]
36. Foster ME, Brennan SS, Morgan A, Leaper DJ. Colonic ischaemia and anastomotic healing. Eur Surg Res 1985;17(3):133-139. [Medline: 3158528]
37. Karup PM, Jorgensen LN, Andreasen AH, Harling H. A nationwide study on anastomotic leakage after colonic cancer surgery.. Colorectal Dis 2010 Oct;14(10):661-667. [doi: 10.1111/j.1463-1318.2012.03079.x]
38. Bellows CF, Webber LS, Albo D, Awad S, Berger DH. Early predictors of anastomotic leaks after colectomy. Tech Coloproctol 2009 Mar;13(1):41-47. [doi: 10.1007/s10151-009-0457-7] [Medline: 19288246]
39. Alberts JC, Parvaiz A, Moran BJ. Predicting risk and diminishing the consequences of anastomotic dehiscence following rectal resection. Colorectal Dis 2003 Sep;5(5):478-482. [Medline: 12925084]
40. Boccola MA, Buettner PG, Rozen WM, Siu SK, Stevenson AR, Stitz R, et al. Risk factors and outcomes for anastomotic leakage in colorectal surgery: a single-institution analysis of 1576 patients. World J Surg 2011 Jan;35(1):186-195. [doi: 10.1007/s00268-010-0831-7] [Medline: 20972678]
41. Shogan BD, Carlisle EM, Alverdy JC, Umanskiy K. Do we really know why colorectal anastomoses leak? J Gastrointest Surg 2013 Sep;17(9):1698-1707. [doi: 10.1007/s11605-013-2227-0] [Medline: 23690209]
42. Matthiessen P, Hallböök O, Rutegård J, Simert G, Sjödahl R. Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial. Ann Surg 2007 Aug;246(2):207-214. [doi: 10.1097/SLA.0b013e3180603024] [Medline: 17667498]
43. Gastinger I, Marusch F, Steinert R, Wolff S, Koeckerling F, Lippert H, Working Group Colon/Rectum Carcinoma. Protective defunctioning stoma in low anterior resection for rectal carcinoma. Br J Surg 2005 Sep;92(9):1137-1142. [doi: 10.1002/bjs.5045] [Medline: 15997447]
44. Hanna MH, Vinci A, Pigazzi A. Diverting ileostomy in colorectal surgery: when is it necessary? Langenbecks Arch Surg 2015 Feb;400(2):145-152. [doi: 10.1007/s00423-015-1275-1] [Medline: 25633276]
45. Anderin K, Gustafsson UO, Thorell A, Nygren J. The effect of diverting stoma on postoperative morbidity after low anterior resection for rectal cancer in patients treated within an ERAS program. Eur J Surg Oncol 2015 Jun;41(6):724-730. [doi: 10.1016/j.ejso.2015.03.234] [Medline: 25908011]
46. Wong NY, Eu KW. A defunctioning ileostomy does not prevent clinical anastomotic leak after a low anterior resection: a prospective, comparative study. Dis Colon Rectum 2005 Nov;48(11):2076-2079. [doi: 10.1007/s10350-005-0146-1] [Medline: 16086220]
47. Mealy K, O'Broin E, Donohue J, Tanner A, Keane FB. Reversible colostomy - what is the outcome? Dis Colon Rectum 1996 Nov;39(11):1227-1231. [Medline: 8918429]

48. Lim SW, Kim HJ, Kim CH, Huh JW, Kim YJ, Kim HR. Risk factors for permanent stoma after low anterior resection for rectal cancer. Langenbecks Arch Surg 2013 Feb;398(2):259-264. [doi: 10.1007/s00423-012-1038-1] [Medline: 23224628]
49. Güenaga KF, Lustosa SA, Saad SS, Saconato H, Matos D. Ileostomy or colostomy for temporary decompression of colorectal anastomosis. Cochrane Database Syst Rev 2007(1):CD004647. [doi: 10.1002/14651858.CD004647.pub2] [Medline: 17253517]
50. Mala T, Nesbakken A. Morbidity related to the use of a protective stoma in anterior resection for rectal cancer. Colorectal Dis 2008 Oct;10(8):785-788. [doi: 10.1111/j.1463-1318.2007.01456.x] [Medline: 18190612]
51. Bernstein CN, Fried M, Krabshuis JH, Cohen H, Eliakim R, Fedail S, et al. World Gastroenterology Organization practice guidelines for the diagnosis and management of IBD in 2010. Inflamm Bowel Dis 2010 Jan;16(1):112-124. [doi: 10.1002/ibd.21048] [Medline: 19653289]
52. Janes SE, Meagher A, Frizelle FA. Management of diverticulitis. BMJ 2006 Feb 4;332(7536):271-275 [FREE Full text] [doi: 10.1136/bmj.332.7536.271] [Medline: 16455722]
53. Sarikaya M, Ergül B, Doğan Z, Filik L, Can M, Arslan L. Intestinal fatty acid binding protein (I-FABP) as a promising test for Crohn's disease: a preliminary study. Clin Lab 2015;61(1-2):87-91. [Medline: 25807642]
54. Kurada S, Alkhouri N, Fiocchi C, Dweik R, Rieder F. Review article: breath analysis in inflammatory bowel diseases. Aliment Pharmacol Ther 2015 Feb;41(4):329-341. [doi: 10.1111/apt.13050] [Medline: 25523187]
55. Desai D, Faubion WA, Sandborn WJ. Review article: biological activity markers in inflammatory bowel disease. Aliment Pharmacol Ther 2007 Feb;25(3):247-255. [doi: 10.1111/j.1365-2036.2006.03184.x]

Abbreviations

AL: anastomotic leakage
COX-2: cyclo-oxygenase 2
CRC: colorectal cancer
CRP: C-reactive protein
CT: computerized tomography
I-FABP: intestinal fatty acid binding protein
MBL: mannose-binding lectin
NSAIDs: non-steroidal anti-inflammatory drugs
OR: odds ratio
REVEAL: Predictive Factors of Anastomotic Leakage after Colorectal Surgery
ROC: receiver operating characteristic
SNAQ: short nutritional assessment questionnaire
VOC: volatile organic compound

Edited by G Eysenbach; submitted 23.12.15; peer-reviewed by I Wani; comments to author 22.01.16; revised version received 07.02.16; accepted 07.02.16; published 09.06.16.

Please cite as:
Jongen ACHM, Bosmans JWAM, Kartal S, Lubbers T, Sosef M, Slooter GD, Stoot JH, van Schooten FJ, Bouvy ND, Derikx JPM
Predictive Factors for Anastomotic Leakage After Colorectal Surgery: Study Protocol for a Prospective Observational Study (REVEAL Study)
JMIR Res Protoc 2016;5(2):e90
URL: http://www.researchprotocols.org/2016/2/e90/
doi:10.2196/resprot.5477
PMID:27282451

Protocol

Determination of Anti-Adeno-Associated Viral Vector Neutralizing Antibodies in Patients With Heart Failure in the Cardiovascular Foundation of Colombia (ANVIAS): Study Protocol

Melvin Y Rincon[1,2], MD, PhD; Carlos E Prada[1,3], MD; Marcos Lopez[4,5], PhD; Victor Castillo[1], MD; Luis Eduardo Echeverria[1], MD; Norma Serrano[1], MSc, MD

[1]Centro de Investigaciones, Fundacion Cardiovascular de Colombia, Floridablanca, Colombia

[2]Department of Gene Therapy and Regenerative Medicine, Free University of Brussels (VUB), Brussels, Belgium

[3]Division of Human Genetics, Cincinnati Children's Hospital Medical Center (CCHMC), Cincinnati, OH, United States

[4]Translational Biomedical Research Group, Biotechnology Laboratories, Fundación Cardiovascular de Colombia, Floridablanca, Colombia

[5]Graduate Program in Biomedical Sciences, Faculty of Health, Universidad del Valle, Cali, Colombia

Corresponding Author:
Melvin Y Rincon, MD, PhD
Centro de Investigaciones
Fundacion Cardiovascular de Colombia
Calle 155A No. 23 - 58
Floridablanca,
Colombia
Phone: 57 7 6796470
Fax: 57 7 6399292
Email: rinconmy@gmail.com

Abstract

Background: Recent progress in the pathophysiology of heart failure (HF) has led to the development of new therapeutic options such as gene therapy and the use of adeno-associated viral (AAV) vectors. Despite the promising results in early clinical trials of gene therapy for HF, various obstacles have been faced, such as the presence of neutralizing antibodies (NAbs) against the capsid vectors. NAb activity limits vector transduction levels and therefore diminishes the final therapeutic response. Recent studies evaluating the prevalence of NAbs in various populations found considerable geographic variability for each AAV serotype. However, the levels of NAbs in Latin American populations are unknown, becoming a limiting factor to conducting AAV vector therapeutic trials in this population.

Objective: The goal of this study is to determine for the first time, the prevalence of anti-AAV NAbs for the serotypes 1, 2, and 9 in HF patients from the city of Bucaramanga, Colombia, using the *in vitro* transduction inhibition assay.

Methods: We will conduct a cross-sectional study with patients who periodically attend the HF clinic of the Cardiovascular Foundation of Colombia and healthy volunteers matched for age and sex. For all participants, we will evaluate the NAb levels against serotypes AAV1, AAV2, and AAV9. We will determine NAb levels using the *in vitro* transduction inhibition assay. In addition, participants will answer a survey to evaluate their epidemiological and socioeconomic variables. Participation in the study will be voluntary and all participants will sign an informed consent document before any intervention.

Results: The project is in the first phase: elaboration of case report forms and the informed consent form, and design of the recruitment strategy. Patient recruitment is expected to begin in the spring of 2016. We expect to have preliminary results, including the titer of the viral vectors, multiplicity of infections that we will use for each serotype, and the general validation of the assay, at the end of 2016. The final results are expected mid-2017.

Conclusions: This project is the first effort to evaluate NAb levels against AAV1, AAV2, and AAV9 serotypes in patients with HF in Latin America. Our results will allow us to check the cross-reactivity response between the serotypes assessed, to describe the epidemiological characteristics of the participant population, and to set up a link with earlier reports of NAb prevalence in the literature.

(JMIR Res Protoc 2016;5(2):e102) doi:10.2196/resprot.5535

KEYWORDS

gene therapy; heart failure; adeno-associated viral vector; neutralizing antibodies; Colombia

Introduction

Heart failure (HF) is the cardiovascular disease (CVD) with the highest mortality and morbidity globally. Recent reports indicate that up to 1% to 2% of adult populations in developed countries have HF, with an increasing prevalence of ≥10% among people ≥70 years old [1]. Despite the significant improvement in management of disease symptoms and the decreased disease progression achieved with newly developed pharmacological therapies and invasive procedures, alternative therapeutic approaches are still urgently needed to provide a definitive cure [2]. Recent advances in structural and molecular cardiology have shown that abnormalities in the calcium cycling proteins play a significant role in the induction and progression of HF. Decreased sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2a) activity has been described to be a critical pathway responsible for pathologic modification of the cardiomyocytes during HF [3]. These findings, together with advances in gene transfer technologies, have led to gene therapy being considered as a new therapeutic option for CVDs, and specially for HF. Encouraging results from early clinical trials involving the use of adeno-associated viral (AAV) vectors delivering the *SERCA2* gene have generated high expectations [4]. Additionally, other proteins have shown promising results in preclinical models of HF, such as S100A1 and adenylyl cyclase 6 [5,6].

Emergence of Gene Therapy as a Therapeutic Option for HF and CVD

Three elements must be considered in the design of a gene therapy strategy: the therapeutic gene that will be cloned into the transgene expression cassette; the target cells or tissues in which the vector will deliver the genetic material; and the viral vector used to facilitate entry of the gene into the target tissue [7]. Viral vectors consist of genetic material surrounded by a protein capsid, which facilitates the transcellular transport and internalization of the therapeutic gene into the target cell [7]. Additionally, the capsid protects the transgene expression cassette from lysosomal degradation during its trafficking to the nucleus [8]. The discovery of viral vectors with cardiomyocyte and endothelial tropism accelerated the progression of gene therapy as a therapeutic option for HF [9]. Novel transductional modifications of the first-generation vectors and translational strategies in the transgene expression cassettes have been developed to achieve higher and longer-term expression of the transfected gene while trying to decrease the amount of adverse effects [10]. As Mingozzi and High state, “The gene is the active agent of therapeutic, but the vector, in most cases derived from a virus, is also a critical determinant of therapeutic success and of the toxicity profile” [11]. Importantly, depending on the viral vector selected, the immune response to the vector or to the cells expressing the modified gene varies and can become a limiting factor for successful therapy [12]. Specific immune responses can prevent vector gene transfer after readministration of the vector, limit the duration of gene expression, or produce an immune response against the genetically modified cells [13].

Viral vectors derived from adenovirus, retrovirus, lentivirus, or AAV have been used as therapeutic tools for a broad spectrum of genetic and nongenetic diseases, including CVD and HF. Lentivirus vectors originate from human immunodeficiency virus 1 and have been used successfully to treat hematopoietic monogenic diseases thanks to their therapeutic long-term effects [14,15]. However, their use in gene therapy applications for CVD or specifically for HF is more limited, given their relatively poor transduction after systemic administration and the risk of insertional mutagenesis [16]. Adenoviral vectors are non-enveloped double-stranded DNA vectors, which are not able to insert the genome into the host cell DNA. Adenovirus serotype 5 has been used predominantly in preclinical and clinical trials of gene therapy for myocardial infarction and ischemic diseases, in which short-term transgenic expression is required [17].

The most commonly used viral vectors for HF and the focus of our project are the AAV vectors. AAV vectors are single-stranded DNA vectors with a favorable safety profile and the ability to achieve long-term transgene expression in a wide range of tissues, including heart [18]. The storage capacity of the AAV vector (up to 4.7 kB) restricts the size of the transgene expression cassette that can be used and needs to be considered beforehand [19]. More than 100 AAV serotypes existing in nature have been reported, many of them with variable tissue tropism, which is determined by the structure of the proteins in the capsid [18]. AAV1, AAV6, AAV8, and AAV9 have been reported as the serotypes with favorable tropism for cardiomyocytes after systemic administration. However, tropism for other cell types, such as hepatocytes, is still present and needs to be carefully considered before any clinical trial [9,20,21]. Satisfactory preclinical results in large experimental animal models with a heart anatomy similar to that of humans led to the clinical translation of AAV-based technology for transgene expression of key proteins involved in the progression of HF, such as SERCA2a [22]. The first clinical trial for HF was conducted using an AAV1 vector, the Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease (CUPID) trial [23]. Simultaneously, two other clinical trials are in the late phases of recruitment, the phase 2 study Investigation of Safety and Feasibility of AAV1/SERCA2a Gene Transfer in Patients With Chronic Heart Failure (SERCA-LVAD; NCT00534703) and the AAV1-CMV-SERCA2a Gene Therapy Trial in Heart Failure (AGENT-HF; NCT01966887), with results expected in 2016.

Immune Response Against AAV Vectors

Immune responses of T cells against antigens of the AAV capsid presented in association with major histocompatibility complex class I on the surface of transduced target cells can reduce long-term gene expression, after an immune rejection of the genetically modified target cells [11]. Transient immunosuppressive therapies or AAV capsid variants that

reduced the presentation of peptides derived from the AAV capsid can decrease this risk of immune responses [24,25]. The vector capsid is, in most cases, an exact replica of the viral capsid, and thus the immune response against the vector may be influenced by previous exposure of the immune system to environmental viruses from which the vector is designed [26]. Humans, early in life, are naturally exposed to wild-type AAV, and consequently the frequency of seropositivity of anti-AAV steadily increases after 2 years of age [26]. Humoral immunity to AAV can also be found in infants, as a result of vertical transmission of anti-AAV antibodies from the mother. In adults, anti-AAV2 antibodies are the most prevalent (up to 70% of healthy humans), followed by serotypes such as AAV5, AAV9, and AAV8, which are much less frequent [27]. Although the risk of inflammatory immune responses after AAV vector transduction is significantly lower than with adenoviral vectors, there are still significant immunological complications that must be evaluated. In particular, the high prevalence of preexisting anti-AAV neutralizing antibodies (NAbs) in the population may result in rapid neutralization of vectors derived from AAV, preventing adequate gene transfer [12]. Similarly, the induction of NAbs after AAV-based gene therapy impedes adequate therapeutic response following readministration of AAV vectors [7,28].

Anti-AAV NAbs

There is a high degree of amino acid sequence conservation between AAV capsids, leading to anti-AAV antibody cross-reactivity in a wide range of serotypes [29]. Although antibodies to AAV2 are clearly the most prevalent in humans (up to 70%), the natural host for this serotype, antibodies that recognize virtually all serotypes of AAV may be found in a high proportion of humans [26]. Studies have shown that, after AAV vectors were introduced into the systemic circulation in humans, the preexisting humoral immunity to AAV vectors profoundly reduced transduction efficiency in the target tissue. Results of the first clinical trial for hemophilia B showed that relatively low titers of NAbs, as low as 1:17, can completely neutralize large vector doses, without detection of transgene expression [12]. The existence of anti-AAV NAbs is one of the main limitations faced in gene therapy clinical trials after intravascular delivery of AAV vectors. In the CUPID 2 trial, patients with high levels of NAbs were excluded. Of the 509 patients initially evaluated, >50% were excluded for presenting levels of NAbs outside of the safety range established in the study [30], suggesting the importance of prior determination of anti-AAV NAb circulating levels in different populations.

The prevalence of NAbs against AAV in humans was initially reported in the 1960s and 1970s, mainly anti-AAV1 and -AAV2 serotypes, the only known serotypes at that time. NAb variation is estimated at between 30% and 80% based on previously published studies in other populations [31,32]. More recent studies have evaluated the prevalence of NAbs in the most commonly used serotypes for preclinical studies (AAV5, AAV7, AAV8, and AAV9) and compared them with previously described serotypes. One study that collected samples from 10 countries on 4 continents (United States, Europe, Africa, and Australia) showed a prevalence of NAbs to AAV2 of between 30% and 60% of the total population [27]. This was significantly higher than the prevalences of NAbs to AAV7, AAV8, and AAV9 serotypes, which were reported to be between 15% and 30%. Notably, higher frequencies of NAbs were observed for all AAV serotypes in Africa than in the other regions [27]. However, none of the existing reported studies have included a Latin American population.

An interesting finding is the significant variability in the prevalence of anti-AAV NAbs, influenced by the geographic origin of the population. While the prevalence of NAbs against AAV1 in Africa and China is around 50% to 70%, in other countries such as Belgium, Greece, Italy, and the United States, it is only 20% to 30% [27]. Overall, the prevalence of anti-AAV NAbs appears to be greater in developing countries. Factors such as living conditions, population density, hygienic conditions, different levels of health care, and the AAV detection method for NAbs can influence these results; in particular, the prevalence of anti-AAV1 NAbs was higher in women than in men [27]. The health status of the target population can also affect the prevalence NAbs against AAV, especially in those patients with a compromised immune system. These people had a lower prevalence of anti-AAV NAbs than that in the healthy population [26,27,33,34]; furthermore, the prevalence of NAbs was higher in elderly than in younger populations [35].

AAV Antibody Determination

Diverse methods have been developed to detect antibodies against different serotypes of AAV. Some of them are based on total binding antibodies to the AAV capsid, and others on the functional determination of antibodies that neutralize AAV vector transduction *in vitro* or *in vivo* [29]. The first reports, in the 1970s, were based on binding of antibodies to AAV capsid vector evaluated by enzyme-linked immunosorbent assay (ELISA) and Western blot [32]. These studies focused on AAV1 and AAV2. The discovery in the last decade of new AAV vectors required more accurate assays to evaluate not only the level of binding but also the effect of the specific NAb for each AAV serotype on vector activity. Given the profound effect of anti-AAV antibody on transduction efficiency, the development of sensitive and reliable methods for measuring patients' titers of NAbs is critical before starting a clinical trial with gene therapy. Furthermore, the method of choice must ensure correlation of titers with the clinical outcome reported for gene therapy.

Elisa

ELISA is based on a capture assay in which the entire AAV capsid or peptides coated on a plate and AAV immunoglobulin antibodies present in serum are detected with a secondary antibody. ELISAs are easier to configure and are relatively sensitive at determining antibody levels. However, the total amount of anti-AAV antibodies is not always proportional to its neutralizing activity, especially in people with low titers, making this assay unreliable for determining the eligibility of people for their participation in clinical trials with AAV vectors.

In Vitro Cell-Based Assays

These are among the most widely used methods to determine anti-AAV NAbs [27,36,37]. Specifically, the *in vitro* transduction inhibition assay has become the standard test to

evaluate the presence of anti-AAV NAbs [37]. Typically, an AAV vector expressing a reporter gene is mixed with serially diluted amounts of the test sample, and this vector serum mixture is incubated with the cell line of choice, which is then analyzed for reporter gene expression. The starting dilution of the test sample, which defines assay sensitivity, varies across studies, ranging from 1:2 to 1:20. The NAb50 titer is reported as the highest serum dilution that inhibits the transduction of the reporter gene by 50% [37]. While NAb *in vitro* assays are relatively easy to set up and give consistent results, they have some limitations: the most important derives from the fact that most of the AAV serotypes are highly inefficient for *in vitro* cell transduction. This limitation can be at least partially overcome with the use of reporter genes with high detection sensitivity (eg, luciferase) and cell lines more permissive for AAV transduction [37]. In addition, several related parameters of the cell culture conditions can contribute to variability of the assay, such as the cell line used, cell density, and the number of passages of cells during cultivation.

In summary, recent reports highlight the importance of identifying the prevalence of NAbs for each AAV serotype in various human populations, due to the serotypes' geographic variability and their major role in selection of participants for AAV vector clinical trials. This increases the importance of conducting NAb prevalence studies in the Latin American population. Considering the major impact of CVD on the health care systems of developing countries, we intend to determine the prevalence of anti-AAV vector NAbs for the serotypes AAV1, AAV2, and AAV9 in patients with HF in the Cardiovascular Foundation of Colombia (FCV) by the *in vitro* transduction inhibition assay.

Methods

We will conduct a cross-sectional study to evaluate NAbs against AAV1, AAV2, and AAV9 serotypes in patients with HF at the FCV-HF clinic. Patients who fulfill the inclusion criteria will be invited to participate in the study. Those who accept will be asked to read and ask the questions they deem relevant to informed consent before signing the form (see Multimedia Appendix 1). Once the patients consent to participate, a standardized and approved survey to evaluate epidemiologic and socioeconomic variables and major CVD risk factors will be applied and complemented with relevant clinical information obtained from the electronic medical record system (SAHI 2.0 software, integrated hospital management system) developed by the FCV. A physical examination will be performed, including evaluation of blood pressure levels, anthropometric measurements, and a record of the last echocardiographic parameters available. Finally, a sample of peripheral blood will be collected from each participant to determine the presence of anti-AAV NAbs.

Study Population

We will evaluate 60 patients with a diagnosis of HF (American Heart Association stage B or higher criteria) followed in the FCV-HF clinic (see Textbox 1 for inclusion criteria for the patient group). All adult patients (≥18 years old) followed in the HF clinic at FCV will be eligible for the study. We will use various methods to recruit patients, including electronic clinical data from the SAHI 2.0 records. Additionally, we will invite 60 healthy volunteers, matched by age and sex, to participate. Participants will be considered as healthy volunteers if they are ≥18 years old, nationals from a Latin America country with a residence address in Colombia, and not meeting any of the exclusion criteria detailed in Textbox 2. We selected the number of participants as convenience size due to the internal financial and technical limitations of the project.

Textbox 1. Inclusion criteria for patients in the ANVIAS study.

- Age ≥18 years
- Diagnosis of heart failure stage B or higher according to the American Heart Association criteria
- National of a Latin America country with residence address in Colombia
- Followed in the Cardiovascular Foundation of Colombia heart failure clinic

Textbox 2. Exclusion criteria for patients simultaneously presenting with heart failure and for volunteer participants the ANVIAS study.

- Multiple blood transfusions
- Recent plasmapheresis
- Infection with human immunodeficiency virus
- Immunosuppression or recent treatment with corticosteroids
- Solid organ or bone marrow transplantation
- Diagnosis of Chagas disease
- Pregnancy
- Preexisting condition of asthma, obstructive sleep apnea, or chronic obstructive pulmonary disease
- Prior hormone replacement therapy
- Heavy drinking, defined as the consumption of ≥5 alcoholic drinks on the same occasion on each of ≥5 days in the past 30 days (US Substance Abuse and Mental Health Services Administration definition)

Storage of Biological Material

Participants will be asked to consent to donate biological material to be stored according to all quality and ethical requirements in the biobank of the FCV. The FCV biobank is a biomedical platform for future research, which is of great relevance in contributing to establishing bridges between basic, translational, and clinical research, and health care practice. Importantly, participants in this proposed study will be required to grant additional consent for taking and storing samples in the biobank (see Multimedia Appendix 1).

Blood Sample Collection and Separation of Components

Samples of peripheral blood will be collected by antecubital venipuncture with a Vacutainer system (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) into 2 tubes containing 4 mL of EDTA anticoagulant and labelled to identify the participant. Then, the sample will be centrifuged to separate the components and stored according to established protocols by the FCV biobank. A physical and digital date and time record of sampling separation and storage components will be kept, as well as the name of the person responsible for the procedures.

Samples will be handled from the first to the final phase by the following FCV biobank storage steps: 1) obtaining informed consent for storage of samples in the biobank: Protocol PR-BIO-01, 2) blood sampling: Protocol PR-BIO-03, 3) transporting biological samples: Protocol PR-BIO-02, 4) receiving and storing samples: Protocol PR-BIO-05, 5) quality control of human biological material, storage, and registration: Protocol PR-BIO-08.

Data Processing and Quality Control

The data will be recorded on case report forms previously designed for that purpose. After completing the case report form, the monitor of the study will review the data to confirm completeness, readability, accuracy, and consistency. All detected errors will be reported, evaluated, and properly corrected by the originator of the forms. All corrections will be noted with dates and initials of the person issuing the correction in accordance with the World Health Organization's Guidelines for Good Clinical Practice [38]. Immediately after the form is correct, the information will be recorded in a database.

Production and Purification of Viral Vectors

We will produce the AAV1, AAV2, and AAV9 vectors using the cotransfection strategy of human embryonic kidney 293 cells specially modified to facilitate transfection of AAV (AAV-293; Agilent Technologies, Santa Clara, CA, USA; catalog #240073) via calcium phosphate (ThermoFisher Scientific, Waltham, MA, USA) [39]. We will use a pAAV with the plasmid of interest, a helper adenoviral plasmid, and a chimeric construct having the AAV2 *rep* gene, along with the corresponding AAV1, AAV2, or AAV9 *cap* gene [9].

We will evaluate the AAV-293 cells for microbial contamination using the polymerase chain reaction protocol for detecting mycoplasma. Following the previously described protocol, 2 days after transfection, we will collect cells and purify the vector particles using precipitation gradient centrifugation methods. The harvested cells will be lysed by successive cycles of freezing, thawing, and sonication, then treated with Benzonase nuclease (Novagen, Madison, WI, USA) and deoxycholic acid (Sigma-Aldrich, St. Louis, MO, USA), and then subjected to 3 successive rounds of cesium chloride density-gradient ultracentrifugation (ThermoFisher Scientific). We will collect the fractions containing AAV vector, concentrate it using 1-mmol/L $MgCl_2$(phosphate buffered saline) (Gibco, BRL), and store it at –80°C until use. Quantification of AAV1, AAV2, or AAV9-cytomegalovirus-luciferase (in viral genomes/mL) vectors will be determined by quantitative real-time polymerase chain reaction probes using SYBR Green Supermix (Bio-Rad, Hercules, CA, USA) and primers specific for luciferase complementary DNA. The forward and reverse primers that we will use are CCCACCGTCGTATTCGTGAG5'-3' and 5'TCAGGGCGATGGTTTTGTCCC-3', respectively.

Typically, we have managed to standardize the protocol and achieve titers in the range of 2×10^{12} to 5×10^{12} viral genomes/mL. To generate standard curves, we will use a plasmid of known copy numbers corresponding to the vectors used to generate AAV vectors carrying the appropriate complementary DNA. Viral vectors will be produced in collaboration with the laboratory of the Department of Gene Therapy and Regenerative

Medicine, Free University of Brussels, by the principal investigator, Dr Melvin Rincon.

Determination of Neutralizing Antibodies

We will determine NAb titers against serotypes AAV1, AAV2, and AAV9 following the recently published protocol in *Human Gene Therapy Methods* by Dr F Mingozzi's group [37]. This protocol is used due to high reproducibility of the results, in addition to the efficiency and safety it offers. Determination of NAb titers is based on an AAV vector expressing a reporter gene, which is incubated with the sample to be evaluated before *in vitro* transduction of a specific cell line. We describe the main features of the protocol below; for a more detailed protocol please review the publication by Meliani et al [37].

Multiplicity of Infection Selection

Importantly, as Meliani et al [37] mention, an optimal multiplicity of infection (MOI) should be determined for each serotype. We will select the MOI for each serotype NAb assay by determining the viral vector needed to give a luciferase signal above background signal and below saturation levels, measured in relative light units, considering that the number of AAV genome copy particles to be used is equal to the desired MOI multiplied by the number of cells to be infected.

For our project, we will transduce human embryonic kidney 293-derived 2V6.11 cells with an increasing MOI of the corresponding serotype (AAV1, AAV2, or AAV9); 24 hours later we will measure luciferase expression and select the most appropriate MOI for each serotype.

Assay Validation

Validation of any assay is fundamental before translation to clinical practice. Simultaneously with execution of the project and, based on initial results from the patients' samples, we will perform a process similar to the following (to be reported in the final paper): 1) determine the optimal cut point (threshold), 2) determine sensitivity, 3) select quality controls, 4) set specificity and assay precision, and 5) determine selectivity. We refer the reader to previously published papers for more detailed information [40,41].

After selecting the desired MOI and establishing the conditions of the assay, we will conduct a 4-day NAb assay protocol, as follows.

Day 1: Cell Culture 2V6.11

We will suspend 2×10^4 2V6.11 cells in 100 µL of Dulbecco's modified Eagle's medium (DMEM)/Ham's nutrient mixture F-12 culture medium (Sigma-Aldrich) supplemented with 10% fetal bovine serum. The cells will be cultured for 24 hours in an incubator (37°C, 5% CO_2) in 96-well culture plates. To induce expression of the *E4* gene, Ponasterone A will be added to the culture medium (Sigma-Aldrich) (10 mL).

Day 2: Sample Controls and AAV Vector Preparation

For transduction, we will prepare serial dilutions of 10 mL of patient serum and a control sample using fetal bovine serum as the diluent (Table 1). One control sample will correspond to 100% transduction of the vector and another to 0% transduction of the vector to allow for determining the background luminescence signal. The viral vector will be diluted to the concentration selected (according to the desired working MOI) in DMEM without the use of fetal bovine serum. Subsequently, we will add 20 µL of the vector to each of the sample dilutions and controls. These samples will be grown for 1 hour at 37°C and, subsequently, 7.5 µL of each neutralized sample will be added to the cell culture medium. Cells will remain in overnight incubation at 37°C and 5% CO_2.

Table 1. Example[a] of half-log dilution preparation for the test sample and control using fetal bovine serum as the diluent before being mixed with the viral vector (20 µL) and added to 96-well plated cultured cells.

Dilution no.	Relation	Volume (µL) of sample/control	Volume (µL) of diluent
1	1:1	40	0
2	1:3.16	12 of dilution 1	26
3	1:10	12 of dilution 2	26
4	1:31.6	12 of dilution 3	26
5	1:100	12 of dilution 4	26
6	1:316	12 of dilution 5	26
7	1:1000	12 of dilution 6	26
8	1:3160	12 of dilution 7	26

[a]Modified from Meliani et al [37].

Day 3: Cell Lysis and Measurement of Luciferase Activity

On this day, we will use the protocol for the Bright-Glo Luciferase Assay System (Promega Corporation, Madison, WI, USA). After incubating the assay for 15 minutes at room temperature, we will add 100 µL of cell lysis medium and the luminescence substrate, then wait for 3 minutes until lysis is complete. Luminescence will be measured using the EnSpire reader (PerkinElmer, Inc, Waltham, MA, USA).

Day 4: Determination of Anti-AAV NAb titers

To calculate the luciferase expression percentage (LEP) and luciferase inhibition percentage (LIP), we will use the formulas LEP=[(test sample luciferase reading−no virus luciferase

signal)/(maximum luciferase signal−no virus luciferase signal)]×100 and LIP = 100 – LEP.

The neutralizing titer of the sample is reported as the first dilution at which ≥50% inhibition of luciferase expression is measured. For example, if ≥50% inhibition is observed at a sample dilution of 1:10, then the neutralizing titer is reported as 1:10. NAb titers will be determined for the selected serotypes in collaboration with the laboratory of the Department of Gene Therapy and Regenerative Medicine at the Free University of Brussels by the principal investigator, Dr Melvin Rincon.

Statistical Analysis

We will describe data from all measurements of continuous variables using measures of central tendency such as means and standard deviations, considering the coefficients of variation between replicates (3) of the experiments. We will report counts and proportions of categorical variables with their respective 95% confidence intervals. For tests between study groups, we will use analysis of variance to assess differences between means and the chi-square test for differences between proportions. Differences with a value of $P<.05$ will be considered significant. We will use Stata 8.0 statistical software (StataCorp LP).

Results

We have completed the first phase of the project. During this stage, all the documents necessary for recording and storing information have been elaborated and submitted to the ethical committee of the FCV for approval. We expect to begin recruiting patients in the spring of 2016. We expect to complete the second phase, in which we will validate all the protocols for the project—including determining the titer of the viral vectors, selecting the MOI that we will use for each serotype, and validating the assay—by the end of 2016. Finally, we will conduct the third phase, in which we will analyze serum samples from patients and healthy volunteers, during 2017. We expect to have the first results in mid-2017.

Discussion

For this project, we will evaluate anti-AAV1, -AAV2, and -AAV9 NAbs by using the *in vitro* transduction inhibition assay, to determine the presence, activity, and titers of NAbs in patient sera. Several critical steps and validation of the protocol should precede analysis of the patient samples (eg, selection of MOI, selection of the cells to be used during the assay). We expect that the final results may indicate the seroprevalence of NAbs for the selected serotypes and allow for comparison with previously reported results from other populations. The causes of the demonstrated high variability between the evaluated populations continue to be debated, and more studies including different healthy populations and under specific pathologic circumstances need to be conducted worldwide. Importantly, the method of determination should be standardized to obtain more reliable and comparable data. Recent reports support the higher sensitivity of intramuscular *in vivo* assays to determine NAb response [42], suggesting that *in vivo* NAb assays are more sensitive than *in vitro* assays for determining inclusion and exclusion criteria in clinical trials; however, the technical difficulties and higher cost associated with using *in vivo* assays in population studies mean that *in vitro* assays still have an important function.

Conclusion

We expect to have preliminary results, including the titer of the viral vectors, the MOI that we will use, and test assay validations, at the end of 2016. The results of this study will become the initial step for bigger population studies to characterize our population and provide the necessary epidemiological information for clinical trials using AAV in Latin America.

Acknowledgments

Ethics approval and consent to participate: This research is classified as “Research with minimal risk,” and all biosecurity measures will be strictly followed by the researchers for taking a blood sample (not more than 10 mL) from participants. All patients who choose to participate in the study and whose whole blood sample (see Multimedia Appendix 1) will be used will sign an informed consent form. The realization of this project does not obstruct the performance of other related work or present a conflict of interest within the work of the scientific community. According to the study design and procedures to be performed, we do not anticipate any disturbance to the environment or human health in the short, medium, or long term. All methods and procedures implemented during this study have the scientific and ethical support of the Cardiovascular Foundation of Colombia, an organization known for the quality of services provided (certification ISO 9001: 2000, ICONTEC), and of its research department, which has been certified for the design, preparation, and development of projects in basic, clinical, epidemiological, and administrative research. The ethics committee of the Cardiovascular Foundation of Colombia, act 376/2015, approved the study.

MYR received funding from the Patrimonio Autonomo Fondo Nacional de Financiamiento para la Ciencia, la Tecnologia y la Innovacion Francisco José de Caldas, Fundación Cardiovascular de Colombia/Colciencias Postdoctoral Fellowship. The project was selected for funding by the Department of Science and Technology of Colombia, COLCIENCIAS, after a peer reviewed evaluation.

Conflicts of Interest

None declared.

Multimedia Appendix 1

[PDF File (Adobe PDF File), 204KB - resprot_v5i2e102_app1.pdf]

References

1. Kalogeropoulos A, Georgiopoulou V, Kritchevsky SB, Psaty BM, Smith NL, Newman AB, et al. Epidemiology of incident heart failure in a contemporary elderly cohort: the health, aging, and body composition study. Arch Intern Med 2009 Apr 13;169(7):708-715 [FREE Full text] [doi: 10.1001/archinternmed.2009.40] [Medline: 19365001]
2. Hajjar RJ. Potential of gene therapy as a treatment for heart failure. J Clin Invest 2013 Jan;123(1):53-61 [FREE Full text] [doi: 10.1172/JCI62837] [Medline: 23281410]
3. Shareef MA, Anwer LA, Poizat C. Cardiac SERCA2A/B: therapeutic targets for heart failure. Eur J Pharmacol 2014 Feb 5;724:1-8. [doi: 10.1016/j.ejphar.2013.12.018] [Medline: 24361307]
4. Mearns BM. Gene therapy: can CUPID rescue the broken hearted? Nat Rev Cardiol 2011 Sep;8(9):481. [doi: 10.1038/nrcardio.2011.109] [Medline: 21788963]
5. Pleger ST, Shan C, Ksienzyk J, Bekeredjian R, Boekstegers P, Hinkel R, et al. Cardiac AAV9-S100A1 gene therapy rescues post-ischemic heart failure in a preclinical large animal model. Sci Transl Med 2011 Jul 20;3(92):92ra64 [FREE Full text] [doi: 10.1126/scitranslmed.3002097] [Medline: 21775667]
6. Roth DM, Lai NC, Gao MH, Drumm JD, Jimenez J, Feramisco JR, et al. Indirect intracoronary delivery of adenovirus encoding adenylyl cyclase increases left ventricular contractile function in mice. Am J Physiol Heart Circ Physiol 2004 Jul;287(1):H172-H177 [FREE Full text] [doi: 10.1152/ajpheart.01009.2003] [Medline: 15001445]
7. Mingozzi F, High KA. Therapeutic in vivo gene transfer for genetic disease using AAV: progress and challenges. Nat Rev Genet 2011 May;12(5):341-355. [doi: 10.1038/nrg2988] [Medline: 21499295]
8. Bartel M, Schaffer D, Büning H. Enhancing the clinical potential of AAV vectors by capsid engineering to evade pre-existing immunity. Front Microbiol 2011;2:204 [FREE Full text] [doi: 10.3389/fmicb.2011.00204] [Medline: 22065962]
9. Vandendriessche T, Thorrez L, Acosta-Sanchez A, Petrus I, Wang L, Ma L, Chuah M K L. Efficacy and safety of adeno-associated viral vectors based on serotype 8 and 9 vs. lentiviral vectors for hemophilia B gene therapy. J Thromb Haemost 2007 Jan;5(1):16-24 [FREE Full text] [doi: 10.1111/j.1538-7836.2006.02220.x] [Medline: 17002653]
10. Ying Y, Müller OJ, Goehringer C, Leuchs B, Trepel M, Katus HA, et al. Heart-targeted adeno-associated viral vectors selected by in vivo biopanning of a random viral display peptide library. Gene Ther 2010 Aug;17(8):980-990. [doi: 10.1038/gt.2010.44] [Medline: 20393510]
11. Mingozzi F, High KA. Immune responses to AAV vectors: overcoming barriers to successful gene therapy. Blood 2013 Jul 4;122(1):23-36 [FREE Full text] [doi: 10.1182/blood-2013-01-306647] [Medline: 23596044]
12. Manno CS, Pierce GF, Arruda VR, Glader B, Ragni M, Rasko JJ, et al. Successful transduction of liver in hemophilia by AAV-Factor IX and limitations imposed by the host immune response. Nat Med 2006 Mar;12(3):342-347. [doi: 10.1038/nm1358] [Medline: 16474400]
13. Kay MA. State-of-the-art gene-based therapies: the road ahead. Nat Rev Genet 2011 May;12(5):316-328. [doi: 10.1038/nrg2971] [Medline: 21468099]
14. Aiuti A, Biasco L, Scaramuzza S, Ferrua F, Cicalese MP, Baricordi C, et al. Lentiviral hematopoietic stem cell gene therapy in patients with Wiskott-Aldrich syndrome. Science 2013 Aug 23;341(6148):1233151 [FREE Full text] [doi: 10.1126/science.1233151] [Medline: 23845947]
15. Biffi A, Montini E, Lorioli L, Cesani M, Fumagalli F, Plati T, et al. Lentiviral hematopoietic stem cell gene therapy benefits metachromatic leukodystrophy. Science 2013 Aug 23;341(6148):1233158 [FREE Full text] [doi: 10.1126/science.1233158] [Medline: 23845948]
16. Rincon MY, VandenDriessche T, Chuah MK. Gene therapy for cardiovascular disease: advances in vector development, targeting, and delivery for clinical translation. Cardiovasc Res 2015 Oct 1;108(1):4-20 [FREE Full text] [doi: 10.1093/cvr/cvv205] [Medline: 26239654]
17. Yuan B, Zhao Z, Zhang Y, Wu C, Jin W, Zhao S, et al. Short-term safety and curative effect of recombinant adenovirus carrying hepatocyte growth factor gene on ischemic cardiac disease. In Vivo 2008;22(5):629-632 [FREE Full text] [Medline: 18853759]
18. Zincarelli C, Soltys S, Rengo G, Koch WJ, Rabinowitz JE. Comparative cardiac gene delivery of adeno-associated virus serotypes 1-9 reveals that AAV6 mediates the most efficient transduction in mouse heart. Clin Transl Sci 2010 Jun;3(3):81-89 [FREE Full text] [doi: 10.1111/j.1752-8062.2010.00190.x] [Medline: 20590676]
19. Rincon MY, Sarcar S, Danso-Abeam D, Keyaerts M, Matrai J, Samara-Kuko E, et al. Genome-wide computational analysis reveals cardiomyocyte-specific transcriptional cis-regulatory motifs that enable efficient cardiac gene therapy. Mol Ther 2015 Jan;23(1):43-52 [FREE Full text] [doi: 10.1038/mt.2014.178] [Medline: 25195597]
20. Inagaki K, Fuess S, Storm TA, Gibson GA, Mctiernan CF, Kay MA, et al. Robust systemic transduction with AAV9 vectors in mice: efficient global cardiac gene transfer superior to that of AAV8. Mol Ther 2006 Jul;14(1):45-53 [FREE Full text] [doi: 10.1016/j.ymthe.2006.03.014] [Medline: 16713360]

21. Pacak CA, Mah CS, Thattaliyath BD, Conlon TJ, Lewis MA, Cloutier DE, et al. Recombinant adeno-associated virus serotype 9 leads to preferential cardiac transduction in vivo. Circ Res 2006 Aug 18;99(4):e3-e9 [FREE Full text] [doi: 10.1161/01.RES.0000237661.18885.f6] [Medline: 16873720]
22. Periasamy M, Kalyanasundaram A. SERCA2a gene therapy for heart failure: ready for primetime? Mol Ther 2008 Jun;16(6):1002-1004. [doi: 10.1038/mt.2008.89] [Medline: 18500238]
23. Jaski BE, Jessup ML, Mancini DM, Cappola TP, Pauly DF, Greenberg B, Calcium Up-Regulation by Percutaneous Administration of Gene Therapy In Cardiac Disease (CUPID) Trial Investigators. Calcium upregulation by percutaneous administration of gene therapy in cardiac disease (CUPID Trial), a first-in-human phase 1/2 clinical trial. J Card Fail 2009 Apr;15(3):171-181 [FREE Full text] [doi: 10.1016/j.cardfail.2009.01.013] [Medline: 19327618]
24. Martino AT, Basner-Tschakarjan E, Markusic DM, Finn JD, Hinderer C, Zhou S, Ertl Hildegund C J, et al. Engineered AAV vector minimizes in vivo targeting of transduced hepatocytes by capsid-specific CD8+ T cells. Blood 2013 Mar 21;121(12):2224-2233 [FREE Full text] [doi: 10.1182/blood-2012-10-460733] [Medline: 23325831]
25. Nathwani AC, Tuddenham EG, Rangarajan S, Rosales C, McIntosh J, Linch DC, et al. Adenovirus-associated virus vector-mediated gene transfer in hemophilia B. N Engl J Med 2011 Dec 22;365(25):2357-2365 [FREE Full text] [doi: 10.1056/NEJMoa1108046] [Medline: 22149959]
26. Calcedo R, Morizono H, Wang L, McCarter R, He J, Jones D, et al. Adeno-associated virus antibody profiles in newborns, children, and adolescents. Clin Vaccine Immunol 2011 Sep;18(9):1586-1588 [FREE Full text] [doi: 10.1128/CVI.05107-11] [Medline: 21775517]
27. Calcedo R, Vandenberghe LH, Gao G, Lin J, Wilson JM. Worldwide epidemiology of neutralizing antibodies to adeno-associated viruses. J Infect Dis 2009 Feb 1;199(3):381-390 [FREE Full text] [doi: 10.1086/595830] [Medline: 19133809]
28. Kwon I, Schaffer DV. Designer gene delivery vectors: molecular engineering and evolution of adeno-associated viral vectors for enhanced gene transfer. Pharm Res 2008 Mar;25(3):489-499 [FREE Full text] [doi: 10.1007/s11095-007-9431-0] [Medline: 17763830]
29. Calcedo R, Wilson JM. Humoral immune response to AAV. Front Immunol 2013;4:341 [FREE Full text] [doi: 10.3389/fimmu.2013.00341] [Medline: 24151496]
30. Greenberg B, Yaroshinsky A, Zsebo KM, Butler J, Felker GM, Voors AA, et al. Design of a phase 2b trial of intracoronary administration of AAV1/SERCA2a in patients with advanced heart failure: the CUPID 2 trial (calcium up-regulation by percutaneous administration of gene therapy in cardiac disease phase 2b). JACC Heart Fail 2014 Feb;2(1):84-92. [doi: 10.1016/j.jchf.2013.09.008] [Medline: 24622121]
31. Blacklow NR, Hoggan MD, Kapikian AZ, Austin JB, Rowe WP. Epidemiology of adenovirus-associated virus infection in a nursery population. Am J Epidemiol 1968 Nov;88(3):368-378. [Medline: 4301609]
32. Blacklow NR, Hoggan MD, Rowe WP. Serologic evidence for human infection with adenovirus-associated viruses. J Natl Cancer Inst 1968 Feb;40(2):319-327. [Medline: 4295610]
33. Liu Q, Huang W, Zhang H, Wang Y, Zhao J, Song A, et al. Neutralizing antibodies against AAV2, AAV5 and AAV8 in healthy and HIV-1-infected subjects in China: implications for gene therapy using AAV vectors. Gene Ther 2014 Aug;21(8):732-738. [doi: 10.1038/gt.2014.47] [Medline: 24849042]
34. Liu Q, Huang W, Zhao C, Zhang L, Meng S, Gao D, et al. The prevalence of neutralizing antibodies against AAV serotype 1 in healthy subjects in China: implications for gene therapy and vaccines using AAV1 vector. J Med Virol 2013 Sep;85(9):1550-1556. [doi: 10.1002/jmv.23647] [Medline: 23852678]
35. Mimuro J, Mizukami H, Shima M, Matsushita T, Taki M, Muto S, et al. The prevalence of neutralizing antibodies against adeno-associated virus capsids is reduced in young Japanese individuals. J Med Virol 2014 Nov;86(11):1990-1997. [doi: 10.1002/jmv.23818] [Medline: 24136735]
36. Boutin S, Monteilhet V, Veron P, Leborgne C, Benveniste O, Montus MF, et al. Prevalence of serum IgG and neutralizing factors against adeno-associated virus (AAV) types 1, 2, 5, 6, 8, and 9 in the healthy population: implications for gene therapy using AAV vectors. Hum Gene Ther 2010 Jun;21(6):704-712. [doi: 10.1089/hum.2009.182] [Medline: 20095819]
37. Meliani A, Leborgne C, Triffault S, Jeanson-Leh L, Veron P, Mingozzi F. Determination of anti-adeno-associated virus vector neutralizing antibody titer with an in vitro reporter system. Hum Gene Ther Methods 2015 Apr;26(2):45-53 [FREE Full text] [doi: 10.1089/hgtb.2015.037] [Medline: 25819687]
38. Idänpään-Heikkilä JE. WHO guidelines for good clinical practice (GCP) for trials on pharmaceutical products: responsibilities of the investigator. Ann Med 1994 Apr;26(2):89-94. [Medline: 8024733]
39. Nair N, Rincon MY, Evens H, Sarcar S, Dastidar S, Samara-Kuko E, et al. Computationally designed liver-specific transcriptional modules and hyperactive factor IX improve hepatic gene therapy. Blood 2014 May 15;123(20):3195-3199 [FREE Full text] [doi: 10.1182/blood-2013-10-534032] [Medline: 24637359]
40. Gupta S, Indelicato SR, Jethwa V, Kawabata T, Kelley M, Mire-Sluis AR, et al. Recommendations for the design, optimization, and qualification of cell-based assays used for the detection of neutralizing antibody responses elicited to biological therapeutics. J Immunol Methods 2007 Apr 10;321(1-2):1-18. [doi: 10.1016/j.jim.2006.12.004] [Medline: 17307199]

41. Gupta S, Devanarayan V, Finco D, Gunn GR, Kirshner S, Richards S, et al. Recommendations for the validation of cell-based assays used for the detection of neutralizing antibody immune responses elicited against biological therapeutics. J Pharm Biomed Anal 2011 Jul 15;55(5):878-888. [doi: 10.1016/j.jpba.2011.03.038] [Medline: 21531522]
42. Wang M, Crosby A, Hastie E, Samulski JJ, McPhee S, Joshua G, et al. Prediction of adeno-associated virus neutralizing antibody activity for clinical application. Gene Ther 2015 Dec;22(12):984-992. [doi: 10.1038/gt.2015.69] [Medline: 26125606]

Abbreviations

AAV: adeno-associated virus
CUPID: Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease
CVD: cardiovascular disease
ELISA: enzyme-linked immunosorbent assay
FCV: Cardiovascular Foundation of Colombia
HF: heart failure
LEP: luciferase expression percentage
LIP: luciferase inhibition percentage
MOI: multiplicity of infection
NAb: neutralizing antibody
SERCA2a: sarcoplasmic reticulum Ca2+-ATPase

Edited by G Eysenbach; submitted 18.01.16; peer-reviewed by H Mishra, J Samulski, H Su; comments to author 18.02.16; revised version received 22.03.16; accepted 04.04.16; published 09.06.16.

Please cite as:
Rincon MY, Prada CE, Lopez M, Castillo V, Echeverria LE, Serrano N
Determination of Anti-Adeno-Associated Viral Vector Neutralizing Antibodies in Patients With Heart Failure in the Cardiovascular Foundation of Colombia (ANVIAS): Study Protocol
JMIR Res Protoc 2016;5(2):e102
URL: http://www.researchprotocols.org/2016/2/e102/
doi:10.2196/resprot.5535
PMID:27282359

Protocol

Hemiablative Focal Low Dose Rate Brachytherapy: A Phase II Trial Protocol

Ana Fernandez Ots[1], MD; Joseph Bucci[1], MB BS FRACP FRANZCR; Yaw Sinn Chin[1], MB BS FRACP FRANZCR; David Malouf[2], MB BS FRACP FRANZCR; Andrew Howie[1], MAppSci; Komiti Ese Enari[1], MAppSci

[1]Cancer Care Centre, Radiation Oncology, St George Hospital, Sydney, Australia

[2]St George Hospital, Urology, Sydney, Australia

Corresponding Author:
Ana Fernandez Ots, MD
Cancer Care Centre
Radiation Oncology
St George Hospital
Short St
Sydney
Australia
Phone: 61 0291133831
Fax: 61 0291133913
Email: anukiots@hotmail.com

Abstract

Background: The objective of focal brachytherapy (BT) is to provide effective prostate cancer control for low-risk disease but with reduced genitourinary, gastrointestinal and sexual side effects in a cost-effective way.

Objective: The aim of this study is to describe a phase II study examining technical and dosimetric feasibility and toxicity, quality of life changes, and local control with post-treatment biopsy outcomes in men with early stage low volume prostate cancer treated with focal iodine-125 seed BT.

Methods: The study design is a prospective, multicenter trial with a planned sample size of 20 patients including men with a minimum age of 60 years, a life expectancy estimated to be greater than 10 years, with low or low-tier intermediate risk prostate cancer, unilateral disease on the biopsy, and a Gleason score of ≤3+4 and <25% cores involved. The investigations specific for the study are multi-parametric magnetic resonance imaging (Mp-MRI) baseline, at 20 and 36 months to rule out high grade disease and a transperineal mapping biopsy (baseline and at 36 months) for more accurate patient selection. The hemigland region will receive 144 Gy. Standard normal tissue constraints will be considered as for a whole gland (WG) implant. Dosimetric parameters will be evaluated at day 30 after the implant. Toxicity and quality of life will be evaluated with international validated questionnaires focusing on urinary, rectal, sexual domain, and general health-related quality of life. The patients will complete this assessment at baseline and then approximately every 6 months after the implant up to 10 years.

Results: To date, one patient is involved in the trial. He underwent the pre-implant investigations which found bilateral disease. Therefore, a standard seed implant was performed. If the results from this trial provide evidence that the treatment is safe, feasible, and improves toxicity, funding will be sought to conduct a large, multicenter, randomized controlled trial (RCT).

Conclusions: This protocol is designed to show feasibility in delivering hemigland focal therapy with seed BT. It may answer crucial questions and obtain data which will enable downstream decisions on focal low dose rate (LDR) prostate BT.

ClinicalTrial: Clinicaltrial.gov NCT02643511; https://www.clinicaltrials.gov/ct2/show/NCT02643511 (Archived by Webcite at http://www.webcitation.org/6ghLCzIhY)

(JMIR Res Protoc 2016;5(2):e98) doi:10.2196/resprot.5433

KEYWORDS

cancer research; prostate; focal therapy

Introduction

Prostate cancer is the most commonly diagnosed non-cutaneous neoplasm in males in the United States and the second leading cause of cancer mortality. Estimated new cases and deaths from prostate cancer in 2014 were 233,000 and 29,480, respectively. [1].

Widespread screening with the prostate-specific antigen (PSA) test, which can identify patients with asymptomatic tumors that have little or no lethal potential, has decreased the age of diagnosis [2]. With an enormous reservoir of cancers in ageing men, there is a major risk of detection of many cancers that will often never cause symptoms or death [3,4]. Surgery and radiotherapy are widely-employed definitive treatment options; however, their corresponding side-effects include urinary, sexual (ie, erectile dysfunction), and gastrointestinal complications [5]. There are reports showing similar or better outcomes for brachytherapy (BT) versus surgery regarding quality of life in the urinary, bowel or sexual domain [6,7] .

It is increasingly apparent that some older men with low volume favorable cancers and significant medical co-morbidities may be appropriately managed with observation [8]. Recently, active surveillance (AS) has been advocated for selected low-risk cancers with the recognition that Gleason 6 disease is rarely a cause of cancer mortality. A recent cohort study published in 2010 showed, at a median follow-up of 6.8 years, the 10-year prostate cancer actuarial survival was 97.2% in patients undergoing AS [9,10]. After 2 to 3 years of follow-up, approximately one third of patients ceased AS and switched to active therapy [11]. The most common reason for this change was a change in risk classification as a result of repeated biopsies, leading to definitive therapy [12]. Despite the fact that AS was associated with the greatest quality-adjusted life expectancy when compared with definitive treatment of low-risk prostate cancer [13], a considerable majority of men in the United States and Europe who are diagnosed with screen-detected localized tumors still receive aggressive treatment [14,15].

What is Focal Therapy?

There is increasing evidence that the largest tumor focus within the prostate (called the index lesion) drives the natural history of prostate cancer [16]. Liu and colleagues have shown that metastases in prostate cancer have a common origin (ie, these metastatic cells originate from the same clone) [17]. If the single lesion harboring this metastatic clone could be accurately identified and then conformally targeted, it seems likely that the side effects of treatment for prostate cancer could be reduced due to a smaller treatment volume. Other lesions could then potentially undergo a surveillance approach. The pathological characteristics of the index lesion, namely, the grade and the presence or absence of extracapsular extension, generally indicate the prognosis. Both the index lesion hypothesis and the monoclonal origin of metastatic prostate cancer open the way to a consideration of focal therapy in the majority of men who have multifocal, bilateral disease in which only the clinically important lesion might be ablated [18].

There is no standard definition for focal therapy, but in general it refers to a tissue preservation technique that does not treat the entire prostate gland but instead focuses the treatment to either an index lesion or some defined part of the prostate [19]. This approach is based on the premise that, in appropriately selected men, treating only part of the prostate can be as clinically effective as treating the whole prostate with far less morbidity. This, therefore, is an attractive option for patients where quality of life issues are important. Prostate focal treatment is a potential compromise between definitive treatment and AS. Advances in ultrasound and magnetic resonance imaging (MRI) techniques, as well as tissue sampling, have enhanced the ability to select these patients [20-23].

Why Low Dose Rate Brachytherapy for Focal Therapy?

A variety of treatment modalities have been used to deliver prostate cancer focal therapy. The literature mainly includes reports on high intensity focused ultrasound (HIFU) [24,25] and cryotherapy [26-28], but neither modality is first line for whole gland (WG) treatment because of toxicity and lack of comparable efficacy.

Low dose rate (LDR) monotherapy has established long-term track record in terms of biochemical control for low and low tier intermediate risk prostate cancer. For favorable risk prostate cancer, LDR BT as monotherapy provides a highly effective treatment option, commonly achieving an undetectable PSA within 4 to 7 years [29,30]. A 15-year biochemical relapse-free survival has been reported at 85.9% for low risk patients [31], and a 10-year disease-specific survival at 96% [32].

The hallmark of LDR prostate BT toxicity is urinary side effects. About 50% will have moderate irritative and obstructive urinary symptoms after the procedure lasting several months. By 12 months, the urinary symptoms of most patients (90%) will return to baseline, although full recovery can be prolonged in 10% to 20% of individuals in 2 to 3 years [33-35]. Mild self-limiting rectal irritation affects 20% to 30% of patients in the first 1 to 2 years after the implant, and rectal bleeding is reported in 2% to 7% of patients [36,37]. The risk of rectal complications has consistently been linked to greater rectal wall doses [38-40]. In a series by Tran et al in which 503 patients were treated with permanent interstitial prostate BT using iodine-125 or palladium-103, 44 patients developed persistent rectal bleeding, including 2 patients with fistula formation. In both of these cases, the volume of rectum receiving greater than or equal to the prescription dose (RV100) exceeded 1 cc [41]. Merrick et al [42] reported on the incidence of BT-related bulbomembranous urethral strictures in a series of 1186 men. The authors described 29 cases (3.6%) noting an association with urethral radiation dose and external beam radiation therapy (EBRT). Kamrava et al [43] compared hemigland BT treatment plans to WG. Hemigland plans revealed a statistically significant decreased radiation dose to organs at risk. The degree of reduction in the dose of 2 cc to these organs was from 64% to 53% for the rectum, 67.5% to 56% to the bladder, and from 95% to 69% to the urethra. One Swiss group used high dynamic range imaging (HDRI) as a partial boost after 64 to 64.4 Gy of EBRT to the prostate, followed by either bilateral or unilateral

HDR BT boost. They found no differences in late rectal toxicity and in severe grade ≥3 late urinary toxicity at five years [44]. However, with a background of a significant dose to the WG it is hard to detect a significant decrease in toxicity that this trial aims to achieve.

All curative treatments for prostate cancer have a major potential impact on sexual function. Erectile dysfunction (ED) rates are low at 1 year after the implant with 70% to 80% of men retaining erectile function; this rate declines to around 50% at 5 years post-implant [45]. Although Princess Margaret Hospital published a report on 1111 men with follow-up ranging to over 9 years, with 82% retaining satisfactory erectile function beyond 5 years [29]. Many patients will have improvement in their function with oral phosphodiesterase5 (PDE-5) inhibitors such as sildenafil, vardenafil, and tadalafil [46]. Merrick et al strongly suggested that BT-induced ED is related to the radiation dose delivered to the penile bulb and the proximal crura [47]. As the proximal penis is the most significant treatment-related predictor of BT-related ED, techniques to minimize the radiation dose to the proximal penis such as hemigland may result in improved rates of potency preservation [47].

Apart from the potential of a more favorable toxicity profile due to a dose reduction to the organs at risk with LDR hemigland BT, there are also some technical advantages of delivering LDR BT. LDR is a less invasive procedure that can be done in two stages with a pre-plan before the implant [48] or in a 1-step procedure planned intra-operatively with real-time dosimetry [49]. Although excellent dose distributions can be achieved with pre-planning techniques, intra-operative planning takes into account the intra-operative geometry of the prostate and the surrounding normal tissues. There are methods to dynamically modify the treatment plan as the implant procedure is ongoing based on the coordinates of the deposited seeds such as minimizing the possibility of tumor under dosage and enhancing the conformality of LDR prostate BT [50].

The proposal described here is based on the long-term evidence in the literature that we have for LDR monotherapy for low and low tier intermediate risk prostate cancer over HDR or other techniques. Other treatments available for focal therapy have lack of comparable efficacy and long-term follow-up. It might be more logical to consider whether a therapy might be suitable for focal application after it has been demonstrated to be effective as a WG treatment.

The radiation source used for LDR, iodine-125, has a lower energy of 0.028 MeV giving us more flexibility for planning purposes than the HDR radiation source iridium-192 with 0.38 MeV. Most importantly, prostate seed BT has a post-implant quality verification process where seeds are identified giving us a permanent record of the prostate region treated enabling salvage approaches easier. Focal therapy utilizing LDR BT has been chosen as the above mentioned data provides the most comprehensive treatment modality that addresses the issues of local efficacy, quality assurance verification, excellent toxicity profile, and the ability to localize previous therapy in the setting of potential salvage therapy.

Summary of the Evidence on Brachytherapy on Focal Therapy

While the use of LDR BT for WG treatment is very well established, there is little data with its use in focal-only treatment. LDR has been delivered to the peripheral zone alone identified by intra-operative magnetic resonance imaging (MRI) [51] with a biochemical free survival (BFS) for low risk patients at 5 and 8 years that was acceptable at 95.6% and 90.0%, respectively, using the Phoenix definition plus PSA velocity greater than 0.75 ng/ml/year. However, the results were poor for intermediate risk patients with a 5 and 8 year progression-free survival (PFS) at 73% and 66%, respectively. Cosset et al [52] have reported their preliminary results on the first 21 patients treated with focal BT with iodine-125 loose seeds targeting the positive region in the biopsy within the prostate and the suspicious sites on MRI, an approach called ultra-focal (UF) BT. After 12 months of follow-up only, a borderline advantage was seen in the International Prostate Symptom Score (IPSS) recovery at 6 months after the implant when compared with a previous cohort treated by WG treatment (P =.04). The pre-implant dosimetric parameters for the UF volume with a minimum dose received by the 90% of the prostate volume (D90) of 183.2 Gy and the volume of the prostate receiving 100% prescription dose of 99% (V100) were successfully achieved [52]. Currently, there are three active phase II trials using LDR BT as focal therapy (Table 1). Morris et al are recruiting patients with low or low tier intermediate risk after MRI elastography transrectal ultrasound biopsy targeting high grade areas [53]. In France, Bachaud is recruiting patients with low risk prostate cancer for a focal target seed implantation [54], and Langley et al in the United Kingdom are evaluating side effects, quality of life, and cancer control in patients with prostate cancer diagnosed on only one side of the prostate gland [55]. Zelefsky opened a phase II study for men with early-stage low-risk prostate cancer treated with hemigland and focal LDR BT examining the tolerance profile. Unfortunately, this trial was terminated due to lack of accrual. [56].

The aim of this study is to address the toxicity, feasibility, and utility of hemiablative focal LDR BT as treatment for localized prostate cancer. We hypothesize that this form of LDR BT is safe and will give similar disease control outcomes when compared to established WB treatment techniques, but with decreased toxicity leading to an improved quality of life. As this is a feasibility study, we are looking at toxicity and safety (adequate implant) in highly selected candidates.

Trial Objectives

The trial objectives for this study are described in Textbox 1.

Table 1. Phase II studies using low dose rate focal brachytherapy.

Study details	Phase II study			
	Morris et al [53]	Bachaud [54]	Langley et al [55]	Zelefsky [56]
Location	British Columbia Cancer Agency (BCCA), Canada	Institut Claudius Regaud, France	Royal Surrey county Hospital NHS, United Kingdom	Memorial Sloan Kettering Cancer Center, United States
Current progress	Recruiting	Recruiting	N/A	Terminated in February 2016 due to lack of accrual
Treatment	LDR focal BT	LDR focal BT; prescription dose (PD) 160 Gy +/- 5%	LDR BT hemigland 145 Gy	Hemigland LDR BT; PD 144 Gy
Patients[a], n	10	17	34	80
Stage	≤T2a	≤T2a	≤T2b	≤T2a
Gleason	≤3 4≤2 cores	≤3+3	≤4+3	Up to Gleason 7 in just 2 cores
PSA	<10	<10	<15	<10
Inclusion tests	Transrectal ultrasound (TRUS)	3D prostate mapping biopsy, MRI	Transperineal template-guided mapping (TTGM) multi-para-metric magnetic resonance imaging (Mp-MRI)	TRUS
Primary outcome	To fit for focal disease and adequate treatment plans	Successful post-implant dosimetry	Urinary, sexual and bowel toxicity, and quality of life	Late toxicity
Secondary outcome	Quality of life, treatment evaluation	Progression-free survival (PFS; (Phoenix definition), qualify of life, biopsy, toxicity	Tumor control	Efficacy, quality of life, post-treatment MRI vs post-biopsy
Timeframe, years	4	3	5	2

[a]Open estimate.

Textbox 1. Trial objectives.

Objectives

- Primary objective

  To demonstrate the feasibility of delivering hemigland focal therapy (the delivery of the prescription dose to the half of the prostate) with a seed BT implant in a multi-center Australian study.

- Secondary objectives
  - To determine acute and late rectal, urinary, and sexual toxicity following hemiablative iodine-125 brachytherapy (BT) treatment.
  - To assess the change from baseline in quality of life indicators at specific time intervals using the following validated international questionnaires after hemiablative iodine-125 (BT) treatment:
    - International Prostate Symptom Score (IPSS)
    - International Index of Erectile Function (IIEF)
    - Expanded Prostate Cancer Index (EPIC)
  - To evaluate the local tumor control in terms of biopsy outcomes after focal BT 36 months after the treatments.
  - To compare target coverage and relative doses to the rectum and the urethra for the same patient performing a hemigland treatment planning versus WG treatment planning, and compare rates of toxicity and quality of life after hemigland implant with historical WG cohorts.

Methods

Study Design

This multi-institution, prospective phase II trial aims to determine whether hemiablative treatment with LDR for prostate cancer is dosimetrically safe and feasible. This study will record data for patient quality of life parameters, in particular in terms of urinary, rectal, and sexual function side effects.

Study Group

Patients with ipsilateral low grade disease (N=20) will be evaluated prospectively after hemiablative focal therapy. Because of the historically small size of trials in this area, probably reflecting the difficulty of recruitment of patients in

this scenario, a pilot will be conducted to establish the feasibility of a full scale trial prior to committing to a large study.

Eligibility Criteria

To be eligible for the study, participants must meet each of the eligibility requirements (Textbox 2). If a participant has one of the following, they will be ineligible for the study: (1) does not meet staging criteria for low risk or low tier intermediate risk prostate cancer, (2) bilateral prostatic disease, (3) prior hormonal therapy, (4) recent IPSS more than 17, (5) unfit for general anesthetic, (6) MRI contraindicated, (7) unable to cease anticoagulant therapy, and (8) life expectancy less than 10 years. The trial schema is shown in Figure 1.

Textbox 2. Eligibility requirements.

Requirements

Patients must have histologically proven adenocarcinoma of the prostate.

Patients must have low or low tier intermediate prostate cancer.

Low risk prostate cancer patients must have:

- Clinical stage ≤ T2a
- Gleason score of 6 and iPSA ≤10 ng/ml
- Less than 25% cores positive

Low tier intermediate risk patients may have:

- Clinical stageT2a
- Gleason score ≤3+4=7
- PSA ≤10 ng/ml
- Less than 25% cores positive

Patients must be fit for general anesthetic.

Patients must have unilateral disease on biopsy.

Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.

Men ≥60 years of age with a life expectancy estimated to be >10 years.

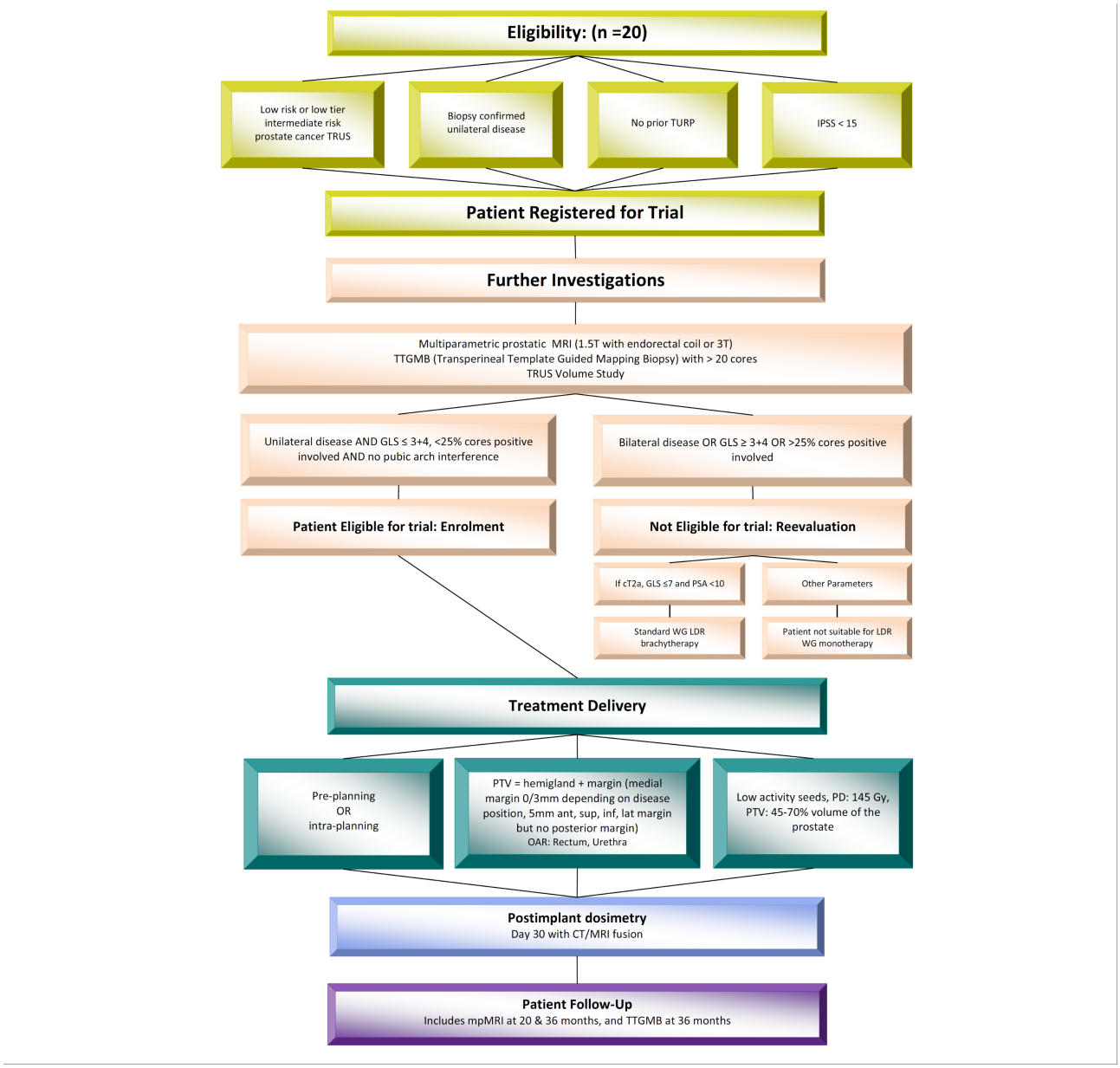
Patients must have no contraindications to interstitial prostate BT.

International Prostate Symptom Score (IPSS) ≤16

Patients on anticoagulant therapy must be able to stop therapy safely for at least 7 days.

Patients must not have any contraindications to MRI.

Figure 1. Trial schema.



Pre-Treatment Evaluation

The components of the pre-treatment evaluation are shown in Textbox 3. The transperineal template is diagramed in Figure 2.

The protocol includes a screening phase with multi-parametric magnetic resonance imaging (Mp-MRI) and mapping biopsy for patient selection. Improved imaging techniques coupled with better sampling of the prostate [57,58] allows to identify men with low volume focal disease selection who may be suitable for tissue preservation strategies. It has been estimated that between one half and two thirds of men with prostate cancer may be amenable to some form of focal therapy [59,60].

Textbox 3. Pre-treatment evaluation.

Pre-treatment

Patient demographics and histological information from transrectal ultrasound (TRUS) prostate biopsy will be collected.

For preplanning technique, ultrasound volume study to assess prostatic volume and pubic arch interference will be performed.

A multi-parametric prostatic MRI (Mp-MRI) (1.5 T with endorectal coil or 3T). The data set should include T1-weighted, T2-weighted, diffusion-weighted, and contrast-enhanced MRI. Imaging could be adequately performed at 1.5 T with endorectal coil or 3T without endorectal coil [57]. Suspicion of bilateral disease or high grade unilateral disease will exclude the patient from the study. Biopsy of any suspicious target lesions as identified on Mp-MRI is recommended.

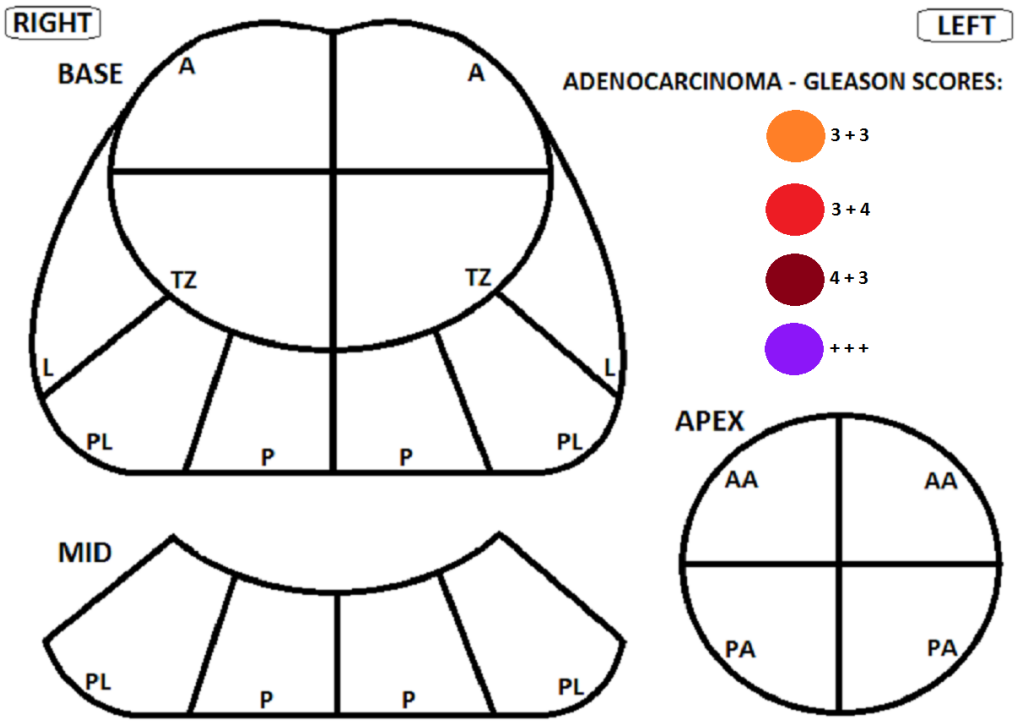
If a TRUS biopsy has only been performed then the patient will also undergo a transperineal template guided mapping (TTGM) biopsy, with a minimum of 20 cores obtained, at the time of the volume study (for preplanning technique) (Figure 2). A single anatomical pathologist will review the biopsy. In addition the following parameters will be recorded to allow for stratification according to:

- T stage: T1c vs T2a
- Gleason: 3+3=6 vs 3+4=7
- Presence of lymphovascular invasion
- Presence of perineural invasion

Baseline quality of life assessments:

- International Prostate Symptoms Score (IPSS) questionnaire
- International Index Erectile Function (IIEF) questionnaire
- Expanded Prostate Cancer Index Composite (EPIC) questionnaire

Figure 2. Transperineal template. Diagram prepared by Warick Delprado at Douglass Hanly Moir Pathology and used by permission.



Informed Consent, Registration, and Enrolment

All patients must sign an informed consent form to be registered in this study. Completed consent forms will be sent to the Radiation Oncology Clinical Trials Office at the St George Cancer Care Centre (STGCCC) and eligibility will be confirmed by the study coordinator. A patient identification number (PIN) will be assigned to the patient. The registration process will include the consent and the prostate Mp-MRI and a transperineal template-guided mapping (TTGM) biopsy of the prostate to rule out high grade disease and ensure eligibility for focal therapy. Only patients still suitable for focal therapy after these studies will be enrolled in the trial and will go ahead with the treatment. They will be followed up to 10 years. Patients not suitable for the trial will go ahead with standard WG BT if they still wish to have active radiation treatment. This is a feasibility study to assess the feasibility of this technique with a permanent seed implant to half of the prostate in terms of acute side effects

and post-implant dosimetry parameters. Normal tissue tolerance will have the priority in the planning algorithm. There is no randomization process.

Investigations

All investigations required before study entry are standard for this grade and presentation of prostate cancer and include a TRUS-guided prostate biopsy for diagnosis and a PSA test within the last 3 months. Investigations specific for the study include a Mp-MRI of prostate using either a 3 Tesla magnet alone or a 1.5 Tesla magnet and an endorectal coil. A baseline Mp-MRI should be performed at least 6 to 8 weeks after the initial biopsy and the Mp-MRI should be repeated at 20 and 36 months after treatment or earlier if PSA is detected to be rising during follow-up. Patients should be scanned on the same scanner for all three examinations, especially when tracking changes in apparent diffusion coefficient (ADC) values over time. A central radiology review of the images will take place in Southern Radiology by Dr Jonathan Seef. In addition, a TTGM prostate biopsy with a minimum of 20 cores and at 36 months post treatment will be included. Central pathology review of the specimens will take place in a center assigned in each participating Australian state.

Interventions

A preplanned technique or intra-operative planning technique will be used depending on the individual institutional preference. Patients participating in this study will undergo hemigland LDR prostate BT performed by experienced BT teams that perform a minimum of 40 cases per year (Figure 3).

The prostate volume study will be performed under sedation or general anesthesia, and patients will be set up in the dorso-lithotomy position. The urethra will be identified by insertion of aerated gel allowing visualization on ultrasound. A TRUS volume of the prostate will be performed. A set of 5 mm slice images are acquired using the transverse mode for 3D reconstruction of the prostate. Pubic arch interference will be identified in case modification of probe angle or leg position if necessary.

For the hemigland preplanning, the pre-implant clinical target volume (CTV) will be defined as half of the prostate excluding the urethra, as visualized and contoured on the reconstructed ultrasound images. The planning target volume (PTV) will be created by adding a 3 to 5 mm margin around the CTV except for the posterior margin that will be 0 mm. The PTV will encompass 45% to 70% of the total prostate volume maximum. A hemiablative approach over two different focal therapy scenarios has been chosen, as shown in Figure 1, with hemiablation or zonal ablation (hockey stick 5 mm beyond midline). An experienced medical physicist will plan the iodine-125 seed and needle positions achieving dosimetric parameter goals. All plans will be approved by both the responsible radiation oncologist and a medical physicist, both of whom are experienced in prostate BT; the STGCCC team of investigators has performed more than 1000 prostate BT procedures.

The treatment planning dosimetric parameters used for optimization aim for prostate PTV V100 is greater than 98%, with a V150 of 55% to 65% and V200 of less than 20%. (V100, V150, and V200 are the percentage of the prostate volume covered by the prescription isodose, the 150%, and the 200% isodose, respectively). Urethral dose (UD) is usually described as the UD5 or UD30, which are the dose to 5% and 30% of the urethra, respectively. UD5 is representative of a urethral maximum dose and should be less than 150% of the prescription dose, while UD30 should be less than 125%. For the rectum, the rectal volume in cubic centimeters receiving 100% of the prescribed dose (RV100) is commonly used and should be less than 1.3 $cm^3$for day 30 dosimetry.

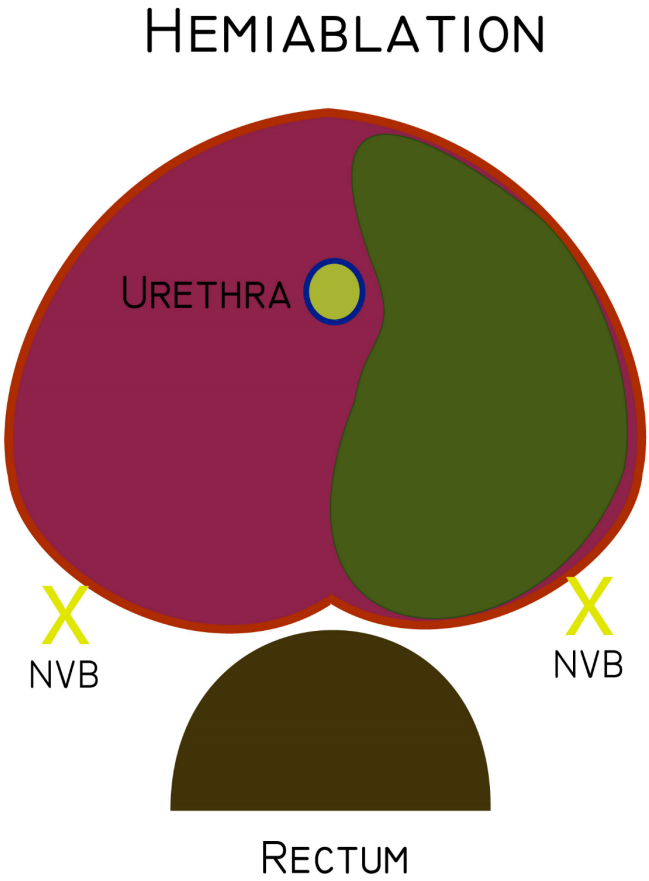
In addition, a whole prostate LDR planning will be performed for a potential matched historical control toxicity comparison with patients from the existing large LDR database based on standard whole prostate dosimetric features as well as other clinical features like prostate volume, IPSS and potency, and medical conditions (eg, diabetes). This will enable us to report the difference in dose for the two plan sets for the targets hypothesized to be responsible for toxicities like urethritis or proctitis. This will require a pre-implant CTV defined as the prostate excluding the urethra, as visualized and contoured on the reconstructed ultrasound images. The PTV will be created adding a 5 mm margin around the CTV except for the posterior margin that will be 0 mm. The same planning dosimetric parameters will be recorded as for the hemigland treatment planning.

For the implant procedure, the patient will be under general anesthesia and set up in the dorsal lithotomy position on the operating table in the BT theatre as per the local institutional seed implant protocol. A TRUS volume of the prostate will be matched to the images of the preplanned study. An intra-operative approach is also acceptable. Iodine-125 seeds will be inserted under US template and fluoroscopy guidance according to the plan.

At the completion of the needle and seed insertion, the Foley catheter will be kept in place and the patient will be taken to the post-anesthesia recovery (PAR) area. Patients will be discharged from PAR when they have made an appropriate recovery from anesthesia and have successfully voided urine after the Foley catheter is removed.

Patients participating in this study will be followed in the usual fashion and only require the following additional tests beyond those of standard practice: Mp-MRI at 18 and 36 months and TTGMB at 36 months.

Figure 3. Hemiablation.



Patient Follow-Up

Postimplant Dosimetry

Post-plan quality assurance using magnetic resonance computed tomography (CT) fusion (MR-CT fusion) is required because it reduces inter-observer variation by improving prostate edge detection, and allows appreciation of treatment margins [61,62]. Fusion can be accurately performed to sub-millimeter accuracy using the seeds as fiducial markers. It is essential to use the appropriate MR sequences in order to facilitate both prostate contouring and seed localization. A Fast Spin Echo T2-weighted MR sequence is used, with the technical parameters described in Textbox 4.

Textbox 4. Technical parameters used with the Fast Spin Echo T2-weighted MR sequence.

Parameters

- Repetition time (TR) = 4500 msec
- Echo time (TE) = 90 msec
- Echo train length (ETL) =10,
- Pixel bandwidth (BW) = 580 Hz/pixel
- Field of view = 20 x 20 cm
- 3 mm slice thickness, 0 mm gap
- Acquired matrix size = 320 x 224 with phase encoding direction along rows
- Flip angle = 90°

CT images are likewise obtained in the supine position, imaging the prostate and all seeds visible on the scout image in 2 mm slices. Aerated gel with Ultravist contrast is inserted for the pelvic CT for urethral localization by the oncologist. No specific bowel preparation is used before either scan but they should be performed sequentially, with the CT following the MRI generally within half an hour. Patients will also undergo a pelvic and chest x-ray to assess for any seed migration.

In order to improve this pilot trial consistency and check the hemi-implant quality, MR-CT fusion for all the participants will be reviewed by one of the two primary investigators with experience in MRI contouring and MRI-CT fusion; Dr A Fernandez has performed more than 100 MRI-CT fusions.

Follow-Up Schedule

Routine assessment following completion of treatment includes PSA and clinical evaluation 4 to 6 weeks after the implant to manage and document any acute toxicity. The assessment will continue every 3 to 6 months depending on symptoms up to 3 years, and then every 6 to 12 months, with a PSA and digital rectal exam at each visit beyond 6 months up to 10 years. The IPSS, the International Index of Erectile Function (IIEF), and the Expanded Prostate Cancer Index Composite (EPIC) questionnaire are recorded at baseline and at each visit as is standard for all men receiving any type of prostate BT in the STGCCC. Specific follow-up for the study will involve a repeat Mp-MRI by 20 and 36 months and a TTGMB at 36 months. Patients will be followed up to 10 years after the implant, although the study finishes after 36 months of enrollment. Once we reach a median of 3-year follow-up (ie, sufficient time to determine rate of local control with the biopsies in 50% patients), then it would be adequate to commence the randomized controlled trial (RCT).

Exit Strategy and Rescue Therapy

Biochemical failure will follow a PSA velocity greater than 0.75 ng/ml years in addition to nadir +2. Both parameters appear to better predict clinical failure after therapies that target less than the WG. Failure may also be proven on the TTGM control biopsies at 36 months or earlier in case of biochemical failure defined by Nguyen et al [51].

Definition of treatment failure will involve relapse in PTV or outside our PTV confirmed by biopsy. Relapse outside the PTV is not essentially a local treatment failure, and may be due to suboptimal patient selection. Due to the additional resources required to continue on this trial, these cases will be recorded as a treatment failure for further validation of the hemifocal BT as a treatment alternative to WG therapy. Interval from treatment to failure will be recorded.

After biochemical or local failure, the patient will exit the study. After appropriate investigations different salvage therapies can be offered to the patients who have failed. For local failure radical prostatectomy, HDR salvage BT or salvage cryotherapy in case of ipsilateral or contralateral relapse, or hemigland focal seed BT in case of contralateral relapse alone will be initiated. A choice of the treatment will be made after appropriate discussion in a multidisciplinary meeting and will be individualized.

Study Endpoints

Primary

Feasibility of the hemigland focal therapy (the delivery of the prescription dose to half of the prostate) using a BT seed implant, while respecting standard tolerance doses of adjacent normal organs is the primary study endpoint.

Secondary

Secondary study endpoints are (1) assessment of rectal, urinary, and sexual toxicity following hemiablative prostate seed BT; (2) change from baseline in quality of life indicators at specific time intervals using validated international questionnaires (IPSS, IIEF, EPIC) following hemiablative iodine-125 BT treatment; (3) evaluation of local tumor control in terms of biopsy outcomes after focal BT 36 months after completion of therapy; and (4) comparison of target coverage and relative doses to the rectum and the urethra for the same patient performing an hemigland treatment planning versus WG treatment planning and toxicity and quality of life after hemigland implant comparison with historical whole gland cohorts.

Measurement of Endpoints

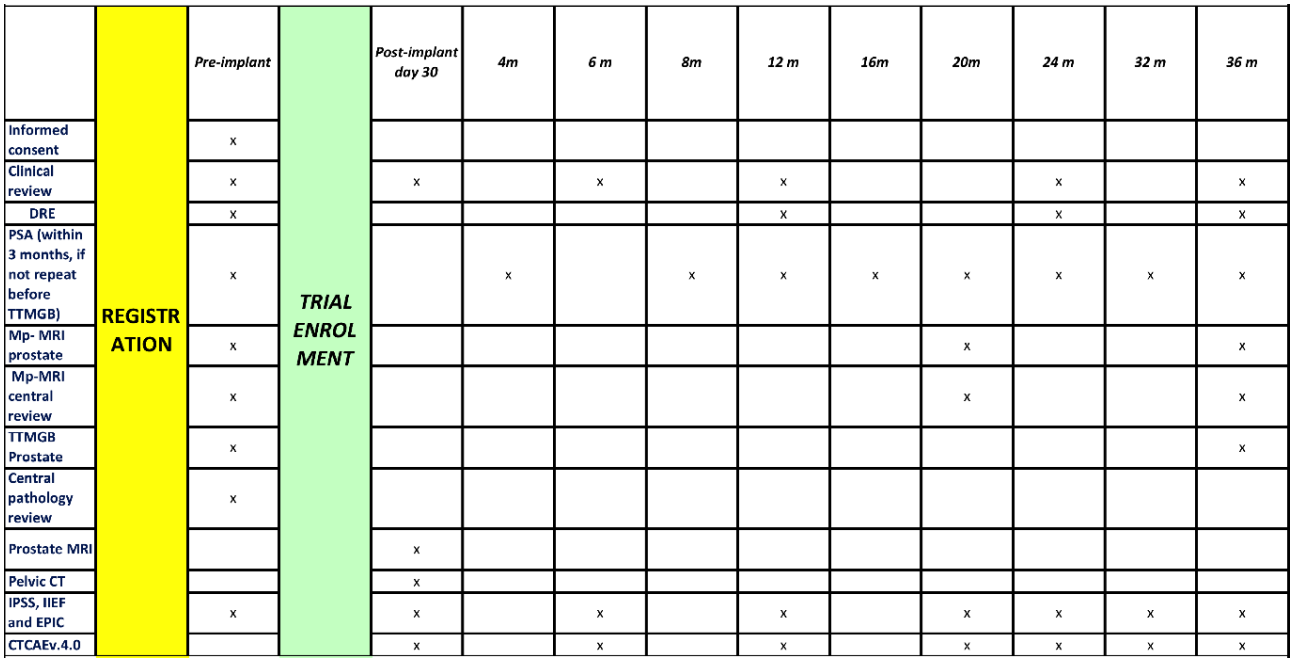
Feasibility

Dose parameters for prostate (V100, V150, V200), rectum (V100), and urethra (D5, D30) will be recorded for the hemigland and the WG treatment planning. Dosimetric parameters in the post-implant dosimetry at day 30 for WG BT are well defined in the literature and they are correlated to efficacy and toxicity. The post-implant dosimetric study for hemigland BT patients will aim for the same dosimetric parameters at day 30 after the implant for tumor coverage and organs at risk dose.

Toxicity Evaluation Assessment

Patients will be assessed on the day of enrollment, at 4 to 6 weeks, and every time they come back for follow-up (every 6 months) to determine acute, sub-acute, and late toxicity after the implant in the urinary, rectal, and sexual domain. An adverse event is any deleterious effect which may occur as a result of the intervention. Treatment-related toxicities will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 as follows: (1) grade 0 is no adverse events, (2) grade 1 is mild events not requiring intervention, (3) grade 2 is moderate events interfering with normal activities, (4) grade 3 is severe events causing inability to carry out normal activities, (5) grade 4 is life threatening or disabling events, and (6) grade 5 is death (Figure 4). A follow-up assessment will be undertaken within seven days in patients reporting greater than grade 1 toxicities, and will continue in this manner until toxicity has resolved, with documentation of action taken at each time point. Failure of an adverse event to resolve and its translation to chronicity at a given time point will be documented by the clinician. Serious adverse events (grade 3 or greater) will require assessment by the clinician and documentation of action taken.

Figure 4. The necessary data to be collected at various time points of the study.



		Pre-implant		Post-implant day 30	4m	6 m	8m	12 m	16m	20m	24 m	32 m	36 m
Informed consent	REGISTRATION	x	TRIAL ENROLMENT										
Clinical review		x		x		x		x			x		x
DRE		x						x			x		x
PSA (within 3 months, if not repeat before TTMGB)		x			x		x	x	x	x	x	x	x
Mp- MRI prostate		x								x			x
Mp-MRI central review		x								x			x
TTMGB Prostate		x											x
Central pathology review		x											
Prostate MRI				x									
Pelvic CT				x									
IPSS, IIEF and EPIC		x		x		x		x		x	x	x	x
CTCAEv.4.0				x		x		x		x	x	x	x

Quality of Life

Quality of life will be assessed using the IPSS, IIEF, and EPIC questionnaires. The change from baseline will be measured at specific time points (Multimedia Appendix 1).

Local Tumor Control

Local tumor control will include negative or indeterminate TTGMB 36 months after the treatment within the whole prostate. Definition of treatment failure will involve relapse in PTV or outside our PTV and confirmed by biopsy. In addition, dosimetric parameters and toxicity rates will be compared with historical WG treatment cohorts.

Data Collection

The necessary data to be collected at various time points of the study is outlined in Figure 4.

Statistical Considerations

It is anticipated that a sample size of 20 patients will be accrued to enable the investigator to deliver hemiablative seed BT with a reasonable amount of confidence. This feasibility study will proceed in 5 participating centers. Failure to accrue 15 patients in 24 months will initiate early closure of this study. The time-frame for completion of recruitment will be approximately 12 months, with a further 24 months required for collection of acute and late toxicity data, maturation of quality of life data, and correlation with the biopsy by 36 months.

We do not consider it necessary to use early stopping rules for poor quality implants (not adequate dosimetric parameters on day 30), or acute treatment-related toxicities because of the low number of patients we are aiming for. An analysis will be performed after 20 patients have participated in the study. Therefore, if greater than 20% of patients have poor quality implants, this procedure will be unacceptable.

Descriptive statistics will be used to describe the frequency at which prostatic cancer low grade disease can be seen on Mp-MRI, and the frequency of unilateral prostatic disease is found after a mapping of the prostate. In addition to standard PSA follow-up, response will be assessed by imaging at 20 and 36 months as well as by TRUS-guided biopsy at 36 months.

Data analysis will be undertaken by Dr Ana Fernandez with the assistance of a qualified statistician.

Resources and Implementation

Ethics

The application for the South Eastern Sydney Local Health District (SESLHD) Human Research Ethics Committee has been recently approved.

Skills and Resources

Three of the investigators are experienced BT proceduralists with extensive experience in the use of TRUS and transperineal needle implantation. The fourth investigator is a BT fellow in training and will be assisting with the procedure.

Planning systems will be institution-dependant but must allow appropriate collection of the above mentioned data. Acceptable planning systems will include Variseed, Nucletron First, PSID, and MIM Symphony. TGA-approved iodine-125 seeds may be purchased from any of the vendors within Australia.

Data Collection

The necessary data to be collected at various time-points of the study is outlined in Figure 4. The principal and co-investigators will be responsible for collection of this data. This data will be manually entered onto paper forms and transferred to a secure database which is password protected and accessible only to the investigators.

Budget and Funding

The investigations beyond normal practice that are required for this protocol are (1) two TTGM biopsies of the prostate, one pretreatment and another one at 36 months following treatment;

and (2) Mp-MRI of the prostate, required at baseline and again 20 and 36 months following completion of treatment to assess response.

The post-implant quality assessment will require a a non-Mp prostatic MRI at day 30. This is not our standard practice but we arrange it sometimes for specific patients that require more accurate post-implant quality evaluation. Apart from the 20 month and 36 month assessments, follow-up after completion of treatment is standard. The costs entailed by the MRI examinations and the TTGM prostate biopsy will be billed to the Internal Hospital Research Budget. Internal funding prior to commencement will be undertaken by each institution. SGCCC has already coordinated local funding using trust fund cost centre number and hence can proceed immediately after ethics approval. A grant application will cover part of the expenses. There will be no out-of-pocket cost for the patients enrolled in the study.

Results

The study opened for recruitment in September 2015. One patient has been involved so far in the study that initially met the eligibility criteria and signed the consent. During the pre-treatment evaluation process he underwent a Mp-MRI which showed Prostate Imaging Recording and Data System Score 5 (PI-RADS 5) on the left lobe and PI-RADS 4 on the right lobe. A PI-RADS 5 represents clinically significant, highly likely to be present and PI-RADS 4 is clinically significant and cancer likely to be present [63]. Subsequently, as per protocol, a TTGMB was performed finding a Gleason score of 3+4= 7 in 3 cores on the right side and in 8 cores of the left side. The histopathology report was reviewed. The patient underwent a standard seed implant prescribing 144 Gy to the whole prostate.

Discussion

This protocol is designed to show feasibility in delivering hemigland focal therapy with seed BT. Our whole-prostate seed BT program has been running for more than 10 years with excellent results (data not published). We believe that our well-established experience with seed BT will ease the performance of the hemigland technique. The reduction in toxicity can be of significant importance, particularly in a well-selected population, therefore we consider the pre-implant investigations crucial.

If the trial is successful, showing feasibility meeting the dosimetric parameters in the post-implant setting, toxicity parameters, quality of life, and tumor local control will be evaluated. Once evaluated we will be able to move towards a RCT scenario comparing standard WG seed implant versus hemigland to confirm the benefit in toxicity and quality of life with the highest level of evidence. Cost effective analysis should be performed in the future given the cost of the pre-implant investigations before establishing the focal therapy technique.

Furthermore, this protocol will give us opportunities to study more data, such as the correlation between Mp-MRI findings with TTGMB which is still in early stages [64,65].

Conflicts of Interest

None declared.

Multimedia Appendix 1

Quality of life instruments: Expanded Prostate Cancer Index Composite (EPIC) questionnaire, International Prostate Symptoms Score (IPSS) questionnaire, International Index Erectile Function (IIEF) questionnaire.

[PDF File (Adobe PDF File), 90KB - resprot_v5i2e98_app1.pdf]

References

1. American Cancer Soceity. Cancer Facts and Figures, 2014. URL: http://www.cancer.org/acs/groups/content/@research/documents/webcontent/acspc-042151.pdf [accessed 2016-02-23] [WebCite Cache ID 6fWdJukvF34]
2. Welch HP, Albertsen PC. Prostate cancer diagnosis and treatment after the introduction of prostate-specific antigen screening: 1986-2005. J Natl Cancer Inst 2009 Oct 7;101(19):1325-1329 [FREE Full text] [doi: 10.1093/jnci/djp278] [Medline: 19720969]
3. Powell IJ, Bock CH, Ruterbusch JJ, Sakr W. Evidence supports a faster growth rate and/or earlier transformation to clinically significant prostate cancer in black than in white American men, and influences racial progression and mortality disparity. J Urol 2010 May;183(5):1792-1796 [FREE Full text] [doi: 10.1016/j.juro.2010.01.015] [Medline: 20299055]
4. Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. N Engl J Med 2004 May 27;350(22):2239-2246. [doi: 10.1056/NEJMoa031918] [Medline: 15163773]
5. Sanda MG, Dunn RL, Michalski J, Sandler HM, Northouse L, Hembroff L, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med 2008 Mar 20;358(12):1250-1261. [doi: 10.1056/NEJMoa074311] [Medline: 18354103]
6. Hashine K, Yuasa A, Shinomori K, Ninomiya I, Kataoka M, Yamashita N. Health-related quality of life after radical retropubic prostatectomy and permanent prostate brachytherapy: a 3-year follow-up study. Int J Urol 2011 Dec;18(12):813-819 [FREE Full text] [doi: 10.1111/j.1442-2042.2011.02866.x] [Medline: 21995507]

7. Frank SJ, Levy LB, van Vulpen M, Crook J, Sylvester J, Grimm P, et al. Outcomes after prostate brachytherapy are even better than predicted. Cancer 2012 Feb 1;118(3):839-847 [FREE Full text] [doi: 10.1002/cncr.26307] [Medline: 21751187]
8. Klotz L. Active surveillance for prostate cancer: a review. Curr Urol Rep 2010 May;11(3):165-171. [doi: 10.1007/s11934-010-0110-z] [Medline: 20425623]
9. Klotz LM, Emberton M. Management of low risk prostate cancer: active surveillance and focal therapy. Curr Opin Urol 2014 May;24(3):270-279. [doi: 10.1097/MOU.0000000000000055] [Medline: 24710055]
10. Liu J, Lichtensztajn DY, Gomez SL, Sieh W, Chung BI, Cheng I, et al. Nationwide prevalence of lymph node metastases in Gleason score 3 + 3 = 6 prostate cancer. Pathology 2014 Jun;46(4):306-310. [doi: 10.1097/PAT.0000000000000097] [Medline: 24798166]
11. Dall'Era M, Albertsen P, Bangma C, Carroll P, Carter H, Cooperberg M, et al. Active surveillance for prostate cancer: a systematic review of the literature. Eur Urol 2012 Dec;62(6):976-983. [doi: 10.1016/j.eururo.2012.05.072] [Medline: 22698574]
12. Bul M, Zhu X, Valdagni R, Pickles T, Kakehi Y, Rannikko A, et al. Active surveillance for low-risk prostate cancer worldwide: the PRIAS study. Eur Urol 2013 Apr;63(4):597-603. [doi: 10.1016/j.eururo.2012.11.005] [Medline: 23159452]
13. Hayes JH, Ollendorf DA, Pearson SD, Barry MJ, Kantoff PW, Stewart ST, et al. Active surveillance compared with initial treatment for men with low-risk prostate cancer: a decision analysis. JAMA 2010 Dec 1;304(21):2373-2380 [FREE Full text] [doi: 10.1001/jama.2010.1720] [Medline: 21119084]
14. Wolters T, Roobol MJ, Steyerberg EW, van den Bergh RC, Bangma CH, Hugosson J, et al. The effect of study arm on prostate cancer treatment in the large screening trial ERSPC. Int J Cancer 2010 May 15;126(10):2387-2393 [FREE Full text] [doi: 10.1002/ijc.24870] [Medline: 19739124]
15. Andriole GL. PSA screening and prostate cancer risk reduction. Urol Oncol 2012;30(6):936-937. [doi: 10.1016/j.urolonc.2012.09.009] [Medline: 23218069]
16. Stamey TA, McNeal JM, Wise AM, Clayton JL. Secondary cancers in the prostate do not determine PSA biochemical failure in untreated men undergoing radical retropubic prostatectomy. Eur Urol 2001 Apr;39 Suppl 4:22-23. [doi: 10.1159/000052577] [Medline: 11340281]
17. Liu W, Laitinen S, Khan S, Vihinen M, Kowalski J, Yu G, et al. Copy number analysis indicates monoclonal origin of lethal metastatic prostate cancer. Nat Med 2009 May;15(5):559-565 [FREE Full text] [doi: 10.1038/nm.1944] [Medline: 19363497]
18. Ahmed HU. The index lesion and the origin of prostate cancer. N Engl J Med 2009 Oct 22;361(17):1704-1706. [doi: 10.1056/NEJMcibr0905562] [Medline: 19846858]
19. Langley S, Ahmed H, Al-Qaisieh B, Bostwick D, Dickinson L, Veiga F, et al. Report of a consensus meeting on focal low dose rate brachytherapy for prostate cancer. BJU Int 2012 Feb;109 Suppl 1:7-16 [FREE Full text] [doi: 10.1111/j.1464-410X.2011.10825.x] [Medline: 22239224]
20. Nishida K, Yuen S, Kamoi K, Yamada K, Akazawa K, Ito H, et al. Incremental value of T2-weighted and diffusion-weighted MRI for prediction of biochemical recurrence after radical prostatectomy in clinically localized prostate cancer. Acta Radiol 2011 Feb 1;52(1):120-126. [doi: 10.1258/ar.2010.100293] [Medline: 21498337]
21. Onik G, Miessau M, Bostwick DG. Three-dimensional prostate mapping biopsy has a potentially significant impact on prostate cancer management. J Clin Oncol 2009 Sep 10;27(26):4321-4326 [FREE Full text] [doi: 10.1200/JCO.2008.20.3497] [Medline: 19652073]
22. Puech P, Potiron E, Lemaitre L, Leroy X, Haber G, Crouzet S, et al. Dynamic contrast-enhanced-magnetic resonance imaging evaluation of intraprostatic prostate cancer: correlation with radical prostatectomy specimens. Urology 2009 Nov;74(5):1094-1099. [doi: 10.1016/j.urology.2009.04.102] [Medline: 19773038]
23. Villers A, Puech P, Mouton D, Leroy X, Ballereau C, Lemaitre L. Dynamic contrast enhanced, pelvic phased array magnetic resonance imaging of localized prostate cancer for predicting tumor volume: correlation with radical prostatectomy findings. J Urol 2006 Dec;176(6 Pt 1):2432-2437. [doi: 10.1016/j.juro.2006.08.007] [Medline: 17085122]
24. Ahmed HU, Freeman A, Kirkham A, Sahu M, Scott R, Allen C, et al. Focal therapy for localized prostate cancer: a phase I/II trial. J Urol 2011 Apr;185(4):1246-1254. [doi: 10.1016/j.juro.2010.11.079] [Medline: 21334018]
25. Muto S, Yoshii T, Saito K, Kamiyama Y, Ide H, Horie S. Focal therapy with high-intensity-focused ultrasound in the treatment of localized prostate cancer. Jpn J Clin Oncol 2008 Mar;38(3):192-199 [FREE Full text] [doi: 10.1093/jjco/hym173] [Medline: 18281309]
26. Onik G, Vaughan D, Lotenfoe R, Dineen M, Brady J. The “male lumpectomy”: focal therapy for prostate cancer using cryoablation results in 48 patients with at least 2-year follow-up. Urol Oncol 2008;26(5):500-505. [doi: 10.1016/j.urolonc.2008.03.004] [Medline: 18774463]
27. Ellis DS, Manny TB, Rewcastle JC. Focal cryosurgery followed by penile rehabilitation as primary treatment for localized prostate cancer: initial results. Urology 2007 Dec;70(6 Suppl):9-15. [doi: 10.1016/j.urology.2007.07.036] [Medline: 18194712]
28. Lambert EH, Bolte K, Masson P, Katz AE. Focal cryosurgery: encouraging health outcomes for unifocal prostate cancer. Urology 2007 Jun;69(6):1117-1120. [doi: 10.1016/j.urology.2007.02.047] [Medline: 17572198]

29. Crook J, Borg J, Evans A, Toi A, Saibishkumar EP, Fung S, et al. 10-year experience with I-125 prostate brachytherapy at the Princess Margaret Hospital: results for 1,100 patients. Int J Radiat Oncol Biol Phys 2011 Aug 1;80(5):1323-1329. [doi: 10.1016/j.ijrobp.2010.04.038] [Medline: 20675072]
30. Stock RG, Klein TJ, Cesaretti JA, Stone NN. Prognostic significance of 5-year PSA value for predicting prostate cancer recurrence after brachytherapy alone and combined with hormonal therapy and/or external beam radiotherapy. Int J Radiat Oncol Biol Phys 2009 Jul 1;74(3):753-758. [doi: 10.1016/j.ijrobp.2008.08.049] [Medline: 19084351]
31. Sylvester JE, Grimm PD, Wong J, Galbreath RW, Merrick G, Blasko JC. Fifteen-year biochemical relapse-free survival, cause-specific survival, and overall survival following I(125) prostate brachytherapy in clinically localized prostate cancer: Seattle experience. Int J Radiat Oncol Biol Phys 2011 Oct 1;81(2):376-381. [doi: 10.1016/j.ijrobp.2010.05.042] [Medline: 20864269]
32. Stock RG, Cesaretti JA, Stone NN. Disease-specific survival following the brachytherapy management of prostate cancer. Int J Radiat Oncol Biol Phys 2006 Mar 1;64(3):810-816. [doi: 10.1016/j.ijrobp.2005.09.005] [Medline: 16309852]
33. Keyes M, Schellenberg D, Moravan V, McKenzie M, Agranovich A, Pickles T, et al. Decline in urinary retention incidence in 805 patients after prostate brachytherapy: the effect of learning curve? Int J Radiat Oncol Biol Phys 2006 Mar 1;64(3):825-834. [doi: 10.1016/j.ijrobp.2005.04.056] [Medline: 16458775]
34. Keyes M, Miller S, Moravan V, Pickles T, McKenzie M, Pai H, et al. Predictive factors for acute and late urinary toxicity after permanent prostate brachytherapy: long-term outcome in 712 consecutive patients. Int J Radiat Oncol Biol Phys 2009 Mar 15;73(4):1023-1032. [doi: 10.1016/j.ijrobp.2008.05.022] [Medline: 19111402]
35. Crook J, Fleshner N, Roberts CG, Pond G. Long-term urinary sequelae following 125iodine prostate brachytherapy. J Urol 2008 Jan;179(1):141-5; discussion 146. [doi: 10.1016/j.juro.2007.08.136] [Medline: 17997424]
36. Keyes M, Spadinger I, Liu M, Pickles T, Pai H, Hayden A, et al. Rectal toxicity and rectal dosimetry in low-dose-rate (125)I permanent prostate implants: a long-term study in 1006 patients. Brachytherapy 2012;11(3):199-208. [doi: 10.1016/j.brachy.2011.05.007] [Medline: 21763213]
37. Zelefsky MJ, Kuban DA, Levy LB, Potters L, Beyer DC, Blasko JC, et al. Multi-institutional analysis of long-term outcome for stages T1-T2 prostate cancer treated with permanent seed implantation. Int J Radiat Oncol Biol Phys 2007 Feb 1;67(2):327-333. [doi: 10.1016/j.ijrobp.2006.08.056] [Medline: 17084558]
38. Waterman FA, Dicker AP. Probability of late rectal morbidity in 125I prostate brachytherapy. Int J Radiat Oncol Biol Phys 2003 Feb 1;55(2):342-353. [Medline: 12527047]
39. Merrick GS, Butler WM, Wallner KE, Galbreath RW, Kurko B, Cleavinger S. Rectal function following brachytherapy with or without supplemental external beam radiation: results of two prospective randomized trials. Brachytherapy 2003;2(3):147-157. [doi: 10.1016/S1538-4721(03)00131-4] [Medline: 15062137]
40. Mueller A, Wallner K, Merrick G, Ford E, Sutlief S, Cavanagh W, et al. Perirectal seeds as a risk factor for prostate brachytherapy-related rectal bleeding. Int J Radiat Oncol Biol Phys 2004 Jul 15;59(4):1047-1052. [doi: 10.1016/j.ijrobp.2003.12.016] [Medline: 15234038]
41. Tran A, Wallner K, Merrick G, Seeberger J, Armstrong J, Mueller A, et al. Rectal fistulas after prostate brachytherapy. Int J Radiat Oncol Biol Phys 2005 Sep 1;63(1):150-154. [doi: 10.1016/j.ijrobp.2005.01.021] [Medline: 16111583]
42. Merrick G, Butler W, Wallner K, Galbreath R, Anderson R, Allen ZE, et al. Risk factors for the development of prostate brachytherapy related urethral strictures. J Urol 2006 Apr;175(4):1376-80; discussion 1381. [doi: 10.1016/S0022-5347(05)00681-6] [Medline: 16516001]
43. Kamrava M, Chung MP, Kayode O, Wang J, Marks L, Kupelian P, et al. Focal high-dose-rate brachytherapy: a dosimetric comparison of hemigland vs. conventional whole-gland treatment. Brachytherapy 2013;12(5):434-441. [doi: 10.1016/j.brachy.2012.09.002] [Medline: 23406987]
44. Schick U, Popowski Y, Nouet P, Bieri S, Rouzaud M, Khan H, et al. High-dose-rate brachytherapy boost to the dominant intra-prostatic tumor region: hemi-irradiation of prostate cancer. Prostate 2011 Sep;71(12):1309-1316. [doi: 10.1002/pros.21347] [Medline: 21308714]
45. Hayden A, Catton CT, Pickles T. Radiation therapy in prostate cancer: a risk-adapted strategy. Curr Oncol 2010 Sep;17 Suppl 2:S18-S24 [FREE Full text] [Medline: 20882127]
46. Shemtov OM, Radomski SB, Crook J. Success of sildenafil for erectile dysfunction in men treated with brachytherapy or external beam radiation for prostate cancer. Can J Urol 2004 Dec;11(6):2450-2455. [Medline: 15636671]
47. Merrick GS, Butler WM, Wallner KE, Lief JH, Anderson RL, Smeiles BJ, et al. The importance of radiation doses to the penile bulb vs. crura in the development of postbrachytherapy erectile dysfunction. Int J Radiat Oncol Biol Phys 2002 Nov 15;54(4):1055-1062. [Medline: 12419431]
48. Kaplan ID, Holupka EJ, Meskell P, Soon SJ, Saltzman B, Church P, et al. Intraoperative treatment planning for radioactive seed implant therapy for prostate cancer. Urology 2000 Sep 1;56(3):492-495. [Medline: 10962322]
49. Beyer DC, Shapiro RH, Puente F. Real-time optimized intraoperative dosimetry for prostate brachytherapy: a pilot study. Int J Radiat Oncol Biol Phys 2000 Dec 1;48(5):1583-1589. [Medline: 11121665]
50. Zelefsky MJ. Three-dimensional conformal brachytherapy for prostate cancer. Curr Urol Rep 2004 Jun;5(3):173-178. [Medline: 15161565]

51. Nguyen PL, Chen M, Zhang Y, Tempany CM, Cormack RA, Beard CJ, et al. Updated results of magnetic resonance imaging guided partial prostate brachytherapy for favorable risk prostate cancer: implications for focal therapy. J Urol 2012 Oct;188(4):1151-1156 [FREE Full text] [doi: 10.1016/j.juro.2012.06.010] [Medline: 22901567]
52. Cosset J, Cathelineau X, Wakil G, Pierrat N, Quenzer O, Prapotnich D, et al. Focal brachytherapy for selected low-risk prostate cancers: a pilot study. Brachytherapy 2013;12(4):331-337. [doi: 10.1016/j.brachy.2013.02.002] [Medline: 23601349]
53. Morris WJ. Focal Therapy for Prostate Cancer - A Pilot Study of Focal Low Dose Rate Brachytherapy (FTPC). URL: https://clinicaltrials.gov/ct2/show/NCT01830166?term=Morris+focal+therapy+brachytherapy&rank=1 [accessed 2016-02-23] [WebCite Cache ID 6fWdV6f5J34]
54. Bachaud JM. Phase II Study of Feasibility of Focal Therapy for Prostate Cancer of Good Prognosis With Permanent I125 Localized Implant. (CURIEFOCALE). URL: https://clinicaltrials.gov/ct2/show/NCT01902680?term=Bachaud+focal+therapy+brachytherapy&rank=1 [accessed 2016-02-23] [WebCite Cache ID 6fWeBCxpf34]
55. Jamieson C, Langley S. Hemi-Ablative Prostate Brachytherapy (HAPpy). URL: https://clinicaltrials.gov/ct2/show/NCT02632669 [accessed 2016-03-01] [WebCite Cache ID 6fhDg9h1E34]
56. Zelefsky M. Assessing the Potential for Reduced Toxicity Using Focal Brachytherapy in Early Stage, Low Volume Prostate Cancer. URL: https://clinicaltrials.gov/ct2/show/NCT01354951?term=focal+prostate&rank=5 [accessed 2016-02-23] [WebCite Cache ID 6fWckbwUL34]
57. Dickinson L, Ahmed HU, Allen C, Barentsz JO, Carey B, Futterer JJ, et al. Magnetic resonance imaging for the detection, localisation, and characterisation of prostate cancer: recommendations from a European consensus meeting. Eur Urol 2011 Apr;59(4):477-494. [doi: 10.1016/j.eururo.2010.12.009] [Medline: 21195536]
58. Bott SR, Henderson A, McLarty E, Langley SE. A brachytherapy template approach to standardize saturation prostatic biopsy. BJU Int 2004 Mar;93(4):629-630. [Medline: 15008745]
59. Bott SR, Ahmed HU, Hindley RG, Abdul-Rahman A, Freeman A, Emberton M. The index lesion and focal therapy: an analysis of the pathological characteristics of prostate cancer. BJU Int 2010 Dec;106(11):1607-1611 [FREE Full text] [doi: 10.1111/j.1464-410X.2010.09436.x] [Medline: 20553262]
60. Karavitakis M, Ahmed HU, Abel PD, Hazell S, Winkler MH. Tumor focality in prostate cancer: implications for focal therapy. Nat Rev Clin Oncol 2011 Jan;8(1):48-55. [doi: 10.1038/nrclinonc.2010.190] [Medline: 21116296]
61. Petrik D, Araujo C, Kim D, Halperin R, Crook JM. Implications of CT imaging for postplan quality assessment in prostate brachytherapy. Brachytherapy 2012;11(6):435-440. [doi: 10.1016/j.brachy.2012.05.001] [Medline: 22732323]
62. Bowes D, Crook JM, Rajapakshe R, Araujo C, Parker B. Defining a magnetic resonance scan sequence for permanent seed prostate brachytherapy postimplant assessment. Brachytherapy 2013;12(1):25-29 [FREE Full text] [doi: 10.1016/j.brachy.2012.03.001] [Medline: 22513105]
63. Weinreb JC, Barentsz JO, Choyke PL, Cornud F, Haider MA, Macura KJ, et al. PI-RADS Prostate Imaging - Reporting and Data System: 2015, Version 2. Eur Urol 2016 Jan;69(1):16-40. [doi: 10.1016/j.eururo.2015.08.052] [Medline: 26427566]
64. Sartor A, Hricak H, Wheeler T, Coleman J, Penson D, Carroll P, et al. Evaluating localized prostate cancer and identifying candidates for focal therapy. Urology 2008 Dec;72(6 Suppl):S12-S24. [doi: 10.1016/j.urology.2008.10.004] [Medline: 19095124]
65. Muller BG, Fütterer JJ, Gupta RT, Katz A, Kirkham A, Kurhanewicz J, et al. The role of magnetic resonance imaging (MRI) in focal therapy for prostate cancer: recommendations from a consensus panel. BJU Int 2014 Feb;113(2):218-227 [FREE Full text] [doi: 10.1111/bju.12243] [Medline: 24215670]

Abbreviations

AS: active surveillance
BT: brachytherapy
CT: computed tomography
CTV: clinical target volume
ED: erectile dysfunction
HDRI: high dynamic range imaging
IIEF: International Index of Erectile Function
IPSS: International Prostate Symptom Score
LDR: low dose rate
Mp-MRI: multi-parametric-magnetic resonance imaging
MR-CT fusion: magnetic resonance imaging computed tomography fusion
MRI: magnetic resonance imaging
PAR: post-anesthesia recovery
PI-RADS 4: Prostate Imaging Recording and Data System Score 4
PI-RADS 5: Prostate Imaging Recording and Data System Score 5
PSA: prostate-specific antigen

PTV: planning target volume
RCT: randomized controlled trial
STGCCC: St George Cancer Care Centre
TRUS: transrectal ultrasound
TTGM: transperineal template-guided mapping
UF: ultra-focal
WG: whole gland

Edited by G Eysenbach; submitted 14.01.16; peer-reviewed by H Ahmed; comments to author 23.02.16; revised version received 25.02.16; accepted 26.02.16; published 13.06.16.

Please cite as:
Fernandez Ots A, Bucci J, Chin YS, Malouf D, Howie A, Enari KE
Hemiablative Focal Low Dose Rate Brachytherapy: A Phase II Trial Protocol
JMIR Res Protoc 2016;5(2):e98
URL: http://www.researchprotocols.org/2016/2/e98/
doi:10.2196/resprot.5433
PMID:27296781

Original Paper

The Patient Outcomes Research To Advance Learning (PORTAL) Network Adult Overweight and Obesity Cohort: Development and Description

Deborah R Young[1*], PhD; Beth A Waitzfelder[2*], PhD; David Arterburn[3*], MD; Gregory A Nichols[4*], PhD; Assiamira Ferrara[5*], MD, PhD; Corinna Koebnick[1*], PhD; Ayae Yamamoto[1*], ScM; Matthew F Daley[6*], MD; Nancy E Sherwood[7*], PhD; Michael A Horberg[8*], MD; Lee Cromwell[9*], MS; Kristina H Lewis[10*], MD, MPH, SM

[1]Kaiser Permanente Southern California, Department of Research & Evaluation, Pasadena, CA, United States
[2]Kaiser Permanente Hawaii, Center for Health Research, Honolulu, HI, United States
[3]Group Health Research Institute, Seattle, WA, United States
[4]Kaiser Permanente Northwest, Center for Health Research, Portland, OR, United States
[5]Kaiser Permanente Northern California, Division of Research, Oakland, CA, United States
[6]Kaiser Permanente Colorado, Institute for Health Research, Denver, CO, United States
[7]HealthPartners Institute, Bloomington, MN, United States
[8]Mid-Atlantic Permanente Research Institute, Rockville, MD, United States
[9]Kaiser Permanente Georgia, Atlanta, GA, United States
[10]Wake Forest Baptist Medical Center, Department of Epidemiology & Prevention, Winston-Salem, NC, United States
[*]all authors contributed equally

Corresponding Author:
Deborah R Young, PhD
Kaiser Permanente Southern California
Department of Research & Evaluation
2nd Fl.
100 S. Los Robles
Pasadena, CA, 91101
United States
Phone: 1 626 564 3887
Fax: 1 626 564 3694
Email: deborah.r.young@kp.org

Abstract

Background: The Patient-Centered Outcomes Research Institute (PCORI) created a new national network infrastructure to enable large-scale observational comparative effectiveness research across diverse clinical care settings. As part of testing the feasibility of this effort, each clinical data research network (CDRN) was required to construct cohorts of patients, including one of patients with overweight and obesity.

Objective: The aim of this paper is to report on the development of the Patient Outcomes Research to Advance Learning (PORTAL) overweight and obese cohort, which includes patients from 10 health plans located across the United States.

Methods: Information was gathered from each plan's electronic health records (EHR). Eligibility included 18 years of age or older, a valid height and weight in 2012 or 2013, and body mass index (BMI) greater than 22.9 kg/m^2. Pre-diabetes and diabetes status was defined using the American Diabetes Association (ADA) criteria, using lab values of glycated hemoglobin (HbA1c) or fasting glucose available in the EHR. Hypertension was identified from the International Classification of Diseases (ICD) diagnosis codes. Individuals were classified into BMI categories: healthy weight (23.0-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), obese class 1 (30.0-34.9 kg/m^2), obese class 2 (35.0-39.9 kg/m^2), obese class 3 (40.0-49.0 kg/m^2), and obese class 4 (>50.0 kg/m^2).

Results: A cohort of 5,293,458 non-pregnant adults was created. Weight status was 20.39% (1,079,289/5,293,458) healthy weight, 40.40% (2,138,520/5,293,458) overweight, 22.78% (1,205,866/5,293,458) obese class 1, 9.86% (521,872/5,293,458)

obese class 2, 5.59% (295,786/5,293,458) obese class 3, and 0.98% (52,125/5,293,458) obese class 4. Race/ethnicity was 49.02% (2,594,776/5,293,458) non-Hispanic white, 22.89% (1,211,677/5,293,458) Hispanic, 10.40% (550,608/5,293,458) Asian, 10.83% (573,506/5,293,458) black, and 6.59% (348,830/5,293,458) other. About 34.33% (1,817,438/5,293,458) met the definition of hypertension, 20.49% (1,660,940/5,293,458) of individuals met the criteria for pre-diabetes, and 14.98% (793,069/5,293,458) met criteria for diabetes. Prevalence of pre-diabetes and diabetes varied across health plans to a greater extent than expected based on hypertension prevalence and BMI status variability.

Conclusions: This large, race, ethnic, and geographically diverse cohort will be useful for future studies of rare exposures or outcomes and differences in health care practices.

(JMIR Res Protoc 2016;5(2):e87) doi:10.2196/resprot.5589

KEYWORDS

overweight; obesity; race and ethnic diversity; pre-diabetes; diabetes

Introduction

In 2014, the Patient-Centered Outcomes Research Institute (PCORI) funded 11 Clinical Data Research Networks (CDRN) and 18 Patient-Powered Research Networks to develop a National Patient-Centered Clinical Research Network (PCORnet), with the purpose of building a common infrastructure across the CDRNs to enable highly representative future clinical outcomes research. The goal of PCORnet is to "transform clinical research by engaging patients, care providers, and health systems in collaborative partnerships to improve healthcare and advance medical knowledge." One of the CDRNs is the Patient Outcomes Research to Advance Learning (PORTAL) network. PORTAL combines four health care delivery systems that have about 11 million members enrolled across nine states (CA, CO, GA, HI, MD, MN, OR, VA, WA) and the District of Columbia, reaching into most regions in the United States and offering a diverse patient population.

The PORTAL health care systems are previously described [1]. In brief, PORTAL includes all Kaiser Permanente regions (Hawaii, Northwest [Northern Oregon and Southwest Washington], Northern California, Southern California, Colorado, Mid-Atlantic States [Maryland, Virginia, and District of Columbia], and Georgia [through 2015]), Group Health Cooperative (Washington), HealthPartners (Minnesota and Wisconsin), and Denver Health. Individuals of all the health care systems except for Denver Health are insured (public or private); Denver Health is a safety net institution that provides medical services regardless of ability to pay.

All CDRNs were required to develop three cohorts to demonstrate each network's ability to identify individuals with a condition of interest and to test the commonality of data elements across sites. They also were required to field a survey of the cohorts to test the ability to reach out to patients. One of the pre-specified cohorts common to all of the PCORnet CDRNs was a cohort of individuals with obesity. The PORTAL overweight and obesity cohort was defined as adult members of our health care systems during 2012 or 2013 that were overweight or obese, defined as having a body mass index (BMI) greater than or equal to 23.0 kg/m^2. Although overweight is defined as BMI greater than 25 kg/m^2we recognize that the World Health Organization (WHO) recommends lower overweight and obesity cut points for Asians: 23.0-27.4 $kg/m^2$for overweight and greater or equal to 27.5 $kg/m^2$for obesity [2]. Given that our health plans have a significant number of Asian individuals, we chose this lower cut point so future studies can examine health risks for Asians deemed overweight by WHO recommendations.

We constructed a cross-sectional cohort of adults enrolled in any of the PORTAL health plans; all of those meeting eligibility criteria are considered cohort members. For all sites except Denver Health, we first identified health plan members with at least 12 months of continuous membership between January 1, 2012 and December 31, 2013, and who were at least 18 years of age on December 31, 2013. Members were further restricted to those who had a weight recorded during 2012 or 2013, had a height recorded in the electronic health record (EHR), and who were not pregnant during 2012-2013. For Denver Health, the initial eligibility criteria included all adults who had a primary care encounter during 2012 or 2013 because Denver Health, as a safety-net organization, does not enroll members.

Methods

Data Harmonization

Each health care system has its unique methods of capturing its electronic health care data, resulting in information that widely varies in terms of content, format, and structure, thus requiring consistent data standards and terminology. We used the Health Care Systems Research Network (formerly HMO Research Network) Virtual Data Warehouse (VDW) for data extraction. The VDW is a federated database in which all data reside at each health system behind each site's secure system, or firewall [3]. The data model consists of taking the clinical and claims datasets from the individual health care systems and converting them into a series of identical dataset standards, automated processes, and common data dictionaries. This allows for a single Statistical Analysis System (SAS) program to be written and distributed to other sites with a minimum of site-specific customization. Sites typically return the datasets to the lead site within 2 weeks. Future studies using data from the PORTAL cohort will use the PCORnet common data model (CDM), which is the data structure built for all PCORnet networks. The CDM and VDW have similar data structures; sites run a program that extract data from the VDW into the CDM. The PCORnet CDM was being developed concurrently with the PORTAL cohort; thus, we used the VDW for data extraction.

Kaiser Permanente Southern California (KPSC) is the lead site for the cohort and obtained its institutional review board's (IRB) approval for human subjects protections for the research. The IRBs at the other sites reviewed the protocol and subsequently ceded review to the KPSC IRB.

Weight and Height

Weight is routinely measured as part of obtaining vital signs during outpatient clinic visits. Height is typically assessed less often, as it is considered to be more static. If BMI was not available in the EHR, it was calculated. If more than one weight, height, or BMI was in the EHR in 2012-2013, the most recent value was used. EHR records of heights less than 4 ft or equal to or greater than 8 ft, and weights less than 50 lbs or equal or greater than 1000 lbs were considered implausible and were removed from the data set. Similarly, calculated BMI less than 5 kg/m^2or equal to or greater than 90 kg/m^2were excluded. A total of 6954 (0.11%, 6954/6,255,688) individuals were excluded from the cohort because they had no biologically plausible weight, height, or BMI values.

We categorized individuals as healthy weight (BMI 23.0-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), obese class 1 (30.0-34.9 kg/m^2), obese class 2 (35.0-39.9 kg/m^2), obese class 3 (40.0-49.9 kg/m^2), or obese class 4 (>50 kg/m^2) [4]. We classified Asian/Pacific Islanders in the same manner for this initial analysis.

Race and Ethnicity

Race and ethnicity was obtained from self-report during enrollment into the health plan, during a health care encounter, or from birth certificates (if applicable). Individuals had the option to identify themselves as Asian, Black or African American, Hispanic, Native Hawaiian or other Pacific Islander, American Indian or Alaskan Native, White, or other. If the information was not available in the VDW or individuals identified themselves as belonging to another race or ethnic group, the individual was categorized as "other/unknown."

Education and Income

Our health plans do not routinely collect individual-level data on educational attainment or income levels, so investigators rely on neighborhood-level information to estimate socioeconomic status. Neighborhood education and income were estimated using geospatial entity object codes (geocodes) that linked addresses to 2010 US census data at the block group level. The probability of different education levels within a block group was used to calculate individual averages. The probability of different family and household income levels within a block group was used to calculate individual averages.

Pre-Diabetes and Diabetes

Pre-diabetes was defined by the American Diabetes Association (ADA) and from the work of Schmittdiel et al as follows: if during the study period the EHR had (1) at least one HbA1C between 5.7% and 6.4%, or (2) at least one fasting plasma glucose measurement between 100 and 125 mg/dL, or (3) at least one oral glucose tolerance test between 140 and 199 mg/dL, or (4) at least one outpatient International Classification of Diseases, Ninth Revision (ICD-9) code of 790.2, 790.29, 790.21, or 790.22 [5,6]. These laboratory and diagnoses criteria qualified for pre-diabetes only if they were not superseded by the criteria used to meet the definition of diabetes (see below).

Diabetes was defined using the methodology developed for Surveillance, Prevention, and Management of Diabetes Mellitus (SUPREME DM), a large multi-site observational diabetes study [7]. The definition was adapted from the ADA definition of diabetes [5]. Briefly, the definition included one inpatient diagnosis of diabetes or any combination of two other events (outpatient diagnosis, dispense of an anti-hyperglycemic medication, HbA1C equal or greater than 6.5%, fasting plasma glucose equal or greater than 126 mg/dL or random plasma glucose equal or greater than 200mg/dL).

Hypertension

Hypertension was considered present if an individual had at least two outpatient or one inpatient ICD-9 codes of 401-405xxx.

Bariatric Surgery

Individuals who had undergone bariatric surgery were identified by an algorithm developed by Arterburn et al in 2009, which used the Current Procedural Terminology 4 (CPT-4) codes (43842, 43843, 43846, 43847), and ICD-9 codes (CPT-4 codes 43659, 43621, 43633) [8]. Verification of this strategy resulted in sensitivity of 99.2% and specificity of 99.9% [8]. Since additional bariatric procedure codes have been created since 2009, the above algorithm was adapted by adding the following codes: 43.82, 43.89, 44.31, 44.38, 44.39, 44.68, 44.69, 44.95, 43633, 43644, 43645, 43770, 43775, 43844, 43845, S2082, S2085. The algorithm was used to search EHR records from the years 2009 to 2013 to identify possible cases of bariatric surgery.

Charlson Index

Presence of comorbid conditions was assessed with a modified Charlson Comorbidity Index [9-11], which used diagnosis codes for 22 health conditions during the two-year period of January 1, 2012 to December 31, 2013 to create a summary score.

PORTAL Health Survey

A random sample of 675 overweight and obese English or Spanish reading or speaking individuals were selected from each of the seven KP health plans and Denver Health to complete a brief health survey, for a total of 5400 individuals. An equal number of participants were selected from the categories of overweight, obese class 1, and obese class 2 (n=1080 per category). We randomly selected 2160 for those with obese class 3 and greater, as we were concerned that the extremely obese may not choose to complete the survey. The survey took about 10 minutes to complete and included items on general health and well-being, physical activity, eating patterns, sleep patterns, and perceived health care sensitivities surrounding weight status. The survey was mailed to individuals with telephone follow-up for those who did not return the survey. A US $20 incentive was offered to complete the survey.

Figure 1. PORTAL overweight and obesity flow chart to construct the cohort.

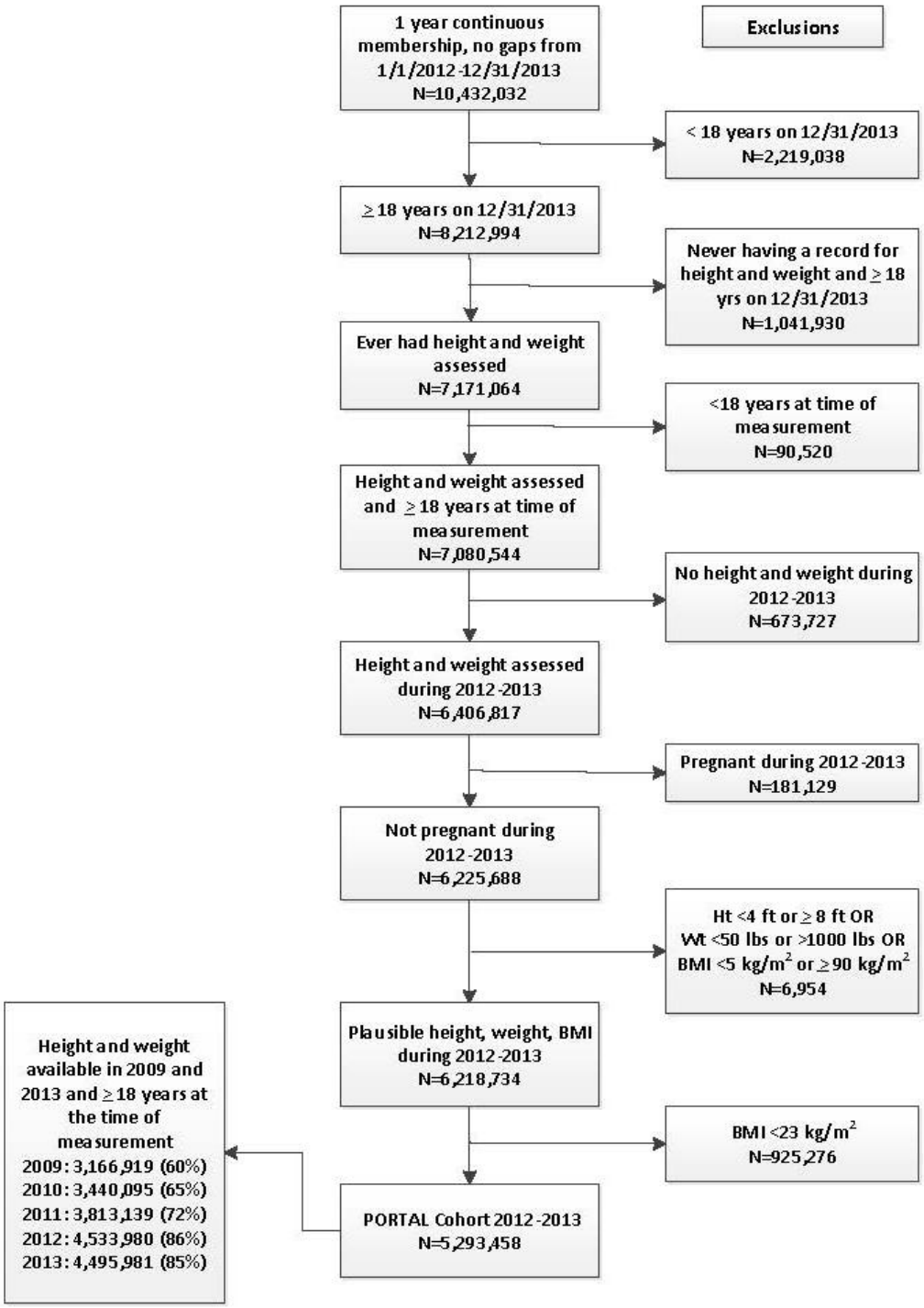
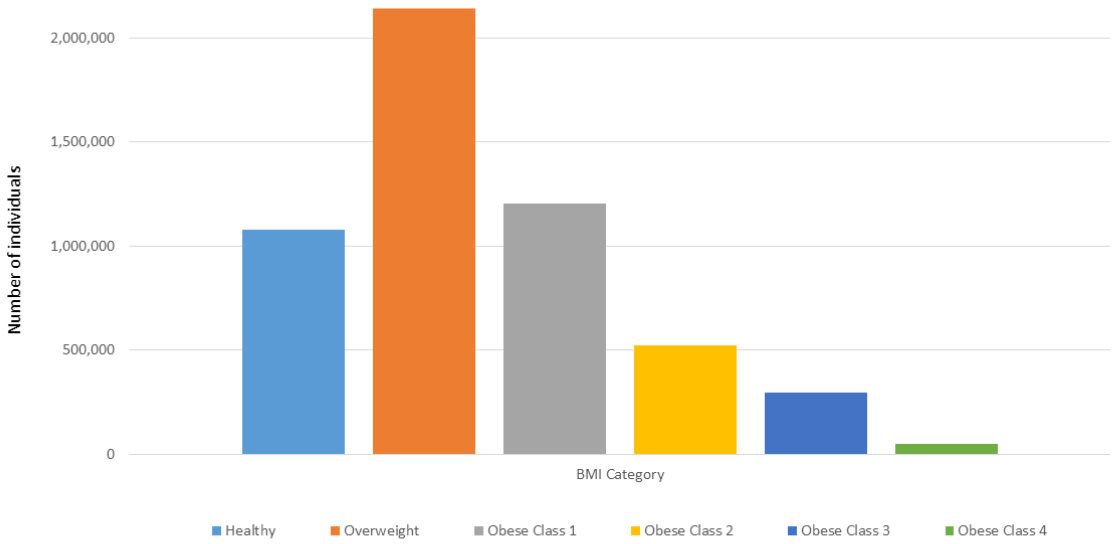


Figure 2. The number of individuals in each BMI category, all PORTAL sites combined.



Results

Cohort

The cohort includes over 5 million adults with a BMI >23.0 kg/m^2. The cohort flow chart with all sites combined is displayed in Figure 1. We identified over 10 million individuals who had continuous membership in 2012 to 2013. After excluding those who were less than 18 years old (n=2,309,558), those who did not have a height and weight recorded (n=1,715,657), who were pregnant during 2012-2013 (n=181,129), and those with implausible height, weight, or BMI measurements (n=6954), a total of 6,218,734 adults remained. We then excluded individuals with a BMI less than 23.0 kg/m^2 (n=925,276), leaving a cohort of 5,293,458 individuals. A subgroup of the cohort includes a nested cohort of 3,166,919 members who were also enrolled in one of the health plans in 2009 that can be used for future analyses. Although these individuals were members in 2009 and 2013, they may have had different health plan coverage from 2010 to 2012.

Cohort demographics are displayed in Multimedia Appendix 1. Across all network sites 51.95% (2,750,077/5,293,458) are women and 49.02% (2,594,776/5,293,458) are white, 22.89% (1,211,677/5,293,458) are Hispanic, 10.40% (550,608/5,293,458) are Asian, and 10.83% (573,506/5,293,458) are Black. Even though only 1% (75,489/5,293,458) of the cohort is Native Hawaiian/other Pacific Islanders and less than 1% (28,964/5,293,458) is American Indian/Alaskan Natives, they total 75,489 and 28,964 individuals, respectively. The race and ethnicity distribution and neighborhood education and income at each of the ten sites is consistent with the underlying demographics of each region's population [3-6]. About 2.58% (136,374/5,293,458) of the cohort is insured through a state-subsidized medical insurance plan (eg, Medicaid); another 22.47% (1,189,209/5,293,458) are Medicare recipients. Most individuals (74.81%, 3,959,913/5,293,458) have private insurance, with employer or self-pay options the most prevalent.

Overall, about 85.03% (5,293,458/6,225,688) of non-pregnant individuals over the age of 18 with valid BMI measures obtained in 2012 to 2013 are members of the cohort (Figure 1). The cohort by BMI category, both by the numbers of individuals and prevalence of individuals in each category are shown in Figure 2 and Multimedia Appendix 1. The most common category is overweight, which includes 40.40% (2,138,520/5,293,458) of the individuals in the cohort. The cohort has 52,125 (0.98%, 52,125/5,293,458) persons categorized as obese class 4 (BMI >50 kg/m^2). The distribution of BMI category is remarkably similar across sites; for example, the prevalence of those in the healthy weight category varied from 17.23% (23,935/138,900) to 21.96% (397,683/1,810,899) and in the obese class 2 category ranged from 8.95% (23,837/266,470) to 11.66% (16,195/138,900) across the 8 sites.

Pre-diabetes varied across sites, with an overall cohort prevalence of 29.49% (1,560,940/5,293,458) and a range from 15.30% (21,248/138,900) to 34.45% (39,171/113,699) across the health plans (Multimedia Appendix 1). Diabetes is prevalent among 14.98% (793,069/5,293,458) of individuals with a range of 12.03% (32,051/266,470) to 20.56% (10,232/49776), and hypertension is prevalent among 34.33% (1,817,436/5,293,458) of individuals with a range of 31.86% (84,886/266,470) to 39.26% (110,560/281,641) in the cohort. Over 25,000 individuals (0.97%, 25,187/5,293,458) were identified as previously having had bariatric surgery.

Table 1. Sociodemographic and BMI categories for those who returned the PORTAL health survey (N=2809) compared with those who did not (N=2591).

		Returned survey, n (%)	Did not return survey, n (%)
Sex			
	Female, n=3290	1737 (52.80)	1553 (47.20)
	Male, n=2110	1072 (50.81)	1038 (49.19)
Age category			
	<20 years, n=80	24 (30.00)	56 (70.00)
	20-29 years, n=546	215 (39.38)	331 (60.62)
	30-39 years, n=866	347 (40.07)	519 (59.93)
	40-49 years, n=1115	539 (48.34)	576 (51.66)
	50-59 years, n=1220	680 (55.74)	540 (44.26)
	60-69 years, n=1019	638 (62.61)	381 (37.39)
	70-79 years, n=442	296 (66.97)	146 (33.03)
	>80 years, n=112	70 (62.50)	42 (37.50)
Race/ethnicity			
	White, n=2535	1435 (56.61)	1100 (43.39)
	Hispanic, n=987	420 (42.55)	567 (57.45)
	Asian, n=304	165 (54.28)	139 (45.72)
	Black, n=1144	596 (52.10)	548 (47.90)
	Native Hawaiian/other Pacific Islander, n=301	168 (55.81)	133 (44.19)
	American Indian/Alaskan Native, n=34	20 (58.82)	14 (41.18)
	Other/unknown, n=95	5 (5.26)	90 (94.74)
BMI category			
	Overweight (25.0-29.9 kg/m ^{2}), n=1080	577 (53.43)	503 (46.57)
	Obese class 1 (30.0-34.9 kg/m ^{2}), n=1080	566 (52.41)	514 (47.59)
	Obese class 2 (35.0-39.9 kg/m^2), n=1080	550 (50.93)	530 (49.07)
	Obese class 3 (40.0-49.9 kg/m^2), n=1811	936 (51.68)	875 (48.32)
	Obese class 4 (>50.0 kg/m^2), n=349	179 (51.29)	170 (48.71)

Health Survey

From the sample of 5400 individuals, 2809 surveys were completed, 114 were deemed ineligible (ie, no valid address, deceased), 924 persons refused, and 1553 did not respond to mail or telephone attempts, resulting in a 53.14% response of those eligible. Among those who were selected for the survey, women (52.80%, 1737/2809) were slightly more likely to complete the survey than men (50.81%, 1072/2809), and more older individuals returned the survey, for example 62.61% (638/1019) of those age 60 to 69 years completed the survey compared with 39.38% (215/546) of those age 20 to 29 years (Table 1). Completion by race/ethnicity was 59% (20/34) American Indian/Alaskan, 56.61% (1435/2535) White, 55.81% (168/301) Native Hawaiian/Pacific Islanders, 54.28% (165/304) Asians, 52.10% (596/1144) Black, and 42.55% (420/987) Hispanics. There was virtually no difference in response by BMI category, with responses ranging from 50.93% (550/1080) to 53.43% (577/1080) across the five categories, or by self-reported education level.

Discussion

Principal Findings

The PORTAL overweight and obesity cohort is large and extends across all regions in the United States. Racial and ethnic diversity, as well as socioeconomic diversity, is large and generally representative of the underlying populations of the health plans' service regions [12]. The large sample size is particularly useful to support the study of rare exposures or outcomes. Available clinical information is robust and reflects "real world" information that clinicians and health plans use to document health care rather than research quality data collected at pre-specified study intervals. However, prior studies have shown that BMI information collected in the medical record is valid [13]. The cohort can be examined retrospectively and

prospectively. For example, exposures identified in 2009 in the sub-cohort can be linked to outcomes identified in 2012 to 2013. The variation across regions, across medical practices, and across different types of health plans with variations in coverage can be examined. A large majority of individuals have access to health insurance (public or private); thus, confounding by health care access is reduced for research focused on health disparities.

The prevalence of individuals across BMI categories and hypertension prevalence was fairly similar across health plans. In contrast, pre-diabetes and diabetes prevalence varied to a greater extent than expected based on hypertension prevalence and BMI status variability. This variability may be due to local differences in testing for pre-diabetes and diabetes, which requires blood work while weight and blood pressure are routinely measured at each visit. The ADA recommends testing for pre-diabetes and diabetes for all adults starting at age 45 years or for those who are overweight and who have additional risk factors, including physical inactivity, hypertension, and being from minority race and ethnicities [5]. However, according to National Health and Nutrition Examination Survey (NHANES) data, only about one-half of those eligible have been tested [14]. Additional research is needed to understand the processes that may explain differences in testing for pre-diabetes and diabetes across sites.

Follow-up of the cohort will be through the clinical information available in EHR. The five year retention is expected to be about 60%, but will vary by health care system. For the 3.1 million individuals who were health plan members in 2009 and 2013, clinical data are available with 5 year follow-up. This information includes repeated measures of height, weight, BMI, prevalent and incident diagnoses from inpatient and outpatient encounters, procedures performed, laboratory test results, pharmaceuticals dispensed, and pathology and radiology results.

PCORnet is created to foster collaborative partnerships across networks and institutions and PORTAL investigators adhere to this principle. The PCORnet CDM (similar to the VDW) has a query function to allow non-PORTAL investigators to inquire about data availability. In general, the information available in the EHR is protected and confidential and remains behind each health plan's firewall. We welcome external collaborations, particularly collaborations that include establishment of research questions, study design decisions, and analysis and interpretation of the data. Current analyses underway include descriptions of cardiometabolic health among cohort members, incidence of outcomes across BMI categories, and survey results.

Limitations

In some regions, individuals with low socioeconomic status may be underrepresented, although all health plans except one include individuals covered under state-subsidized insurance, and Denver Health's mission is to serve those with limited ability to pay for medical services. There is also marginal underrepresentation of those with high incomes. While a large population, the cohort does not include individuals from all 50 states and, therefore, cannot be considered as fully representative of the United States. Because data are collected as part of clinical care, some data elements may not be research quality and are likely to have errors or misclassifications imbedded in them. The classifications of disease status (eg, hypertension, diabetes status) are based on data available in the VDW and have not been chart-reviewed for their validity. However, the quality of diagnosis codes is relatively high in managed care systems and has been validated for many health conditions [15-17]. The cohort does not include individuals with BMI values less than 23.0 kg/m^2; therefore we cannot directly compare the cohort to national data sets, such as NHANES.

Conclusion

The PORTAL overweight and obesity cohort is a rich resource of considerable diversity. It represents the ability of clinical data to be combined across health plans to be available for future epidemiological and comparative effectiveness research.

Acknowledgments

This work was supported by a contract awarded by the Patient-Centered Outcomes Research Institute (PCORI).

Conflicts of Interest

None declared.

Multimedia Appendix 1

Sociodemographic, BMI category, chronic conditions, and health insurance status across the 10 PORTAL obesity cohort sites (N= 5,293,458).

[PDF File (Adobe PDF File), 171KB - resprot_v5i2e87_app1.pdf]

References

1. McGlynn EA, Lieu TA, Durham ML, Bauck A, Laws R, Go AS, et al. Developing a data infrastructure for a learning health system: the PORTAL network. J Am Med Inform Assoc 2014;21(4):596-601 [FREE Full text] [doi: 10.1136/amiajnl-2014-002746] [Medline: 24821738]
2. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004 Jan 10;363(9403):157-163. [doi: 10.1016/S0140-6736(03)15268-3] [Medline: 14726171]

3. Ross TR, Ng D, Brown JS, Pardee R, Hornbrook MC, Hart G, et al. The HMO Research Network Virtual Data Warehouse: a public data model to support collaboration. EGEMS (Wash DC) 2014;2(1):1049 [FREE Full text] [doi: 10.13063/2327-9214.1049] [Medline: 25848584]
4. Sturm R. Increases in morbid obesity in the USA: 2000-2005. Public Health 2007 Jul;121(7):492-496 [FREE Full text] [doi: 10.1016/j.puhe.2007.01.006] [Medline: 17399752]
5. American Diabetes Association. (2) Classification and diagnosis of diabetes. Diabetes Care 2015 Jan;38 Suppl:S8-S16. [doi: 10.2337/dc15-S005] [Medline: 25537714]
6. Schmittdiel JA, Adams SR, Segal J, Griffin MR, Roumie CL, Ohnsorg K, et al. Novel use and utility of integrated electronic health records to assess rates of prediabetes recognition and treatment: brief report from an integrated electronic health records pilot study. Diabetes Care 2014 Feb;37(2):565-568 [FREE Full text] [doi: 10.2337/dc13-1223] [Medline: 24271190]
7. Nichols GA, Schroeder EB, Karter AJ, Gregg EW, Desai J, Lawrence JM, et al. Trends in diabetes incidence among 7 million insured adults, 2006-2011: the SUPREME-DM project. Am J Epidemiol 2015 Jan 1;181(1):32-39 [FREE Full text] [doi: 10.1093/aje/kwu255] [Medline: 25515167]
8. Arterburn D, Livingston EH, Schifftner T, Kahwati LC, Henderson WG, Maciejewski ML. Predictors of long-term mortality after bariatric surgery performed in Veterans Affairs medical centers. Arch Surg 2009 Oct;144(10):914-920. [doi: 10.1001/archsurg.2009.134] [Medline: 19841358]
9. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373-383. [Medline: 3558716]
10. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992 Jun;45(6):613-619. [Medline: 1607900]
11. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi J, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005 Nov;43(11):1130-1139. [Medline: 16224307]
12. Koebnick C, Langer-Gould AM, Gould MK, Chao CR, Iyer RL, Smith N, et al. Sociodemographic characteristics of members of a large, integrated health care system: comparison with US Census Bureau data. Perm J 2012;16(3):37-41 [FREE Full text] [Medline: 23012597]
13. Arterburn D, Ichikawa L, Ludman EJ, Operskalski B, Linde JA, Anderson E, et al. Validity of clinical body weight measures as substitutes for missing data in a randomized trial. Obes Res Clin Pract 2008 Dec;2(4):277-281 [FREE Full text] [doi: 10.1016/j.orcp.2008.09.002] [Medline: 19956347]
14. Bullard KM, Ali MK, Imperatore G, Geiss LS, Saydah SH, Albu JB, et al. Receipt of glucose testing and performance of two US diabetes screening guidelines, 2007-2012. PLoS One 2015;10(4):e0125249 [FREE Full text] [doi: 10.1371/journal.pone.0125249] [Medline: 25928306]
15. Coleman KJ, Lutsky MA, Yau V, Qian Y, Pomichowski ME, Crawford PM, et al. Validation of autism spectrum disorder diagnoses in large healthcare systems with electronic medical records. J Autism Dev Disord 2015 Jul;45(7):1989-1996. [doi: 10.1007/s10803-015-2358-0] [Medline: 25641003]
16. Karter AJ, Ferrara A, Liu JY, Moffet HH, Ackerson LM, Selby JV. Ethnic disparities in diabetic complications in an insured population. JAMA 2002 May 15;287(19):2519-2527. [Medline: 12020332]
17. Lo RV, Haynes K, Goldberg D, Forde KA, Carbonari DM, Leidl KB, et al. Validity of diagnostic codes to identify cases of severe acute liver injury in the US Food and Drug Administration's Mini-Sentinel Distributed Database. Pharmacoepidemiol Drug Saf 2013 Aug;22(8):861-872 [FREE Full text] [doi: 10.1002/pds.3470] [Medline: 23801638]

Abbreviations

ADA: American Diabetes Association
BMI: body mass index
CDRN: Clinical Data Research Network
CDM: Common Data Model
CPT-4: Current Procedural Terminology 4
EHR: Electronic Health Records
HbA1c: glycated hemoglobin
ICD-9: International Classification of Diseases, Ninth Revision
IRB: institutional review board
KPSC: Kaiser Permanente Southern California
NHANES: National Health and Nutrition Examination Survey
PCORI: Patient-Centered Outcomes Research Institute
PCORnet: Patient-Centered Clinical Research Network
PORTAL: Patient Outcomes Research to Advance Learning
VDW: Virtual Data Warehouse
WHO: World Health Organization

Edited by G Eysenbach; submitted 09.02.16; peer-reviewed by G Block, E Schroeder; comments to author 09.03.16; revised version received 16.03.16; accepted 16.03.16; published 15.06.16.

Please cite as:
Young DR, Waitzfelder BA, Arterburn D, Nichols GA, Ferrara A, Koebnick C, Yamamoto A, Daley MF, Sherwood NE, Horberg MA, Cromwell L, Lewis KH
The Patient Outcomes Research To Advance Learning (PORTAL) Network Adult Overweight and Obesity Cohort: Development and Description
JMIR Res Protoc 2016;5(2):e87
URL: http://www.researchprotocols.org/2016/2/e87/
doi:10.2196/resprot.5589
PMID:27307352

Original Paper

Partnership for Healthier Asians: Disseminating Evidence-Based Practices in Asian-American Communities Using a Market-Oriented and Multilevel Approach

Karen Kim[1], MD; Michael Quinn[2], PhD; Edwin Chandrasekar[3], MPPM; Reena Patel[3], MPH; Helen Lam[1], PhD, RN

[1]The University of Chicago, Comprehensive Cancer Center, Chicago, IL, United States

[2]The University of Chicago, Department of Internal Medicine, Chicago, IL, United States

[3]Asian Health Coalition, Chicago, IL, United States

Corresponding Author:
Helen Lam, PhD, RN
The University of Chicago
Comprehensive Cancer Center
5841 South Maryland Ave
MC1140
Chicago, IL, 60637
United States
Phone: 1 773 702 2613
Fax: 1 773 702 9311
Email: hvallina@bsd.uchicago.edu

Abstract

Background: One of the greatest challenges facing health promotion and disease prevention is translating research findings into evidence-based practices (EBP). There is currently a limited research base to inform the design of dissemination action plans, especially within medically underserved communities.

Objective: The objective of this paper is to describe an innovative study protocol to disseminate colorectal cancer (CRC) screening guidelines in seven Asian subgroups.

Methods: This study integrated a market-oriented Push-Pull-Infrastructure Model, Diffusion of Innovation Theory, and community-based participatory research approach to create a community-centered dissemination framework. Consumer research, through focus groups and community-wide surveys, was centered on the adopters to ensure a multilevel intervention was well designed and effective.

Results: Collaboration took place between an academic institution and eight community-based organizations. These groups worked together to conduct thorough consumer research. A sample of 72 Asian Americans participated in 8 focus groups, and differences were noted across ethnic groups. Furthermore, 464 community members participated in an Individual Client Survey. Most participants agreed that early detection of cancer was important (434/464, 93.5%), cancer could happen to anyone (403/464, 86.9%), CRC could be prevented (344/464, 74.1%), and everyone should screen for CRC (389/464, 83.8%). However, 35.8% (166/464) of participants also felt that people were better off not knowing it they had cancer, and 45.5% (211/464) would screen only when they had symptoms. Most participants indicated that they would screen upon their doctor's recommendation, but half reported that they only saw a doctor when they were sick. Data collection currently is underway for a multilevel intervention (community health advisor and social marketing campaign) and will conclude March 2016. We expect that analysis and results will be available by June 2016.

Conclusions: This study outlines a complementary role for researchers and community organizations in disseminating EBP, and incorporates social interactions and influences to move individuals from simple awareness to decisions towards positive action.

(JMIR Res Protoc 2016;5(2):e123) doi:10.2196/resprot.5625

KEYWORDS

Evidence-based practice; community-based participatory research; Asian Americans; dissemination and implementation; community health advisors

Introduction

One of the greatest challenges facing health promotion and disease prevention is translating research findings into evidence-based practices (EBP). Despite significant accomplishments in basic, clinical, and population health research, a wide gap persists between what we know and what we do. Failing to translate knowledge into practice is costly and harmful; it leads to overuse of ineffectual care, underuse of effective care, and errors in execution [1]. In recent years, there has been a growing effort to bridge the knowledge and practice gap, yet there is a limited research base to inform the design of dissemination action plans, resulting in slow and uneven adoption of EBP [2-6]. EBP is essential in health care, since it provides direction and rationale for guiding health behaviors, decision-making, and treatments [7]. Based on marketing and diffusion theories, many researchers agree that a fundamental obstacle to successfully disseminating EBP to a wider audience is the lack of systems and infrastructure to carry out marketing and distribution [8-12]. Marketing and distribution systems bring products and services from development to use through a system of intermediaries [13]. These intermediaries identify potential users, promote the product to them, provide them with easy access to the product through multiple channels, and support the product after purchase [14,15]. Building a successful marketing and distribution system to bring EBP to medically underserved communities has great potential to reduce unnecessary disease burden.

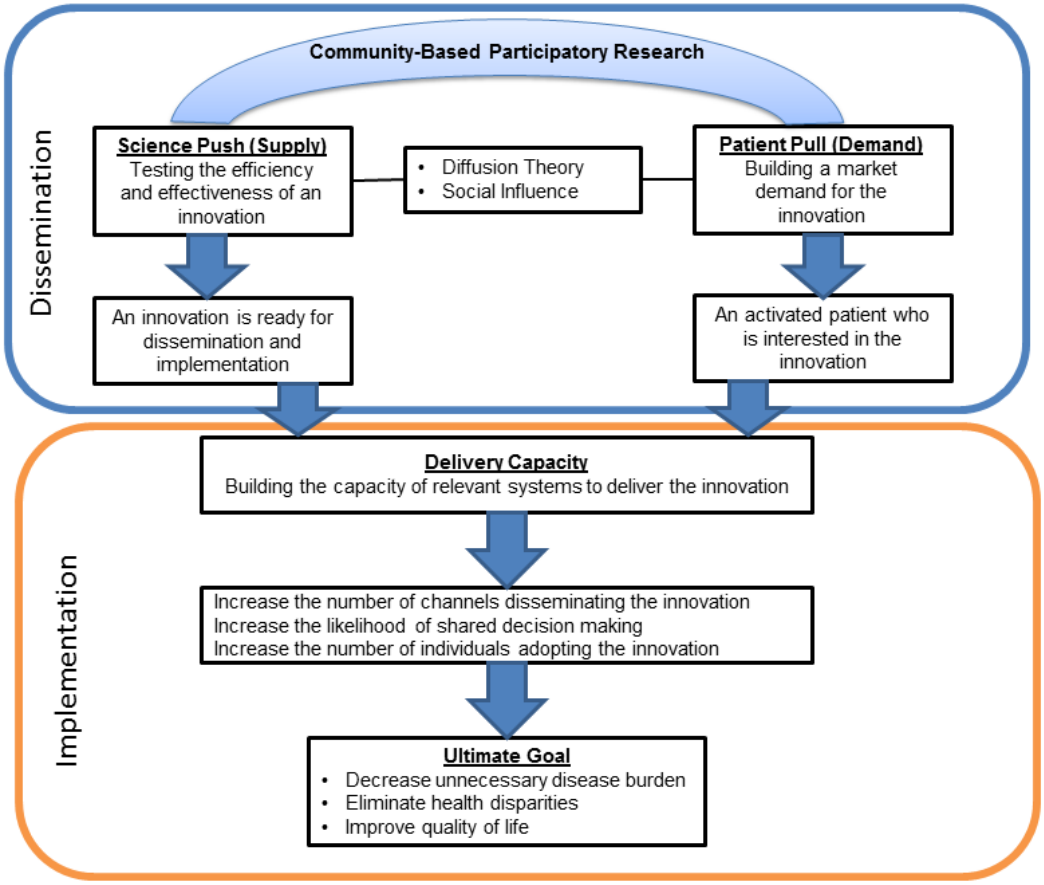
Asian Americans (AAs) are the fastest growing minority group in the United States, and there are approximately 17.3 million AAs nationwide [16]. More than 65% of AAs are foreign-born with greater than 30% having limited English proficiency [17]. AAs are the first and only racial/ethnic group to experience cancer as the leading cause of death [18]. Although colorectal cancer (CRC) is the third most common cancer in the United States, it is the second most common cancer among AAs [19,20]. Disturbingly, 50% of new cases diagnosed yearly in the United States could have been avoided with routine CRC screening [21,22]. Although there was a significant increase in CRC screening in the overall US population between 2008 and 2010, AAs remained the only racial/ethnic subgroup without any improvement [23]. In addition, important differences exist in knowledge, attitudes, and beliefs among Asian subgroups [24]. In this project, we aim to develop a community-centered dissemination system for EBP in Asian communities.

Methods

Conceptual Framework

We integrated a market-oriented Push-Pull-Infrastructure Model [25] with Diffusion of Innovations Theory [26], and Community-Based Participatory Research (CBPR) approach to create a community-centered EBP dissemination framework (Figure 1). The Push-Pull-Infrastructure Model implies that a sole emphasis on pushing (supplying) knowledge from science is ineffective. The supply of knowledge must be accompanied by both an increase pull (demand) for innovations and an increase in capacity of the infrastructure to deliver the innovations [11]. To date, most efforts in dissemination research have focused mainly on disseminating innovations, with little emphasis on increasing demand among potential users [27]. Consumers' preexisting dispositions, preferences, perceptions, capacities, and behaviors determine their response to the innovation and shape their decision-making processes [9]. Partnering with the community is a critical component to translate research into a wider population practice [28-30], and community involvement may enhance the translation and dissemination process [31-34]. In this new model, we use a CBPR approach to bridge the gap between research and practice, as well as academia and community. A successful market depends on the availability of information about the available products and the ability of individuals to access that information, and it can be achieved by using multiple formal and informal media, including newspapers and websites [26]. However, this one-way communication, even if it is repeated through multiple channels, is typically insufficient to move an individual toward a positive action. Persuasion through a two-way communication of social influence has proven more effective [35]. In this project, we used community health advisors (CHAs) who were familiar with the culture, language, and local community, to spread information and generate demand from community members. A social norm marketing campaign in the form of small media, which was found to be effective in promoting CRC screening [36], was conducted to build public awareness and generate demand. This project was approved by the University of Chicago Institutional Review Board (IRB: 052689-0). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation, and with the Helsinki Declaration of 1975.

Figure 1. A community-centered dissemination framework for evidence-based practice.



Creating a Research-Community Dissemination Infrastructure

We invited six Asian-American community-based organizations (CBOs) to join our EBP dissemination community task force during year one. These six CBOs provide direct services to five Asian subgroups (Cambodian, Chinese, Korean, Laotian, and Vietnamese). In Year two, we invited two additional CBOs that serve Filipinos and Southern Asians. Recognizing that the complexity in translating lessons learned from science into practice required a multilevel approach, we also assembled an academic EBP steering committee to accelerate the integration. The academic EBP steering committee consisted of seven different internal departments from the academic institution. Our EBP dissemination community task force and academic EBP steering committee met periodically, separately and jointly, to communicate project progress and disseminate study findings.

Assessing Community Partners' Capacity and Readiness for Evidence-Based Practice Dissemination

The adoption of EBP depends on the capacity of CBOs to implement and sustain particular activities. An initial assessment of each CBO's capacity, based on the strength of its leadership, existing programs and outreach, strategic plan, financial stability, and support staff, was important for the implementation of dissemination-related activities. Assessments were completed via a paper-and-pencil survey. Not all items contributed equally to the implementation process, so the research team used a Delphi method to develop a score system to consider the significance of each item. The Delphi expert panel included three academic experts and two community experts. The research team also developed an EBP readiness survey based on literature review and expert inputs. The EBP readiness survey assessed the stage of our CBO partners along a continuum of readiness. The 7-item EBP readiness survey measured four domains related to the readiness to adopt EBP. These four domains were (1) a defined need for EBP, (2) readiness for change in organizational culture, (3) time, resources, and personnel for EBP, and (4) ability to sustain the change. Under each item, CBO partners chose the stage statement that described their current state of readiness for EBP. Findings from the organizational capacity assessment and EBP readiness survey were used to inform the dissemination process and capacity building.

Conducting Consumer Research

Although evidence-based CRC screening guidelines have been widely communicated through mainstream media channels, these messages likely have limited reach among AAs because dissemination methods and content are not culturally sensitive

or language-specific. Consumer research is one of the significant components of the Market-Orientated Push and Pull Model. Consumer research allows researchers to listen to their consumers to ensure that marketing strategies are well designed, well implemented, and effective by centering the product on their consumers, keeping the product relevant, and understanding which of the product's *constellation of benefits* to prioritize. In this project, we used a two-step approach to conduct consumer research in our partner communities.

First, we conducted 8 focus groups with a total of 72 participants from 7 Asian subgroups (Cambodian, Chinese, Filipino, Korean, Laotian, South Asian, and Vietnamese) to elicit beliefs and attitudes related to CRC screening. These focus groups were facilitated by bilingual, bicultural CBO staff members, who participated in a 4-hour training session to enhance their facilitation skills. A focus group guide was developed to ensure consistency across groups. Eligibility criteria for the focus group required that participants were (1) between age 40 and 65, (2) lived in different households, and (3) were capable of giving consent. The focus groups were conducted in participants' native language and tape recorded. The tape recordings were then translated into English by the facilitator. A team of five people worked together to perform content analysis, using template analysis method based on the Theory of Planned Behavior Model.

Secondly, findings from the focus groups were used to develop an Individual Client Survey. The goal of the Individual Client Survey was to determine behavioral beliefs, normative beliefs, and perceived control beliefs regarding CRC screening within the target population. The development of the Individual Client Survey included (1) developing a pool of survey statements (n=91) from the focus group findings, (2) soliciting feedback from CBO partners (n=11) regarding relevance and cultural appropriateness, and (3) weighting the statements for their relevance and significance. The final survey instrument contained 20 statements and was approved by all community partners. Besides the English version, the final survey instrument was translated into six different languages. The survey used a cross-sectional design with a purposeful (based on age group and sex) and convenient sample. A total of 470 surveys were collected from 7 different Asian communities (Table 1). Findings from the Individual Client Survey were then used to design a dissemination plan, train community health advisors, and develop a social marketing campaign.

Table 1. Individual Client Survey participants by Asian subgroups.

Asian Subgroup	n
Cambodian	50
Chinese	55
Filipinos	67
Korean[a]	121
Laotian	70
South Asians	49
Vietnamese	58
Total	470

[a]Two Korean community based organizations participated in the Individual Client Survey.

Generating Public Awareness Through Social Marketing and Social Influence.

In this project, we used consumer-centered social marketing. Consumer-centered social marketing goes beyond pushing the product to the consumer by building demand for the product. The marketing campaign aimed to address sociocultural norms as well as linguistic barriers regarding CRC screening. Although social marketing campaigns can create public awareness, which is the first step toward taking action, information alone is not enough to prompt interest, shape attitudes, and bring about behavior change. Ultimately, the goal of dissemination is not to simply get the word out, but to take the user from awareness to understanding, to commitment, and then to action. We used CHAs as an influencer, each of whom was a bilingual, bicultural community health professional who understood the social norms of the community. To build on these strengths, and to equip them to carry out this work, all CHAs attended a 6-hour training on CRC screening, motivational interviewing techniques, and the application of Stage of Change Theory.

Investigating the Effectiveness of Community Health Advisor Intervention in Conjunction with Social Marketing

We will use a multiple baseline design to evaluate the effectiveness of our CHA intervention. If every group shows a similar change after crossing to the intervention condition and does not change at other times, the findings will provide compelling evidence that the changes resulted from the intervention [37]. In addition, multiple baseline design guards the internal validity of the study by ruling out the possibility that a single external event (eg, a celebrity cancer diagnosis) could explain the results. In this project, each community will experience a transition from the baseline condition to the intervention condition, but these transitions will be observed over different time periods. The study procedure is outlined as follows:

A baseline CRC screening education session will be conducted in each community prior to the rollout of the CHA intervention and social marketing campaign.

Partner CBOs will be asked to post event flyers as usual, but to refrain from active recruitment.

Participants at each educational session will be asked to fill out a survey, which includes demographic items and beliefs statements selected from the Individual Client Survey.

Partner CBOs will be divided into two cohorts: cohort 1 (Chinese, Filipino, and Laotian) and cohort 2 (Cambodian, Korean, South Asian, and Vietnamese).

Depending on the cohort assignment, partner CBOs will be asked to implement the CHA intervention and social marketing campaign, or do nothing.

The CHA intervention will be a 12-week long intervention and will be carried out concurrently with the social marketing campaign.

At the end of each intervention period, an educational session will be conducted in each community, and no-cost Fecal Immunochemical Test (FIT) kits will be offered to participants.

Participants who took home a FIT kit will have two weeks to return the kit for testing.

The primary outcomes will be the number of participants in each education session, the number of no-cost FIT kits distributed after the education session, and the number of FIT kits returned. Other secondary outcomes will include beliefs and attitudes in CRC screening and intention to screen within the next 12 months. Beliefs and attitudes regarding CRC screening will be measured using items selected from the Individual Client Survey. Participants will also be asked whether they spoke with the CHA prior to the session. The unit of analysis will be cohort (n=2). Statistical tests will be carried out to assess post-intervention differences within and between cohorts, as well as over time.

Evaluating the Implementation Process and Translatability Using the RE-AIM Framework.

Glasgow and associates (1999) designed an evaluation framework to assess the impact of interventions based on five factors: *Reach*, *Efficacy*, *Adoption*, *Implementation*, and *Maintenance* (RE-AIM [38]). This framework expands the assessment of interventions beyond efficacy to multiple criteria that are better able to identify the translatability and public health impact of interventions. In this project, the evaluation will focus on organization level measurements and include both qualitative and quantitative data. Quantitative data will be collected through weekly CHA reports. Each CHA will be required to maintain a daily activity log and to submit weekly reports including number of individuals educated, number of group education sessions (>5 participants) conducted, number of printed materials distributed, and number of follow-up encounters. Qualitative data will also be collected during site visits at week 3, week 7, and week 10. This data will include, but are not limited to, compliance to the intervention protocol, barriers, facilitators, and concerns. Post-intervention focus groups with implementation CHAs will be conducted to obtain feedback regarding the implementation process and experience. In-depth interviews with partner CBO leadership will also be conducted to assess the CBPR process, satisfaction with the project, and sustainability of the dissemination infrastructure.

Results

Assessing Community Partners' Capacity and Readiness for EBP Dissemination

Of the seven partner CBOs, only one CBO had an organization capacity weighted score above the 70th percentile, and two CBOs had a weighted score below the 50th percentile. Of the four stages of readiness for EBP dissemination (stage 1 = there is no agenda or promotion for EBP in the organization; stage 4 = totally ready for EBP dissemination), two CBOs were at stage 3, two were between stage 2 and 3, and three were at stage 2. In general, there was some understanding of the needs for EBP, but there was a lack of mechanism in the organization to move EBP forward. Although three of the CBOs included EBPs in their organizational agenda and were specially discussed, they had not yet been promoted by leadership.

Consumer Research

A convenience sample of 72 AAs participated in 8 focus groups. Most of the participants were female (47/72, 65%), and average age was 55 years. All participants were born outside of the United States, and 20 of 72 (28%) had been in the United States 10 years or less. Although differences were noted across ethnic groups, many respondents were unaware of CRC risk, screening benefits, or screening access. Many respondents attributed CRC to pollution in their home countries, stress of immigrant life, or diet. Respondents from countries with more advanced healthcare systems, such as Korea, were more knowledgeable of screening options.

A total of 470 participants completed the Individual Client Survey from 7 Asian subgroups, with 464 surveys entered for final statistical analysis. Most participants (457/464, 98.5%) were foreign-born, and 222 of 464 (47.8%) had lived in the United States more than 20 years. The average age was 56 years, and 146 of 464 respondents had completed less than 9 years of education. Most participants agreed that early detection of cancer was important (434/464, 93.5%), cancer could happen to anyone (403/464, 86.9%), CRC could be prevented (344/464, 74.1%), and everyone should screen for CRC (389/464, 83.8%). However, 35.8% (166/464) of participants also felt that people were better off not knowing it they had cancer, and 45.5% (211/464) would screen only when they had symptoms. Most participants (402/464, 86.6%) said that they would screen upon their doctor's recommendation, but approximately half of the participants (231/464, 49.8%) reported that they only saw a doctor when they were sick.

Currently, we are conducting our social marketing campaign and implementing the CHA intervention. Data collection is underway and will conclude March 2016. We expect that analysis and results will be available by June 2016.

Discussion

There is a limited research base to inform the design of successful action plans for dissemination and implementation

EBP, especially in underserved and marginalized populations. Little attention has been paid to contextual factors, as well as what the users really need and want during the dissemination process. Users' preexisting dispositions, preferences, perceptions, and capacities impact individual decision-making processes. Although several conceptual frameworks have been developed, and are useful for generating hypotheses for future research [11,39,40], we urgently need practical frameworks for developing and testing dissemination approaches. A multi-level approach is needed to accelerate integration of lessons learned from science into community health care. The combination effect of a multilevel intervention may have a synergistic effect greater than the sum of the individual parts of the intervention. Such synergy can occur when a set of necessary conditions must be jointly present for change to take place, or when an intervention at one level facilitates or reinforces an intervention at another [41]. This project targeted three different levels (community, interpersonal, and individual) to accelerate the adoption of CRC screening guidelines. Our community-centered Dissemination and Implementation Model provides a systematic approach that is feasible to implement in real-life settings, even within resource-restricted communities. The model also outlines a complementary role for researchers and community organizations in disseminating EBP. Our focus on partnerships and understanding potential adopters has the potential to produce wanted and sustainable innovations. Finally, our model incorporates social interactions and influences to move individuals from simple awareness, to decisions, and then to positive action. By triggering a demand for evidence-based innovations, we can increase the success of our dissemination efforts and the adoption of EBP among the underserved and vulnerable populations most in need of effective, evidence-based practice.

Acknowledgments

This material is the result of work supported by the Agency for Healthcare Research and Quality (AHRQ: 1R24HS022063-01) and the Chicago Community Trust and Retirement Research Foundation. We thank our community partners (Alliance of Filipinos for Immigrant Rights and Empowerment, Cambodian Association of Illinois, Chinese American Service League, Hanul Family Alliance, Korean American Community Services, Lao American Organization of Elgin, Muslim Women Resource Center and Chinese Mutual Aid Association) for their cooperation and feedback in developing survey instruments, their recruitment of participants, and their assistance with the CHA intervention. We thank all project participants for their time and sharing personal information about their health and well-being.

Authors' Contributions

KK acted as the principal investigator, conceptualized and secured funding for the study, and materially edited the manuscript. She was also responsible for overseeing all aspects of the study. MQ acted as co-investigator, had the principal responsibility for survey development and data analysis, conceptualized, materially edited the manuscript, and had the principal responsibility for the project evaluation. EC acted as the community co-investigator, conceptualized, secured private funding for the study, and assisted data collection. RP coordinated project activities, and was responsible for data collection and communication with partner organizations. HL had the principal responsibility for the preparation and editing of the manuscript, conceptualized, had the principal responsibility for the study coordination and data management, and was responsible for survey development and data analysis.

Conflicts of Interest

None declared.

References

1. Berwick DM. Disseminating innovations in health care. JAMA 2003 Apr 16;289(15):1969-1975. [doi: 10.1001/jama.289.15.1969] [Medline: 12697800]
2. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA 1999 Oct 20;282(15):1458-1465. [Medline: 10535437]
3. Lomas J. Finding audiences, changing beliefs: the structure of research use in Canadian health policy. J Health Polit Policy Law 1990;15(3):525-542. [Medline: 2273216]
4. Lomas J. Words without action? The production, dissemination, and impact of consensus recommendations. Annu Rev Public Health 1991;12:41-65. [doi: 10.1146/annurev.pu.12.050191.000353] [Medline: 2049143]
5. Jencks SF, Cuerdon T, Burwen DR, Fleming B, Houck PM, Kussmaul AE, et al. Quality of medical care delivered to Medicare beneficiaries: a profile at state and national levels. JAMA 2000 Oct 4;284(13):1670-1676. [Medline: 11015797]
6. Young WW, Marks SM, Kohler SA, Hsu AY. Dissemination of clinical results: mastectomy versus lumpectomy and radiation therapy. Med Care 1996 Oct;34(10):1003-1017. [Medline: 8843927]
7. Kreps G. The evolution and advancement of health communication inquiry. In: Gudykunst WB, editor. Communication Yearbook 24. Thousand Oaks, CA: Routledge; 2001.
8. Harris JR, Cheadle A, Hannon PA, Forehand M, Lichiello P, Mahoney E, et al. A framework for disseminating evidence-based health promotion practices. Prev Chronic Dis 2012;9:E22 [FREE Full text] [Medline: 22172189]

9. Dearing JW, Kreuter MW. Designing for diffusion: how can we increase uptake of cancer communication innovations? Patient Educ Couns 2010 Dec;81 Suppl:S100-S110 [FREE Full text] [doi: 10.1016/j.pec.2010.10.013] [Medline: 21067884]
10. Kerner JF, Guirguis-Blake J, Hennessy KD, Brounstein PJ, Vinson C, Schwartz RH, et al. Translating research into improved outcomes in comprehensive cancer control. Cancer Causes Control 2005 Oct;16 Suppl 1:27-40. [doi: 10.1007/s10552-005-0488-y] [Medline: 16208572]
11. Wandersman A, Duffy J, Flaspohler P, Noonan R, Lubell K, Stillman L, et al. Bridging the gap between prevention research and practice: the interactive systems framework for dissemination and implementation. Am J Community Psychol 2008 Jun;41(3-4):171-181. [doi: 10.1007/s10464-008-9174-z] [Medline: 18302018]
12. Maibach EW, Van Duyn MA, Bloodgood B. A marketing perspective on disseminating evidence-based approaches to disease prevention and health promotion. Prev Chronic Dis 2006 Jul;3(3):A97 [FREE Full text] [Medline: 16776898]
13. Coughlan A, Anderson E, Stern L, El-Ansary A. Marketing channels. Upper Saddle River, NJ: Pearson Prentice Hall; 2006.
14. Kotler P. Marketing management. Upper Saddle River, NJ: Prentice Hall; 2000.
15. Andreasen A. Marketing social change: changing behavior to promote health, social development, and the environment. San Francisco, CA: Jossey-Bass; 1995.
16. Humes KR, Jones NA, Ramirez RR. Department of Commerce, Economics and Statistics Administration 2010. 2010. 2010 census brief: overview of race and Hispanic origin URL: http://www.census.gov/prod/cen2010/briefs/c2010br-02.pdf [accessed 2016-04-05] [WebCite Cache ID 6gY4yvnTq]
17. Grieco E, Acosta Y, Petricia de la Cruz G. United States Census Bureau. 2012. American Community Survey Reports 2012 URL: https://www.census.gov/prod/2012pubs/acs-19.pdf [accessed 2016-04-05] [WebCite Cache ID 6gY5nbz7X]
18. National Center for Health Statistics. U.S. Department of Health and Human Services. 1998. Health, United States, 1998: with socioeconomic status and health chartbook URL: http://www.cdc.gov/nchs/data/hus/hus98.pdf [accessed 2016-04-05] [WebCite Cache ID 6gY6l28KJ]
19. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013 Jan;63(1):11-30. [doi: 10.3322/caac.21166] [Medline: 23335087]
20. Wong ST, Gildengorin G, Nguyen T, Mock J. Disparities in colorectal cancer screening rates among Asian Americans and non-Latino whites. Cancer 2005 Dec 15;104(12 Suppl):2940-2947 [FREE Full text] [doi: 10.1002/cncr.21521] [Medline: 16276538]
21. Pignone M, Rich M, Teutsch SM, Berg AO, Lohr KN. Screening for colorectal cancer in adults at average risk: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2002 Jul 16;137(2):132-141. [Medline: 12118972]
22. Centers for Disease Control and Prevention (CDC). Vital signs: colorectal cancer screening, incidence, and mortality--United States, 2002-2010. MMWR Morb Mortal Wkly Rep 2011 Jul 8;60(26):884-889 [FREE Full text] [Medline: 21734636]
23. Brown ML, Klabunde CN, Cronin KA, White MC, Richardson LC, McNeel TS. Challenges in meeting Healthy People 2020 objectives for cancer-related preventive services, National Health Interview Survey, 2008 and 2010. Prev Chronic Dis 2014;11:E29 [FREE Full text] [doi: 10.5888/pcd11.130174] [Medline: 24576396]
24. Le TD, Carney PA, Lee-Lin F, Mori M, Chen Z, Leung H, et al. Differences in knowledge, attitudes, beliefs, and perceived risks regarding colorectal cancer screening among Chinese, Korean, and Vietnamese sub-groups. J Community Health 2014 Apr;39(2):248-265 [FREE Full text] [doi: 10.1007/s10900-013-9776-8] [Medline: 24142376]
25. Orleans C, Gruman J, Anderson N. Roadmap for the next frontier: getting evidence-based behavioral medicine into practice. 1999 Mar 4 Presented at: Society of Behavioral Medicine Annual Meeting; March 4, 1999; San Diego, CA.
26. Rogers E. Diffusion of Innovations, 5th ed. New York, NY: Free Press; 2003.
27. Kerner J, Rimer B, Emmons K. Introduction to the special section on dissemination: dissemination research and research dissemination: how can we close the gap? Health Psychol 2005 Sep;24(5):443-446. [doi: 10.1037/0278-6133.24.5.443] [Medline: 16162037]
28. Klesges LM, Estabrooks PA, Dzewaltowski DA, Bull SS, Glasgow RE. Beginning with the application in mind: designing and planning health behavior change interventions to enhance dissemination. Ann Behav Med 2005 Apr;29 Suppl:66-75. [doi: 10.1207/s15324796abm2902s_10] [Medline: 15921491]
29. Ashing-Giwa KT. Can a culturally responsive model for research design bring us closer to addressing participation disparities? Lessons learned from cancer survivorship studies. Ethn Dis 2005;15(1):130-137. [Medline: 15720060]
30. Jones L, Wells K. Strategies for academic and clinician engagement in community-participatory partnered research. JAMA 2007 Jan 24;297(4):407-410. [doi: 10.1001/jama.297.4.407] [Medline: 17244838]
31. Soong CS, Wang MP, Mui M, Viswanath K, Lam TH, Chan SS. A “Community Fit” community-based participatory research program for family health, happiness, and harmony: design and implementation. JMIR Res Protoc 2015;4(4):e126 [FREE Full text] [doi: 10.2196/resprot.4369] [Medline: 26510960]
32. Minkler M. Community-based research partnerships: challenges and opportunities. J Urban Health 2005 Jun;82(2 Suppl 2):ii3-i12 [FREE Full text] [doi: 10.1093/jurban/jti034] [Medline: 15888635]
33. McDavitt B, Bogart LM, Mutchler MG, Wagner GJ, Green HD, Lawrence SJ, et al. Dissemination as dialogue: building trust and sharing research findings through community engagement. Prev Chronic Dis 2016;13:E38 [FREE Full text] [doi: 10.5888/pcd13.150473] [Medline: 26986541]

34. Seifer SD, The Examining Community-Institutional Partnerships for Prevention Research Group. Building and sustaining community-institutional partnerships for prevention research: findings from a national collaborative. J Urban Health 2006 Nov;83(6):989-1003 [FREE Full text] [doi: 10.1007/s11524-006-9113-y] [Medline: 17082993]
35. Dearing JW. Applying Diffusion of Innovation Theory to intervention development. Res Soc Work Pract 2009 Sep 1;19(5):503-518 [FREE Full text] [doi: 10.1177/1049731509335569] [Medline: 20976022]
36. Baron RC, Rimer BK, Coates RJ, Kerner J, Kalra GP, Melillo S, Task Force on Community Preventive Services. Client-directed interventions to increase community access to breast, cervical, and colorectal cancer screening a systematic review. Am J Prev Med 2008 Jul;35(1 Suppl):S56-S66. [doi: 10.1016/j.amepre.2008.04.001] [Medline: 18541188]
37. Hawkins NG, Sanson-Fisher RW, Shakeshaft A, D'Este C, Green LW. The multiple baseline design for evaluating population-based research. Am J Prev Med 2007 Aug;33(2):162-168. [doi: 10.1016/j.amepre.2007.03.020] [Medline: 17673105]
38. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. Am J Public Health 1999 Sep;89(9):1322-1327. [Medline: 10474547]
39. Greenhalgh T, Robert G, Macfarlane F, Bate P, Kyriakidou O. Diffusion of innovations in service organizations: systematic review and recommendations. Milbank Q 2004;82(4):581-629 [FREE Full text] [doi: 10.1111/j.0887-378X.2004.00325.x] [Medline: 15595944]
40. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. Implement Sci 2009;4:50 [FREE Full text] [doi: 10.1186/1748-5908-4-50] [Medline: 19664226]
41. Cleary PD, Gross CP, Zaslavsky AM, Taplin SH. Multilevel interventions: study design and analysis issues. J Natl Cancer Inst Monogr 2012 May;2012(44):49-55 [FREE Full text] [doi: 10.1093/jncimonographs/lgs010] [Medline: 22623596]

Abbreviations

AA: Asian American
CBO: community-based organization
CBPR: community-based participatory research
CHA: community health advisor
CRC: colorectal cancer
EBP: evidence-based practice
FIT: Fecal Immunochemical Test

Edited by G Eysenbach; submitted 08.02.16; peer-reviewed by D Aron; comments to author 03.04.16; revised version received 18.04.16; accepted 18.04.16; published 16.06.16.

Please cite as:
Kim K, Quinn M, Chandrasekar E, Patel R, Lam H
Partnership for Healthier Asians: Disseminating Evidence-Based Practices in Asian-American Communities Using a Market-Oriented and Multilevel Approach
JMIR Res Protoc 2016;5(2):e123
URL: http://www.researchprotocols.org/2016/2/e123/
doi:10.2196/resprot.5625
PMID:27312079

Protocol

Is the volume of the caudate nuclei associated with area of secondary hyperalgesia? – Protocol for a 3-Tesla MRI study of healthy volunteers

Morten Sejer Hansen[1], MD; Mohammad Sohail Asghar[1], MD, PhD; Jørn Wetterslev[2], MD, PhD; Christian Bressen Pipper[3], MSc, PhD; Johan Johan Mårtensson[4], PhD; Lino Becerra[5], PhD; Anders Christensen[6], MD, PhD; Janus Damm Nybing[6], MSc; Inger Havsteen[6], MD; Mikael Boesen[6], MD, PhD; Jørgen Berg Dahl[7], MD, DMSc, MBA

[1]Department of Anaesthesiology, 4231, Centre of head and orthopaedics, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

[2]Copenhagen Trial Unit, Centre for Clinical Intervention Research, Department 7812, Copenhagen, Denmark

[3]Copenhagen University, Faculty of health, Section of biostatistics, Copenhagen, Denmark

[4]Lund University, Department of psychology, Lund, Sweden

[5]Childrens Hospital, Harvard University, Boston, MA, United States

[6]Department of Radiology, Copenhagen University Hospital, Bispebjerg and Frederiksberg Hospitals, Copenhagen, Denmark

[7]Department of Anaesthesiology, dep. Z, Copenhagen University Hospital, Bispebjerg and Frederiksberg Hospitals, Copenhagen, Denmark

Corresponding Author:
Morten Sejer Hansen, MD
Department of Anaesthesiology, 4231
Centre of head and orthopaedics
Rigshospitalet, Copenhagen University Hospital
Blegdamsvej 9
Copenhagen, 2100
Denmark
Phone: 45 26373611
Fax: 45 35452950
Email: morten.sejer.hansen@regionh.dk

Abstract

Background: Experience and development of pain may be influenced by a number of physiological, psychological, and psychosocial factors. In a previous study we found differences in neuronal activation to noxious stimulation, and microstructural neuroanatomical differences, when comparing healthy volunteers with differences in size of the area of secondary hyperalgesia following a standardized burn injury.

Objective: We aim to investigate the degree of association between the volume of pain-relevant structures in the brain and the size of the area of secondary hyperalgesia following brief thermal sensitization.

Methods: The study consists of one experimental day, in which whole-brain magnetic resonance imaging (MRI) scans will be conducted including T1-weighed three-dimensional anatomy scan, diffusion tensor imaging, and resting state functional MRI. Before the experimental day, all included participants will undergo experimental pain testing in a parallel study (Clinicaltrials.gov Identifier: NCT02527395). Results from this experimental pain testing, as well as the size of the area of secondary hyperalgesia from the included participants, will be extracted from this parallel study.

Results: The association between the volume of pain-relevant structures in the brain and the area of secondary hyperalgesia will be investigated by linear regression of the estimated best linear unbiased predictors on the individual volumes of the pain relevant brain structures.

Conclusions: We plan to investigate the association between experimental pain testing parameters and the volume, connectivity, and resting state activity of pain-relevant structures in the brain. These results may improve our knowledge of the mechanisms responsible for the development of acute and chronic pain.

ClinicalTrial: Danish Research Ethics Committee (identifier: H-15010473). Danish Data Protection Agency (identifier: RH-2015-149). Clinicaltrials.gov NCT02567318; http://clinicaltrials.gov/ct2/show/NCT02567318 (Archived by WebCite at http://www.webcitation.org/6i4OtP0Oi)

(JMIR Res Protoc 2016;5(2):e117) doi:10.2196/resprot.5680

KEYWORDS

Pain; Magnetic resonance imaging; Hyperalgesia; Central sensitization; Quantitative sensory testing; Anaesthesiology; Physiology

Introduction

The experience and development of pain may be influenced by a number of physiological, psychological, and psychosocial factors. However, our knowledge of the mechanisms responsible for acute and chronic pain is still not complete. A standardized burn injury in the skin provokes reversible primary and secondary hyperalgesia in healthy volunteers. Injury-induced primary hyperalgesia is located in the traumatized area and is characterized by reduced thresholds for thermal and mechanical stimulation. Secondary hyperalgesia is located around the traumatized area, and is characterized by reduced thresholds for mechanical stimulation [1,2].

Previous studies have demonstrated that secondary hyperalgesia to punctate mechanical stimuli is a result of changes in the central nervous system, in part due to sensitization in response to nerve signals by A-fiber nociceptors [1,3-5]. Secondary hyperalgesia can be provoked by a number of different conditioning stimuli, and according to previous studies this is a robust phenomenon that can be applied to investigate basic pain physiology [2,6,7]. Central neuronal sensitization is presumed to play an important role in a number of different pain conditions, such as osteoarthritis, fibromyalgia, and postoperative pain [3].

To investigate the basic physiological mechanisms of pain, our research group has worked extensively with experimental physiological pain models [8-10]. In previous studies, we found indications of large inter-individual variations in the size of the area of secondary hyperalgesia following identical experimental pain stimulation. Moreover, we observed that the area of secondary hyperalgesia may be an identifiable phenotypic indicator and predictor of individual pain responses [10,11].

To further explore the pathophysiology of central sensitization, we first investigated functional changes in the brain by magnetic resonance imaging (MRI) after induction of secondary hyperalgesia by a first degree burn injury. The first degree burn injury was induced 100 minutes before initiation of MRI, and interestingly we found differences in neuronal activation to noxious stimulation in healthy volunteers that developed either large or small areas of secondary hyperalgesia. These findings suggest differences in central pain processing related to phenotypical expression of secondary hyperalgesia. Furthermore, we found indications of differences in the volumes of the caudate nuclei, as well as other microstructural neuroanatomical differences between the two groups [11], encouraging further studies with larger sample sizes to elucidate the importance of each finding in the pathophysiology of pain and central sensitization.

The basal ganglia have proved to be essential in the pain processing in humans [12-14]. Moreover, the role of the caudate nuclei in the processing and modulation of pain have been investigated in human [12-27] as well as animal [28-39] studies. The caudate nuclei are believed to play a role in integration and control of sensory, motor, and motivational information, and thus essential in coordinating behavioral responses [14]. The caudate nuclei have also been demonstrated to be involved in the sensory processing and spatial location of noxious stimuli [24], in the suppression and modulation of pain [26], and are activated during pain expectancy [40].

Reduced grey matter volume of the caudate nuclei has been demonstrated in patients with trigeminal neuralgia [20], knee osteoarthritis [22], lumbar disc herniation [21], and migraines [15,27]. Moreover, reduced regional cerebral blood flow in the caudate nuclei has been seen in patients with fibromyalgia [23], familial restless legs syndrome [25], and chronic fatigue syndrome [16]. Thus, the caudate nuclei are essential sites of pain processing, and may play a role in the development of secondary hyperalgesia, and consequently in the processes involved with central sensitization.

A recent study confirmed that areas of secondary hyperalgesia have a low intra-individual variation compared to the inter-individual variation [41]. This finding enables us to phenotype healthy volunteers based on the size of the area of secondary hyperalgesia. It remains uncertain whether these phenotypes are related to other pain syndromes or entities, are involved in the risk of developing chronic pain, or influence factors in the individual's pain sensitivity. Likewise, it is unclear if important structures such as the caudate nuclei (or other CNS differences) are closely related to secondary hyperalgesia phenotyping, warranting more research in this area.

With this study we aim to investigate the association between the volume of pre-defined pain-relevant structures in the brain and the size of the areas of secondary hyperalgesia.

Methods

Study Design

This study is a confirmatory study designed to investigate the association between the size of the area of secondary hyperalgesia following brief thermal sensitization (BTS; see *Clinical Evaluations*) and the volume of the caudate nuclei in healthy volunteers. On the experimental day, a whole brain MRI scan will be conducted including T1-weighed three-dimensional (3D) anatomy scan, diffusion tensor imaging, and resting-state functional MRI (rs-fMRI), in consecutive sequence (see *Clinical Evaluations*). No other tests or assessments will be performed on the experimental day. The total duration of the experimental day is approximately 50 minutes.

Before the experimental day, all included participants will undergo pain testing in a parallel study (Clinicaltrials.gov Identifier: NCT02527395). Results from the pain testing, as well as the size of the area of secondary hyperalgesia from the included participants, will be extracted from this parallel study. The experimental day will be conducted at a maximum of 2

months and a minimum of 2 weeks after the completion of the BTS and additional pain testing.

Setting

The MRI scans will be conducted at the Department of Radiology, Bispebjerg and Frederiksberg Hospitals, Copenhagen, Denmark. The data analysis will be conducted at the Department of Anesthesiology, Centre of Head and Orthopedics, Rigshospitalet, Copenhagen, Denmark.

Study Participants

Healthy male volunteers will be included in the study. The study participants will receive information regarding possible risks and side effects, and will be provided with written and oral information concerning the study. The participants will receive €67 (US $74) for their participation in the study. Inclusion and exclusion criteria are presented in Table 1.

Table 1. Inclusion, and exclusion criteria.

Inclusion criteria	Exclusion criteria
Age ≥18 years and ≤35 years	Study participants who cannot cooperate to the test
Male sex	Study participants with a substance abuse, assessed by the investigator
Study participants who have a weekly intake of >21 units of alcohol, or a have consumed >3 units of alcohol within 24 hours before experimental day	Study participants who have consumed analgesics within 3 days before experimental day
Speak and understand the Danish language	Study participants who have consumed antihistamines within 48 hours before experimental day
Signed informed consent	Study participants who have consumed antidepressant medication within 30 days before the study
Have participated and completed the study: " *To determine the degree of association between Heat Pain Detection Threshold and area of secondary hyperalgesia following Brief Thermal Sensitization in healthy male volunteers"* (Clinicaltrials.gov Identifier: NCT02527395)	Study participants who have consumed prescription medicine within 30 days before the study
	Study participants with neurological illnesses
	Study participants with chronic pain
	Study participants with psychiatric diagnoses
	Study participants with eczema, wounds, or sunburns on the sites of stimulation
	Study participants with a Body Mass Index of >30 kg/m^2 or <18 kg/m^2
	Study participants with contraindications to MRI[a]
	Study participants that decline information regarding potential pathological findings in relation to the MRI
	Study participants that have any kind of trauma resulting in pain and administration of analgesics in the period between experimental pain testing and MRI scan
	Study participants that experience a head trauma in the period between the experimental pain testing and the MRI scan

[a]Contraindications to MRI includes: claustrophobia, pacemaker implant, artificial heart valve, cochlear/stapes prosthetics, irremovable insulin pump, neurostimulator, metal clips from previous surgical procedures, other metallic foreign objects, shrapnel or shell splinter, catheters (eg, Swan Ganz), shunts and drainage tubes, and surgical procedures within 6 weeks before the study (subjected to individual evaluation).

Before the experimental day, each participant will be tested with the experimental pain models: BTS, heat pain detection threshold (HPDT), and pain during 1 minute of thermal stimulation of the skin (p-TS), as well as two psychological tests: Pain Catastrophizing Scale (PCS) and Hospital Anxiety and Depression Score (HADS; see Multimedia Appendix 1 and Clinicaltrials.gov identifier: NCT02527395). The results will be blinded to the investigator evaluating the MRI scans. Prior to, as well as on the experimental day, the investigator will interview all participants, and those that have one or more psychiatric or neurological diagnoses or illnesses will be excluded. All participants with prior history of psychiatric or neurological illness will also be excluded.

Clinical Evaluations

Pain Testing

BTS, HPDT and p-TS are not performed as a part of this study per se, but all participants in the present study have been tested using these methods in a parallel non-imaging study (Clinicaltrials.gov Identifier: NCT02527395). Data concerning secondary hyperalgesia from this concurrent study will be extrapolated and included in the present study. The BTS method is briefly explained below. For further details, please refer to Multimedia Appendix 1.

Brief Thermal Sensitization

A computer-controlled thermode (Somedic MSA Thermotester; size 2.5 x 5 cm) is placed on the participant's skin, centrally on the anterior part of the right thigh. The initial temperature of

the thermode is 32°C, and the temperature is increased 1°C/second until it reaches 45°C. The temperature of the thermode remains a constant 45°C for 3 minutes, and while the thermode still has contact with the skin, the assessment of secondary hyperalgesia is conducted. The assessment of secondary hyperalgesia takes approximately 1-2 minutes, with a maximum duration of heat stimulation of 5 minutes.

Assessment of Secondary Hyperalgesia

The area of secondary hyperalgesia is quantified after stimulation with a 19G monofilament (von Frey hair) in 4 linear paths arranged in 90° around the center of stimulation. Stimulation will begin 15 cm from the center of stimulation and advance in steps of 5 mm with 1 second intervals towards the center of stimulation. When the participant states a clear change in sensation (ie, intense pricking, burning, tenderness) the place will be marked with a felt pen and the transverse and longitudinal axes will be measured for later area calculation.

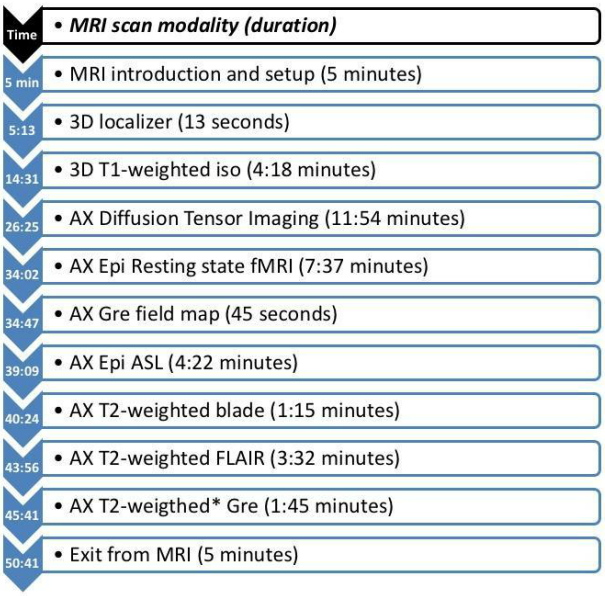
MRI Scans

The MRI scans will be performed with a Siemens MAGNETOM Verio 3-tesla, with b17 software, and a 32-channel head coil. The specific MRI sequence and settings are detailed in Multimedia Appendix 2.

Anatomical MRI Scans

T1-weighted images are recorded in order to construct detailed anatomical images of the brain. These images will be used to perform morphometry/volumetric analysis of cortical and subcortical structures in order to determine possible differences in the study population. To look for potentially confounding structural lesions and perfusion asymmetry, T2-weighted, T2-FLAIR, diffusion weighted imaging, gradient echo, and arterial spin labeling will also be performed as part of the imaging protocol (Figure 1).

Figure 1. Schematic presentation of experimental day. Abbreviations: MRI, Magnetic Resonance Imaging; fMRI, Functional Magnetic Resonance Imaging.



Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) is sensitive to the diffusion of water molecules. The net-diffusion of water molecules roughly occurs along the direction of the axons; hence, DTI can be utilized to perform white matter tractography (neuronal connections of the brain), or to detect changes in the white matter by using Tract-Based Spatial Statistics.

Resting State Imaging

In rs-fMRI the intrinsic connectivity networks of the brain are mapped by indirectly measuring so-called *spontaneous brain activity*. Rs-fMRI measures spontaneous changes in blood-oxygenation-level-dependent signal by detecting concomitant changes in magnetization that accompanies regional changes in brain blood flow.

Other Scans

As a supplement to the previously mentioned MRI scans, it is necessary to perform a number of technical MRI scans as well (ie, B0 field maps). These supplementary scans are necessary and important for later data analyses, and will not result in any further discomfort for the participants. For schematic presentation of the general procedure and the MRI scan sequence on the experimental day, please refer to Figure 1.

Participants will be informed that they must stay awake during the MRI scan period, and if they fall asleep they are obliged to inform the investigator. Participants that fall asleep during the MRI scan period will be excluded from the study.

Outcomes

Primary Outcome

We aim to investigate the association between the volume of the left and right caudate nuclei and the size of the area of secondary hyperalgesia induced by brief thermal sensitization.

The association will be expressed in adjusted and non-adjusted $R^2$and prediction intervals for the area of secondary hyperalgesia, given fixed values of the caudate nucleus' volume.

Secondary Outcomes

We aim to investigate the association between cortical and subcortical brain areas relevant for pain processing and the area of secondary hyperalgesia (primary somatosensory cortex, anterior- and mid-cingulate cortex, basal ganglia [putamen, accumbens nucleus, and globus pallidus], insula, and the cerebellum [12,42]). We will also use diffusion tensor imaging to investigate the association between the area of secondary hyperalgesia and white matter microstructure using tract based spatial statistics (TBSS) [43], and determine the connections between the pain-related areas, as specified previously using white-matter tractography.

Exploratory Outcomes

We will investigate the association between the volume of the left and right caudate nuclei and the following six parameters: (1) HPDT score, (2) p-TS max, (3) p-TS visual analog scale-area under the curve (VAS-AUC), and (4) the score of PCS-total, PCS-subscores, HADS-total, and HADS-subscores. When comparing healthy volunteers with a large (upper quartile) versus small (lower quartile) area of secondary hyperalgesia following BTS, we plan to investigate (5a) structural differences (volume) and the association with the size of the area of secondary hyperalgesia, (5b) differences in the association between area of secondary hyperalgesia and regions of interest extracted from TBSS, and (5c) differences in white matter microstructure in connections between pre specified pain related areas by white-matter tractography. In addition, we will examine (6) differences in resting state networks measured by rs-fMRI using independent component analysis (ICA; dual regression method).

Hypothesis

The area of secondary hyperalgesia and the volume of the caudate nuclei are associated, with an inverse correlation (ie, a large area of secondary hyperalgesia is associated with a small volume of the caudate nuclei).

Sample Size Estimation

Based on results from a previous study [11], sample size calculations are based on a Z-test of the Fisher transformed Pearson correlation. With a true correlation of r=-0.4 between the area of secondary hyperalgesia and the caudate nuclei, and a significance level of 2.5% to 5% according to the single step method (refer to *Statistical Significance*), a sample size of 52 is needed to obtain a power of 0.80 (β=0.20).

Data Analysis Plan

T1-Weighted 3D Anatomical Images

Anatomical images will be pre-processed using the FreeSurfer imaging analysis suite version 5.3. FreeSurfer is a semi-automatic software package that performs volumetric segmentation of cortical and subcortical structures [44-46]. All volumes will be adjusted for total intracranial volume, and will result in volume estimates (mm^3). This analysis is performed to avoid possible confounding results due to differential head-size between participants. The size of the area of secondary hyperalgesia will be blinded until completion of the T1-weighted 3D anatomical image analyses.

Diffusion Tensor Imaging

Diffusion-weighted images will be pre-processed using the Functional Magnetic Resonance Imaging Brain Software Library (FSL) software package version 5.0. This analysis includes corrections of potential head movement and inspection of image quality. The resulting data will then be processed via dtifit and tract-based spatial statistic. The re-aligned images will then be fed into bedpostx for local modelling of diffusion parameters. Using bedpostx in conjunction with TBSS allows for the modelling of crossing fibers. The re-aligned images will be fed into probtrackx2 for tractography between the anatomical areas mentioned above.

Resting-State Functional Magnetic Resonance Imaging

Rs-fMRI scans will be analyzed using FSL MELODIC. Pre-processing steps will include spatial smoothing, motion correction, high pass filtering, and brain extraction. In the pre-processing steps we will apply ICA using predefined (no less than 60) ICA's without automatic dimension detection. Rs-fMRI scans will be co-registered initially to the individual T1-weighted 3D anatomical scans (after neutral flipping and brain extraction), and subsequently to the Montreal Neurological Institute (MNI)-152 brain atlas using non-linear registration. A full quality assurance will be performed consisting of inspection of head movement (<3 mm and <3 degrees), acceptable co-registration, and inspection of image quality.

Rs-fMRI data will be analysed using a model-free ICA and the dual regression method, as described by Abou-Elseoud et al [47], to determine differences in network connectivities with the whole brain. Standard, published brain networks in healthy participants will be used to identify the different networks using publicly available datasets from the Oxford FSL Group publication [48]. Once we have run an ICA analysis, the resulting components will be spatially cross-correlated with Oxford's templates to identify those that better match the canonical networks described in the Oxford FSL Group publication [48].

Noise reduction will be performed manually. Randomized command with 10.000 random computations will be performed with a design matrix consisting of the unpaired t-tests (predefined high responders vs. low responders, and repeated with area of secondary hyperalgesia as co-variate). Results will be displayed upon the MNI-152 normal brain atlas after dimension change as $P<0.05$ after correction for multiple comparisons. Activated areas will be identified semi-automatically.

Statistical Analyses

Statistical Analysis of Primary Outcome

The estimates of the volumes, from the T1-weighted 3D anatomical scans of the caudate nuclei (mm^3), will be exported to a spreadsheet for regression analysis to assess the association between volume of caudate nuclei and secondary hyperalgesia

areas. The association of the volume of the left and right caudate nuclei and the area of secondary hyperalgesia will be investigated by linear regression of the estimated best linear unbiased predictors (EBLUPS) on the individual volumes of the left and right caudate nuclei. The ability of the volume of caudate nuclei to predict individual variation in the area of secondary hyperalgesia will be investigated by linear regression on the EBLUPS as a function of the individual volumes of the caudate nuclei.

Significance of the caudate nuclei as a predictor will be assessed by analysis of variance (ANOVA) methods and the predictive ability will be quantified by summary of prediction error, including 95% prediction interval for the prediction of the size of the area of secondary hyperalgesia. Relevant examples will be presented illustrating how accurately the volume of the caudate nuclei predicts the area of secondary hyperalgesia in the individual participants or vice versa. The association will be expressed in $R^2$and prediction intervals for the area of secondary hyperalgesia given fixed values of the caudate nucleus' volume. All analyses of structural MRI data (both in the primary, secondary, and exploratory outcomes) will be adjusted for age.

Statistical Analysis of Secondary Outcome #1

From the T1-weighted 3D anatomical scans, volume estimates of the cortical and subcortical brain areas relevant for pain processing (mm^2, mm^3) will be exported to a spreadsheet for regression analysis to assess the association between volume of the relevant areas for pain processing and areas of secondary hyperalgesia. The association of the volume of areas relevant for pain processing and the area of secondary hyperalgesia will be investigated by linear regression of the EBLUPS in relation to the volumes of individual areas relevant for pain processing. The association will be expressed in $R^2$and prediction intervals for the area of secondary hyperalgesia given fixed values of the volume of the relevant brain areas for pain processing.

Significance of the predictor will be assessed by ANOVA methods and in cases of significance the predictive ability will be quantified by summary of prediction error, including 95% prediction interval. Relevant examples will be presented illustrating how accurately the volume of the individual areas relevant for pain processing predicts the area of secondary hyperalgesia in individual participants, or vice versa. The association will be expressed in $R^2$and prediction intervals for the area of secondary hyperalgesia given fixed values of the caudate nucleus' volume.

Statistical Analysis of Secondary Outcome #2

The exact values of white matter structure expressed as the diffusion coefficient (Fractional Anisotropy value) of the relevant pain related areas will be extracted, and separate statistical analyses will be performed. To test the association between the white matter microstructure extracted following analysis using TBSS/DTI and the area of secondary hyperalgesia, individual measures computed from the TBSS and DTI will be investigated by linear regression.

Statistical Analysis of Exploratory Associations #1-4

From the T1-weighted 3D anatomical scans, volume estimates of the caudate nuclei (mm^3) will be exported to a spreadsheet for regression analysis to assess the association between volume of caudate nucleus and the score of HPDT, p-TS-max, p-TS VAS-AUC, PCS, and HADS respectively. The association of the volume of the right and left caudate nucleus and HPDT, p-TS-max, p-TS VAS-AUC, PCS and HADS will be investigated by linear regression of the EBLUPS in relation to the volume of caudate nucleus.

Significance of the ability of the caudate nucleus' volume as a predictor will be assessed by ANOVA methods. The ability of the caudate nucleus' volume to predict individual variations in HPDT, p-TS-max, p-TS VAS-AUC, PCS, and HADS will be investigated by linear regression on the EBLUPS of the individual volumes of the caudate nucleus. Significance of the caudate nucleus as a predictor will be assessed by ANOVA methods and in case of significance, the predictive ability will be quantified by summary of prediction error, including 95% prediction interval. Relevant examples will be presented illustrating how accurately the volume of the caudate nucleus predicts HPDT, p-TS-max, p-TS VAS-AUC, PCS, and HADS in individual participants, or vice versa.

Statistical Analysis of Exploratory Associations #5-6:

Quantile-quantile plots and Shapiro Wilk's test will be applied in assessment of normal distribution. If data are not normally distributed, Mann-Whitney U-test will be applied. If data are normally distributed, unpaired t-tests will be applied to investigate structural differences in brain volume, differences in white matter, and differences in rs-fMRI between the groups. To investigate potential differences in rs-fMRI, correction for multiple comparisons will be conducted by the MRI software using False-Discovery-Rate. Values of secondary hyperalgesia areas will be entered into the FSL-software, and a t-test will be performed.

Missing Data

For all analyses, an intention-to-test analysis will be performed including all subjects that participated in the experimental day. Analyses will be based on all observed data. In case of missing data exceeding 5%, and indication of violation of *missing completely at random* by a statistically significant Littles test, a sensitivity analysis based on an appropriate model for *missing data at random* or *missing data not at random* will be performed.

Statistical Significance

Earlier studies have demonstrated that the volumes of the right and left hemispheric caudate nuclei are associated with one another [11]. To preserve a family-wise error rate of 5% for the two co-primary outcomes of associations between the right and left caudate nuclei and the area of secondary hyperalgesia, we will adjust for multiple comparisons of the co-primary outcomes. The two *P*-values will be evaluated at a significance level between 2.5% and 5% according to the single step method. For this method the significance level is determined by the correlation between the two resulting test statistics. If they are

perfectly correlated the result will be 0.05, whereas if they are independent it will be 0.025.

P-values in the secondary and exploratory outcomes are evaluated at a 5% significance level, and to adjust for multiple comparisons, *P*-values are adjusted by means of single-step correction [49]. In the analysis of rs-fMRI data, the software's standard methods and False-Discovery-Rate will be applied for correction for multiple comparisons.

Software

All statistical analyses not computed by the standard MRI software will be generated using the open source statistical programming environment R (R Foundation for Statistical Computing, Vienna, Austria).

Discussion

We plan to investigate the association between experimental pain testing parameters and the volume, connectivity, and resting state activity of pain-relevant structures in the brain. We have designed this study to investigate basic pain physiology in healthy pain-free individuals, and we aim to investigate if any basic characteristics in the pain-free individual predict experimental pain responses. Current knowledge of basic pain physiology in humans is still sparse, and in order to compensate for the many factors that can affect pain responses, we have chosen to include a very homogenous population, consisting of healthy male volunteers between the ages of 18 and 35. The strict inclusion criteria diminish the influence of factors related to differences in the brain's structure and function (eg, sex, age). Thus, this study aims to investigate aspects of basic pain physiology in healthy male individuals, and relevant caution should be taken when applying the results in a more heterogeneous population.

Our hypothesis, as well as our sample size estimation, are based upon previous results from Asghar et al [11]. Moreover, we wish to investigate if the volume of the caudate nuclei is associated with the size of the secondary hyperalgesia areas, indicating that this structure may be involved in the processes of central sensitization. Decreased volumes of the caudate nuclei have been demonstrated in a wide array of chronic pain patients, suggesting that these patients have a decreased ability to suppress and modulate pain stimuli [15,16,20-23,25]. With this study we plan to investigate if healthy participants with low volumes of caudate nuclei have a higher degree of central sensitization, and thus may be at a higher risk of developing chronic pain conditions.

The results of this study may also be informative for future studies and trials in the clinical setting, where pain remains a serious problem for postoperative patients. Knowledge of predictive factors and baseline pain dispositions in patients awaiting surgery may improve the design of trials on postoperative pain interventions, and improve our knowledge of the mechanisms responsible for the development of acute and chronic pain.

Ethics

MRI uses a strong magnetic field and, unlike other imaging modalities, does not use radiation. MRI is non-invasive and has no known side effects. Due to the strong magnetic field, persons in the MRI room are not allowed to wear any metallic objects, and study participants will be informed of this prior to the MRI scans. Special MRI-compatible equipment will be used to monitor the participants inside the MRI scanner. Study participants will wear ear plugs and/or ear protection to avoid noise disturbances from the MRI scans, and will be equipped with an alarm call button in case of emergency.

A consultant radiologist will review all MRI scans. In the rare case of pathological findings, the radiology department at Bispebjerg and Frederiksberg Hospital has instructions for further treatment procedures. Briefly, the participant will be informed of the possible pathological findings and the participant will be scheduled for further radiological testing and referred to a specialist in neurology. Prior to inclusion in the study, participants will be informed of this procedure. If the participants do not wish to be informed of potential pathological findings, we reserve the right to exclude them before commencement of the MRI scan.

Likewise, the experimental pain testing conducted in the parallel study (Clinicaltrials.gov identifier: NCT02527395) do not cause damage to the skin or have any other long-term adverse effects. In rare cases, changes comparable with a first degree sunburn may appear. This study will be conducted in accordance with the principles of the Declaration of Helsinki. The protocol is approved by the local Danish Research Ethics Committees (identifier: H-15010473), and the Danish Data Protection Agency (identifier: RH-2015-149). This study is also reported on the international database (clinicaltrials.gov identifier: NCT02567318).

Informed written consent will be received from all volunteers before inclusion in the trial. Relevant provisions of the Research Ethics Committee regarding informed consent will be followed. Negative, positive, conclusive, and inconclusive test results will be published. We aim to publish the results in two separate publications, the first of which will report the primary and secondary outcomes, and the exploratory outcomes 1-4, and the second publication will report the exploratory outcomes 5 and 6.

Acknowledgments

This work was supported by grants from the Augustinus foundation, Toyota Fonden – Denmark, DASAIM pain research award, and the Aase and Ejnar Danielsen's foundation. The funders had no role in the conception or design of the study, or on the decision to publish the results.

Authors' Contributions

MSH contributed to the conception and design of the study, and manuscript writing. JBD, MSA, and JW contributed to the conception and the design of the study, and critical revision of the manuscript. CBP contributed to the design of the study, with emphasis on the statistical and sample size analyses, and critical revision of the manuscript. JM contributed to the conception and the design of the study, with emphasis on the MRI data processing, and critical revision of the manuscript. AC, JDN, MB and IH contributed to the conception and the design of the study with emphasis on the MRI theory and sequence, and critical revision of the manuscript. LB contributed to the conception and the design of the study with emphasis on the MRI theory, and critical revision of the manuscript. All authors have read and approved the final manuscript. We wish to thank the staff of the department of Radiology, Bispebjerg and Frederiksberg Hospital, for support in obtaining the MRI scans.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Other tests and evaluations.

[PDF File (Adobe PDF File), 48KB - resprot_v5i2e117_app1.pdf]

Multimedia Appendix 2

MRI-sequence.

[PDF File (Adobe PDF File), 31KB - resprot_v5i2e117_app2.pdf]

References

1. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain 2009 Sep;10(9):895-926 [FREE Full text] [doi: 10.1016/j.jpain.2009.06.012] [Medline: 19712899]
2. Naert AL, Kehlet H, Kupers R. Characterization of a novel model of tonic heat pain stimulation in healthy volunteers. Pain 2008 Aug 15;138(1):163-171. [doi: 10.1016/j.pain.2007.11.018] [Medline: 18207325]
3. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain 2011 Mar;152(3 Suppl):S2-15 [FREE Full text] [doi: 10.1016/j.pain.2010.09.030] [Medline: 20961685]
4. Ziegler EA, Magerl W, Meyer RA, Treede RD. Secondary hyperalgesia to punctate mechanical stimuli. Central sensitization to A-fibre nociceptor input. Brain 1999 Dec;122 (Pt 12):2245-2257 [FREE Full text] [Medline: 10581220]
5. Treede R. Chapter 1 pain and hyperalgesia: definitions and theories. Handb Clin Neurol 2006;81:3-10. [doi: 10.1016/S0072-9752(06)80005-9] [Medline: 18808823]
6. Petersen KL, Rowbotham MC. A new human experimental pain model: the heat/capsaicin sensitization model. Neuroreport 1999 May 14;10(7):1511-1516. [Medline: 10380972]
7. Staahl C, Olesen A, Andresen T, Arendt-Nielsen L, Drewes A. Assessing efficacy of non-opioid analgesics in experimental pain models in healthy volunteers: an updated review. Br J Clin Pharmacol 2009 Sep;68(3):322-341 [FREE Full text] [doi: 10.1111/j.1365-2125.2009.03433.x] [Medline: 19740390]
8. Dirks J, Petersen K, Dahl J. The heat/capsaicin sensitization model: a methodologic study. J Pain 2003 Apr;4(3):122-128. [Medline: 14622709]
9. Mathiesen O, Imbimbo BP, Hilsted KL, Fabbri L, Dahl JB. CHF3381, a N-methyl-D-aspartate receptor antagonist and monoamine oxidase-A inhibitor, attenuates secondary hyperalgesia in a human pain model. J Pain 2006 Aug;7(8):565-574. [doi: 10.1016/j.jpain.2006.02.004] [Medline: 16885013]
10. Werner MU, Petersen KL, Rowbotham MC, Dahl JB. Healthy volunteers can be phenotyped using cutaneous sensitization pain models. PLoS One 2013 May;8(5):e62733 [FREE Full text] [doi: 10.1371/journal.pone.0062733] [Medline: 23671631]
11. Asghar MS, Pereira MP, Werner MU, Mårtensson J, Larsson HB, Dahl JB. Secondary hyperalgesia phenotypes exhibit differences in brain activation during noxious stimulation. PLoS One 2015;10(1):e0114840 [FREE Full text] [doi: 10.1371/journal.pone.0114840] [Medline: 25615578]
12. Borsook D, Upadhyay J, Chudler EH, Becerra L. A key role of the basal ganglia in pain and analgesia--insights gained through human functional imaging. Mol Pain 2010;6:27 [FREE Full text] [doi: 10.1186/1744-8069-6-27] [Medline: 20465845]
13. Barker RA. The basal ganglia and pain. Int J Neurosci 1988 Jul;41(1-2):29-34. [Medline: 3045040]
14. Chudler EH, Dong WK. The role of the basal ganglia in nociception and pain. Pain 1995 Jan;60(1):3-38. [Medline: 7715939]
15. Absinta M, Rocca MA, Colombo B, Falini A, Comi G, Filippi M. Selective decreased grey matter volume of the pain-matrix network in cluster headache. Cephalalgia 2012 Jan;32(2):109-115. [doi: 10.1177/0333102411431334] [Medline: 22174349]

16. de Lange FP, Kalkman JS, Bleijenberg G, Hagoort P, van der Werf SP, van der Meer JW, et al. Neural correlates of the chronic fatigue syndrome--an fMRI study. Brain 2004 Sep;127(Pt 9):1948-1957 [FREE Full text] [doi: 10.1093/brain/awh225] [Medline: 15240435]
17. Freund W, Klug R, Weber F, Stuber G, Schmitz B, Wunderlich AP. Perception and suppression of thermally induced pain: a fMRI study. Somatosens Mot Res 2009 Mar;26(1):1-10. [doi: 10.1080/08990220902738243] [Medline: 19283551]
18. Freund W, Stuber G, Wunderlich AP, Schmitz B. Cortical correlates of perception and suppression of electrically induced pain. Somatosens Mot Res 2007 Dec;24(4):203-212. [doi: 10.1080/08990220701723636] [Medline: 18097993]
19. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum 2002 May;46(5):1333-1343 [FREE Full text] [doi: 10.1002/art.10225] [Medline: 12115241]
20. Li M, Yan J, Li S, Wang T, Zhan W, Wen H, et al. Reduced volume of gray matter in patients with trigeminal neuralgia. Brain Imaging Behav 2016 Feb 22. [doi: 10.1007/s11682-016-9529-2] [Medline: 26899433]
21. Luchtmann M, Steinecke Y, Baecke S, Lützkendorf R, Bernarding J, Kohl J, et al. Structural brain alterations in patients with lumbar disc herniation: a preliminary study. PLoS One 2014;9(3):e90816 [FREE Full text] [doi: 10.1371/journal.pone.0090816] [Medline: 24595036]
22. Mao CP, Bai ZL, Zhang XN, Zhang QJ, Zhang L. Abnormal subcortical brain morphology in patients with knee osteoarthritis: a cross-sectional study. Front Aging Neurosci 2016;8:3 [FREE Full text] [doi: 10.3389/fnagi.2016.00003] [Medline: 26834629]
23. Mountz JM, Bradley LA, Modell JG, Alexander RW, Triana-Alexander M, Aaron LA, et al. Fibromyalgia in women. Abnormalities of regional cerebral blood flow in the thalamus and the caudate nucleus are associated with low pain threshold levels. Arthritis Rheum 1995 Jul;38(7):926-938. [Medline: 7612042]
24. Oshiro Y, Quevedo AS, McHaffie JG, Kraft RA, Coghill RC. Brain mechanisms supporting spatial discrimination of pain. J Neurosci 2007 Mar 28;27(13):3388-3394 [FREE Full text] [doi: 10.1523/JNEUROSCI.5128-06.2007] [Medline: 17392455]
25. San Pedro EC, Mountz JM, Mountz JD, Liu HG, Katholi CR, Deutsch G. Familial painful restless legs syndrome correlates with pain dependent variation of blood flow to the caudate, thalamus, and anterior cingulate gyrus. J Rheumatol 1998 Nov;25(11):2270-2275. [Medline: 9818676]
26. Wunderlich AP, Klug R, Stuber G, Landwehrmeyer B, Weber F, Freund W. Caudate nucleus and insular activation during a pain suppression paradigm comparing thermal and electrical stimulation. Open Neuroimag J 2011;5:1-8 [FREE Full text] [doi: 10.2174/1874440001105010001] [Medline: 21643502]
27. Yuan K, Zhao L, Cheng P, Yu D, Zhao L, Dong T, et al. Altered structure and resting-state functional connectivity of the basal ganglia in migraine patients without aura. J Pain 2013 Aug;14(8):836-844. [doi: 10.1016/j.jpain.2013.02.010] [Medline: 23669074]
28. Koyama T, Kato K, Mikami A. During pain-avoidance neurons activated in the macaque anterior cingulate and caudate. Neurosci Lett 2000 Mar 31;283(1):17-20. [Medline: 10729623]
29. Li BY, Xu T. Influence of morphine microinjected into head of caudate nucleus on electric activities of nociceptive neurons in parafascicular nucleus of rat thalamus. Zhongguo Yao Li Xue Bao 1990 Mar;11(2):103-107 [FREE Full text] [Medline: 2275381]
30. Lineberry CG, Vierck CJ. Attenuation of pain reactivity by caudate nucleus stimulation in monkeys. Brain Res 1975 Nov 7;98(1):119-134. [Medline: 809117]
31. Mikhaĭlov AV. Responses of caudate nucleus neurons to electrocutaneous stimulation of a paw. Fiziol Zh SSSR Im I M Sechenova 1980 Sep;66(9):1325-1332. [Medline: 7418914]
32. Mulgaonker VK, Mascarenhas JF. Effect of mid-dorsal caudate nucleus on conditioning for pain stimulus in rats. Indian J Physiol Pharmacol 1991 Jan;35(1):61-64. [Medline: 1917015]
33. Tong ZQ, Chen SC. Effects of stimulation of caudate nucleus on the unit discharges of somato-visceral converging neurons of parafascicular nucleus of thalamus in rats. Sheng Li Xue Bao 1988 Dec;40(6):586-591. [Medline: 3249950]
34. Tong ZQ, Chen SC, Zhang FT. Effects of stimulation of the rabbit caudate nucleus on units responsive to noxious stimuli in the parafascicular nucleus of the thalamus. Sheng Li Xue Bao 1985 Apr;37(2):128-136. [Medline: 3834590]
35. Yang F, Lin RJ, Zhou BH, Li P. Effect of lithium applied iontophoretically on electrical activities of pain-related neurons in caudate-putamen nucleus of rat. Sheng Li Xue Bao 1993 Dec;45(6):519-527. [Medline: 8146676]
36. Yang J, Chen J, Liu W, Song C, Wang C, Lin B. Arginine vasopressin in the caudate nucleus plays an antinociceptive role in the rat. Life Sci 2006 Oct 26;79(22):2086-2090. [doi: 10.1016/j.lfs.2006.07.005] [Medline: 16884741]
37. Yang J, Li P, Zhang X, Zhang J, Hao F, Pan Y, et al. Arginine vasopressin in hypothalamic paraventricular nucleus is transferred to the caudate nucleus to participate in pain modulation. Peptides 2011 Jan;32(1):71-74. [doi: 10.1016/j.peptides.2010.10.014] [Medline: 20965220]
38. Wang D, Yang J, Gu Z, Song C, Liu W, Zhang J, et al. Arginine vasopressin induces rat caudate nucleus releasing acetylcholine to participate in pain modulation. Peptides 2010 Apr;31(4):701-705. [doi: 10.1016/j.peptides.2009.11.027] [Medline: 19948196]
39. Yang J, Pan Y, Zhao Y, Qiu P, Lu L, Li P, et al. Oxytocin in the rat caudate nucleus influences pain modulation. Peptides 2011 Oct;32(10):2104-2107. [doi: 10.1016/j.peptides.2011.08.021] [Medline: 21903147]

40. Keltner JR, Furst A, Fan C, Redfern R, Inglis B, Fields HL. Isolating the modulatory effect of expectation on pain transmission: a functional magnetic resonance imaging study. J Neurosci 2006 Apr 19;26(16):4437-4443 [FREE Full text] [doi: 10.1523/JNEUROSCI.4463-05.2006] [Medline: 16624963]
41. Hansen M, Wetterslev J, Pipper C, Østervig R, Asghar MS, Dahl JB. The area of secondary hyperalgesia following heat stimulation in healthy male volunteers: inter- and intra-individual variance and reproducibility. PLoS One 2016;11(5):e0155284. [doi: 10.1371/journal.pone.0155284] [Medline: 27167119]
42. Davis KD, Moayedi M. Central mechanisms of pain revealed through functional and structural MRI. J Neuroimmune Pharmacol 2013 Jun;8(3):518-534. [doi: 10.1007/s11481-012-9386-8] [Medline: 22825710]
43. Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 2006 Jul 15;31(4):1487-1505. [doi: 10.1016/j.neuroimage.2006.02.024] [Medline: 16624579]
44. Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 2002 Jan 31;33(3):341-355 [FREE Full text] [Medline: 11832223]
45. Fischl B, Salat DH, van der Kouwe AJ, Makris N, Ségonne F, Quinn BT, et al. Sequence-independent segmentation of magnetic resonance images. Neuroimage 2004;23 Suppl 1:S69-S84. [doi: 10.1016/j.neuroimage.2004.07.016] [Medline: 15501102]
46. Fischl B, van der Kouwe A, Destrieux C, Halgren E, Ségonne F, Salat DH, et al. Automatically parcellating the human cerebral cortex. Cereb Cortex 2004 Jan;14(1):11-22 [FREE Full text] [Medline: 14654453]
47. Abou-Elseoud A, Starck T, Remes J, Nikkinen J, Tervonen O, Kiviniemi V. The effect of model order selection in group PICA. Hum Brain Mapp 2010 Aug;31(8):1207-1216. [doi: 10.1002/hbm.20929] [Medline: 20063361]
48. Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, et al. Correspondence of the brain's functional architecture during activation and rest. Proc Natl Acad Sci U S A 2009 Aug 4;106(31):13040-13045 [FREE Full text] [doi: 10.1073/pnas.0905267106] [Medline: 19620724]
49. Hothorn T, Bretz F, Westfall P. Simultaneous inference in general parametric models. Biom J 2008 Jun;50(3):346-363. [doi: 10.1002/bimj.200810425] [Medline: 18481363]

Abbreviations

3D: three-dimensional
ANOVA: analysis of variance
BTS: brief thermal sensitization
DTI: diffusion tensor imaging
EBLUPS: estimated best linear unbiased predictors
HADS: Hospital Anxiety and Depression Scale
HPDT: heat pain detection threshold
ICA: independent component analysis
MNI: Montreal Neurological Institute
MRI: magnetic resonance imaging
PCS: Pain Catastrophizing Scale
p-TS: pain during 1 minute of thermal stimulation
rs-fMRI: resting-state functional magnetic resonance imaging
TBSS: tract based spatial statistics
VAS-AUC: visual analog scale-area under the curve

Edited by G Eysenbach; submitted 22.02.16; peer-reviewed by T Rempe, D De Ridder; comments to author 28.03.16; accepted 08.04.16; published 17.06.16.

Please cite as:
Hansen MS, Asghar MS, Wetterslev J, Pipper CB, Johan Mårtensson J, Becerra L, Christensen A, Nybing JD, Havsteen I, Boesen M, Dahl JB
Is the volume of the caudate nuclei associated with area of secondary hyperalgesia? – Protocol for a 3-Tesla MRI study of healthy volunteers
JMIR Res Protoc 2016;5(2):e117
URL: http://www.researchprotocols.org/2016/2/e117/
doi:10.2196/resprot.5680
PMID:

Protocol

The Functional Fitness MOT Test Battery for Older Adults: Protocol for a Mixed-Method Feasibility Study

Lex D de Jong[1*], PhD, PT; Andy Peters[2*], BA (Hons), M Phil, CPsychol; Julie Hooper[3*], PhD; Nina Chalmers[4*], BSc, PT; Claire Henderson[3*], BSc, PT; Robert ME Laventure[5*], BEd, MEd; Dawn A Skelton[1*], BSc, PhD, MD hc

[1]Glasgow Caledonian University, Institute for Applied Health Research, School of Health and Life Sciences, Glasgow, United Kingdom

[2]NHS Lothian Delivering Better Care Hub, Western General Hospital, Edinburgh, United Kingdom

[3]Slateford Physiotherapy Clinic, Slateford Medical Centre, Edinburgh, United Kingdom

[4]Sighthill Physiotherapy Clinic, Sighthill Medical Centre, Edinburgh, United Kingdom

[5]Loughborough University, British Heart Foundation National Centre for Physical Activity and Health, Loughborough, United Kingdom

[*]all authors contributed equally

Corresponding Author:
Dawn A Skelton, BSc, PhD, MD hc
Glasgow Caledonian University
Institute for Applied Health Research
School of Health and Life Sciences
Cowcaddens Road
Glasgow, G4 0BA
United Kingdom
Phone: 44 3318792
Fax: 44 (0)1413313005
Email: Dawn.Skelton@gcu.ac.uk

Abstract

Background: Increasing physical activity (PA) brings many health benefits, but engaging people in higher levels of PA after their 60s is not straightforward. The Functional Fitness MOT (FFMOT) is a new approach which aims to raise awareness about the importance of components of fitness (strength, balance, flexibility), highlight benefits of PA, engages older people in health behavior change discussions, and directs them to local activity resources. This battery of tests combined with a brief motivational interview has not been tested in terms of feasibility or effectiveness.

Objective: To assess whether the FFMOT, provided in a health care setting, is appealing to older patients of a community physiotherapy service and to understand the views and perceptions of the older people undergoing the FFMOT regarding the intervention, as well as the views of the physiotherapy staff delivering the intervention. Secondary aims are to assess the feasibility of carrying out a phase 2 pilot randomized controlled trial of the FFMOT, in the context of a community physiotherapy service, by establishing whether enough patients can be recruited and retained in the study, and enough outcome data can be generated.

Methods: A mixed-methods feasibility study will be conducted in two physiotherapy outpatient clinics in the United Kingdom. A total of 30 physically inactive, medically stable older adults over the age of 60 will be provided with an individual FFMOT, comprising a set of six standardized, validated, age-appropriate tests aimed at raising awareness of the different components of fitness. The results of these tests will be used to provide the participants with feedback on performance in comparison to sex and age-referenced norms. This will be followed by tailored advice on how to become more active and improve fitness, including advice on local opportunities to be more active. Subsequently, participants will be invited to attend a focus group to discuss barriers and motivators to being more active, health behavior change, and the scope for individuals to improve their PA levels. To inform the design of a future trial, descriptive (eg, recruitment and retention rates), quantitative (Community Healthy Activities Model Program for Seniors; CHAMPS physical activity questionnaire), and qualitative data (focus group discussions, semi-structured staff interviews) will be collected.

Results: Recruitment and enrolment for the trial started in September 2015. Follow-up will be completed in June 2016. Results are expected to be available at the end of 2016.

Discussion: Allied health professionals play a key role in encouraging older adults to increase their PA, but with little evidence on how best to do this within their clinical practice. The purpose of this feasibility study is to examine the introduction of a new

service: The FFMOT. The views and perceptions of the older people undergoing the FFMOT and relating to its delivery in clinical practice will be explored. Data, which will inform the feasibility of a randomized controlled trial of effectiveness of the FFMOT in promoting improved PA, will be reported.

Trial Registration: International Standard Randomized Controlled Trial Number (ISRCTN): ISRCTN38950042; http://www.isrctn.com/ISRCTN38950042

(JMIR Res Protoc 2016;5(2):e108) doi:10.2196/resprot.5682

KEYWORDS

physical activity; physical fitness; physical therapists; aged; health behavior; health services for the aged; feasibility studies

Introduction

Increasing physical activity (PA) brings many health benefits, improved health care outcomes, and reduced health care costs [1]. PA recommendations for the health of older adults include being active daily and doing activities that improve strength and balance at least twice a week. Over a week, activity should add up to at least 150 minutes of moderate intensity activity in bouts of 10 minutes or more [1]. However, only one in five people aged 65-74 years and one in ten over-75 years achieve recommended activity levels [2].

The Scottish Government has recommended that allied health professionals play a central role in encouraging people to be more active [3]. Physiotherapists are expected to raise the question of activity levels at each initial consultation, and promote PA at any given opportunity to improve the overall health and well-being of people using their services. However, engaging older people in higher levels of PA is not straightforward. In fact, evidence for the effectiveness of interventions to promote healthier levels of PA among adults [4-6] and older adults [7] is not compelling. Recently, one study showed that older people recruited through general practice and undergoing a 6-month group exercise intervention, increased their moderate intensity activity by about 15 minutes a day a year after the intervention finished [8]. However, this approach is costly and many older people do not find group exercise appealing. Therefore, not only effective but cost-effective approaches to increase PA are needed.

Rikli and Jones [9] previously developed and validated a battery of performance tests to provide a means of assessing key physiological parameters that are associated with functional mobility in independent older adults between 60-90 years. This test battery was recently adapted and further developed into the Functional Fitness MOT (FFMOT) [10]. The FFMOT is a new approach that aims to raise awareness of the importance of components of fitness such as strength, balance, and flexibility among the over-60s, highlight the benefits of PA, engage older people in health behavior change discussions, and direct them to appropriate local activity resources. It involves one face-to-face session to measure participants' fitness using seven age-appropriate functional fitness tests. Immediate feedback is given on the person's abilities in each test in relation to normal values for their age and sex, followed by tailored advice on how to become more active and improve fitness. This brief motivational set of tests and discussion is based on the principles of health behavior change, incorporating awareness raising, breaking down barriers, improving self-efficacy, building on history of activity, incorporating needs and preferences, and goal setting [11]. To date the FFMOT has been piloted in non-clinical settings only [10].

Due to the lack of in-depth research and existing data about the FFMOT in a clinical setting, a feasibility study is indicated [12]. Therefore, in line with Medical Research Council guidance [13], the first phase of this work program is a feasibility study to evaluate the approach in clinical settings. According to the guidelines for the design of feasibility studies proposed by Bowen et al [12], the key areas of focus for this study are (1) *acceptability, demand, implementation, and practicality* for the participants, that is, to assess whether the FFMOT, provided in a health care setting, is appealing to older patients of a community physiotherapy service, and to understand their views and perceptions undergoing the FFMOT regarding the intervention, and (2) *acceptability, demand, implementation, practicality, and integration* for the staff delivering the FFMOT, that is, to assess their views on delivering the intervention to the target participants and within the setting of a community physiotherapy clinic. Secondary aims are to assess *limited efficacy*, that is, the feasibility of carrying out a phase 2 pilot randomized controlled trial of the FFMOT, in the context of a community physiotherapy service, by establishing whether enough patients can be recruited and retained in the study, and relevant outcome data can be generated.

Methods

Design

This is a mixed-method phase I feasibility study with a pre-post design.

Participants

A convenience sample will be identified and recruited from one UK health board area, from among the current caseloads of community physiotherapists working in two physiotherapy clinics for musculoskeletal (MSK) conditions. Participants are eligible for participation if they are (1) aged 60 years or above, (2) not physically active for at least 30 minutes in 5 days or more, or for at least 150 minutes (2½ h) in total in the past week, as indicated by the questions on the Scottish Physical Activity Screening Question [14], and (3) interested in increasing their level of PA (where this is seen as an appropriate goal by the screening physiotherapist). Participants are excluded if the screening physiotherapist identifies health risks (contraindications to exercise; eg, cardiovascular disease) which prevents participation, and if they have been diagnosed with

moderate/severe cognitive impairment, a learning disability, severe mental illness, or the screening physiotherapist believes that any of these impairments/disorders are present.

Where patients are deemed eligible, the screening physiotherapist will introduce the nature of the study verbally to them. The screening physiotherapist will then ask potential participants if they wish to receive a study information pack and, if so, they will be given the pack during the appointment. Participants who are interested will then complete a contact details form and post it to the main researcher, who will subsequently telephone them in order to explain the consent procedures, and make an appointment for them to attend an FFMOT session. All participants will continue to receive standard physiotherapy assessment and intervention as deemed appropriate by the screening physiotherapist, irrespective of their involvement in the study.

Sample Size

This study is a feasibility study so no formal power calculation has been carried out. However, rates of participant retention at 3-month follow-up in feasibility studies of exercise interventions for adults range between 71-100% [15-18]. Adopting a conservative estimate of 70% retention, 30 participants will be recruited with the aim of retaining 21 at the 3-month follow-up. Six blocks of FFMOT sessions will be provided over 12 weeks, with provision to run two to three additional blocks beyond this if required to achieve the recruitment target.

Physiotherapy Staff

All physiotherapists working at the two participating physiotherapy clinics, who assess and treat MSK outpatients, will be eligible to screen patients as potential participants.There are 3 physiotherapists involved in coordinating the study within the service. They will also supervise the 2 trained technical instructors (TIs) who will deliver the FFMOT. The TIs will receive training in both the delivery of the FFMOT [19] and in motivation and support strategies for engaging older adults in PA [20].

Functional Fitness MOT

Each recruited participant will be provided with an individual FFMOT session, which lasts for 45-60 minutes. The FFMOT in this study comprises 6 of the 7 standardized, validated, age-appropriate tests aimed at raising awareness of the different components of fitness:

1) 30 Second Chair Stand [21,22], as an indicator of lower limb strength and endurance;

2) Chair Sit and Reach [21,23,24], as an indicator of lower limb flexibility;

3) Back Scratch [21], as an indicator of upper body shoulder flexibility;

4) 8 Foot Up and Go [21,25], as an indicator of dynamic balance;

5) Handgrip Strength [26], as an indicator of strength;

6) Single Leg Stance [27,28], as an indicator of static balance.

The 6-minute walk test, for endurance, will not be used within this FFMOT battery due to space constraints within the clinic.

The results of these tests will be used to discuss the different components of fitness, to highlight the individual's strengths and weaknesses in these components, and to provide the participants with personal feedback on performance in comparison to sex and age-referenced norms. This then allows discussion around the person's activity history, needs, and preferences so that information about local opportunities to engage in PA can be introduced and encouraged. Specific goal setting (short and longer term) is discussed and each participant is provided with information about appropriate local activity opportunities and home exercises, based on their FFMOT results. This information will be provided in the form of written booklets/leaflets and links to websites of some of the opportunities available. For those who wish to exercise at home, home exercise booklets will be provided [29].

Data Collection

Descriptive Data

The following information from every patient screened during the recruitment phase will be collected: (1) the clinic at which the patient was assessed/treated, (2) sex, (3) age, (4) postcode, (5) patient responses to the 3 questions in the Scottish Physical Activity Screening Question, (6) eligibility criteria, (7) whether the study was introduced verbally to the patient, and (8) whether the patient accepted the study information pack. Recruitment and retention rates at the key stages of the study (eg, attendance for the FFMOT and focus group, return of completed follow-up questionnaires) will also be monitored and recorded.

The Community Healthy Activities Model Program for Seniors (CHAMPS) Activities Questionnaire for Older Adults [30] will be administered before the FFMOT. This questionnaire is a valid and reliable instrument to measure recent levels and types of PA in detail in this age group. Twelve weeks after the FFMOT session a follow-up CHAMPS, and a bespoke post-intervention questionnaire will be sent by post. The latter questionnaire aims to measure the participants' contact with community organizations and facilities with a PA focus since attending the FFMOT session.

Qualitative Data

Between 2-4 weeks after participants have attended the FFMOT session, they will be invited to attend a 60-90 minute focus group. Each group will consist of a maximum of 12 participants. The focus groups will be moderated by the first author (LDdJ) according to a bespoke, predesigned discussion guide. The discussion guide contains a set of semi-structured, open-ended questions. The interview process during the focus group comprises a 4-step approach to ask the participants the following:

1. Their reason(s) for taking part in the study.

2. Their PA awareness (eg, reasons for not adhering to PA guidelines, perception changes after the FFMOT, views on and awareness about the importance and benefits of PA, perceived importance of and changes in PA behavior since the FFMOT,

and changes in awareness of local opportunities to become more physically active).

3. The FFMOT and its appeal (eg, how it felt to undergo it, what was liked and disliked, clarity of the feedback by the TIs, impact of the test results when compared with other people of the same age group, reasons for (not) recommending it to others, suggestions for improvement to make it more appealing, and views on timing and location of provision of the service).

4. Their experiences of the study procedures (eg, concerns about taking part, clarity of the participant information sheet, experiences with completing the consent procedure and CHAMPS questionnaires).

Four semi-structured individual interviews, of up to 60 minutes, with the supervising physiotherapists and the 2 TIs will be held no more than 2 weeks after all FFMOT sessions have been provided. The interview process for these interviews comprise a 3-step approach to ask the staff about the following:

1. Previous experiences in working with older people, therapy, fitness testing, exercise, research, and background knowledge of fitness tests/testing.

2. Perceptions of the FFMOT (eg, views on the pretrial training, appropriateness and constraints of the screening criteria and fitness tests, experiences with administering the tests, representativeness of the participants' results, issues during administration of the tests, views on the appeal, benefits, disadvantages, and value of the FFMOT, suggestions for improvement).

3. The FFMOT in the context of a community physiotherapy service (eg, appropriateness of the physiotherapy service to deliver the FFMOT, views on feasibility, barriers and motivators to deliver it in a physiotherapy service, views on improvements in the delivery of the FFMOT).

All focus group discussions and staff interviews will be audio recorded onto an encrypted digital recorder.

Analysis

As this is a feasibility study, the analyses will be primarily descriptive. Reasons for exclusion, participant recruitment and retention rates, number of completed questionnaires returned, and incidence of missing questionnaire item responses will be explored. Additional analyses will be conducted of any demographic differences (including sex, age, the clinic where screening occurred, the Scottish Index of Multiple Deprivation [31] rank of participant's home postcode, and travelling distance from home to clinic between (a) eligible and non-eligible patients, (b) eligible patients who accepted an information pack and those who did not, (c) eligible patients who were recruited and those who were not, and (d) completers and non-completers. CHAMPS data will be compared between baseline and 12-week follow-up to provide an initial estimate of effect size to inform the design of a future trial. A previous study [8] using CHAMPS has shown positively skewed distributions, so it is likely that similar logarithmic transformations (CHAMPS score +1) will have to be carried out. Qualitative data (focus group and staff interview audio recordings) will be fully transcribed and coded using thematic analysis. Thematic analysis will be carried out by two of the authors (LDdJ, DAS), with all authors agreeing the final themes.

Informed Consent

Written informed consent will be obtained from all participants. The decision regarding participation in the study is entirely voluntary. The researcher will emphasize to potential participants that consent regarding study participation can be withdrawn at any time without giving any reason, and without affecting their physiotherapy/medical care. It will also be emphasized to potential participants that all of the information that is collected about them during this project (personal, medical, and audio recordings) will be anonymized, will not affect their confidentiality in any way, and that it will not be possible to identify information about them when the results of the study are published.

Ethical and Organizational Review

A favorable ethical opinion of this study was granted by the NHS South East Scotland Research Ethics Committee 01, Scotland UK (Reference 15/SS/0118). Approval was also granted by the NHS Lothian Research & Development Office (Reference 2015/0283). The study is sponsored by Glasgow Caledonian University (Reference RIE13-127).

Results

Recruitment and enrolment for the trial started in September 2015. Follow-up will be completed in June 2016. Results are expected to be available at the end of 2016.

Discussion

Allied health professionals are tasked with playing a key role in encouraging older adults to increase their PA. Older adults need unique consideration in how they are recommended to become more physically active, in particular doing activities that improve strength and balance, but there is little evidence for allied health professionals on how best to do this within their clinical practice. The FFMOT is a new approach that aims to raise awareness among the over-60s of the importance of components of fitness such as strength, balance and flexibility, highlight the benefits of PA, engage older people in health behavior change discussions, and direct them to appropriate local activity resources. However, there is no existing data about whether the FFMOT could work in this setting, and therefore performing a feasibility study is indicated. The purpose of this mixed-method phase I feasibility study with a pre-post design is to examine the introduction of the FFMOT for older adults, within two community physiotherapy MSK clinics in the United Kingdom. Specifically, the views and perceptions of a convenience sample of older people undergoing the FFMOT relating to the delivery of the FFMOT in clinical practice will be explored. Patient recruitment/retention rates, and the extent to which outcome data can be collected, will be evaluated with a view of planning a future randomized controlled trial of the FFMOT compared with the usual treatment provided (recommendations for increased activity). Participants included in this study will be provided with single, 45-60 minute consultation, including age-appropriate functional tests, which

could potentially increase their motivation to become more physically active. Increased PA could help them improve their gait, balance, mobility, and general health in the longer term. If this feasibility study suggests the FFMOT can work in the clinical setting, then a definitive RCT will be proposed in order to look at whether the FFMOT is efficacious and effective at increasing PA in older adults.

Acknowledgments

This study was funded by a grant from the Edinburgh and Lothians Health Foundation (reference number 10-338). Andy Peters is supported by Edinburgh Clinical Trials Unit.

Conflicts of Interest

DAS and RMEL are Directors of Later Life Training Ltd, a not for profit organization that delivers training on motivation to exercise, and exercise delivery for older people. RMEL is a Consultant for the BHF National Centre for Physical Activity and Health, and delivers FFMOT training across the UK. The other authors declare that they have no competing interests.

Authors' Contributions

AP, JH, NC, CH, RMEL, and DAS conceived the study and participated in its design, and together with LDdJ wrote and refined the trial protocol. LDdJ has had the responsibility of preparing this manuscript. All authors have been involved in revising it critically for important intellectual content, and read and approved the final manuscript.

References

1. Department of Health, Physical Activity, Health Improvement and Protection. Start Active, Stay Active: A Report on Physical Activity from the Four Home Countries' Chief Medical Officers Department. 2011 Jul 11. URL: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/216370/dh_128210.pdf [accessed 2016-02-18] [WebCite Cache ID 6fOWaCLp4]
2. Long-term Conditions Alliance Scotland. PATH to Active Ageing. Promoting the Benefits of Physical Activity for Older People. Glasgow: Long-term Conditions Alliance Scotland; 2012. URL: https://agescotland.files.wordpress.com/2013/01/active_ageing_report_revised-1.pdf [accessed 2016-04-03] [WebCite Cache ID 6gUlP2sUB]
3. The Scottish Government. AHPs as Agents of Change in Health and Social Care. The National Delivery Plan for the Allied Health Professions in Scotland, 2012–2015. Edinburgh: The Scottish Government; 2012. URL: http://www.gov.scot/resource/0039/00395491.pdf [accessed 2016-02-18] [WebCite Cache ID 6fOWwMKpj]
4. Hillsdon M, Foster C, Thorogood M. Interventions for promoting physical activity. Cochrane Database Syst Rev 2005(1):CD003180 [FREE Full text] [doi: 10.1002/14651858.CD003180.pub2] [Medline: 15674903]
5. National Institute for Health and Care Excellence (NICE). Physical activity: brief advice for adults in primary care. Manchester: National Institute for Health and Care Excellence (NICE); 2013. URL: https://www.nice.org.uk/guidance/ph44/resources/physical-activity-brief-advice-for-adults-in-primary-care-1996357939909 [accessed 2016-02-18] [WebCite Cache ID 6fOX2uKk9]
6. Richards J, Hillsdon M, Thorogood M, Foster C. Face-to-face interventions for promoting physical activity. Cochrane Database Syst Rev 2013;9(9):1-87. [doi: 10.1002/14651858.CD010392.pub2] [Medline: 24085592]
7. van der Bij AK, Laurant MG, Wensing M. Effectiveness of physical activity interventions for older adults: a review. Am J Prev Med 2002 Feb;22(2):120-133. [Medline: 11818183]
8. Iliffe S, Kendrick D, Morris R, Griffin M, Haworth D, Carpenter H, et al. Promoting physical activity in older people in general practice: ProAct65+ cluster randomised controlled trial. Br J Gen Pract 2015 Nov;65(640):e731-e738. [doi: 10.3399/bjgp15X687361] [Medline: 26500320]
9. Rikli RE, Jones CJ. Development and validation of a functional fitness test for community-residing older adults. J Aging Phys Act 1999;7:129-161.
10. BHF National Centre for Physical Activity and Health. The Functional Fitness MOT Programme Impact Assessment. 2014 Jul. URL: http://www.laterlifetraining.co.uk/wp-content/uploads/2014/08/Functional-Fitness-MOT-impact-assessment_GCU_LLT_BHFNCPAH_2014.pdf [accessed 2016-05-23] [WebCite Cache ID 6hiPa9bod]
11. National Institute for Health and Clinical Excellence (NICE). Behaviour change: general approaches. Manchester: National Institute for Health and Clinical Excellence (NICE); 2007 Oct 24. URL: https://www.nice.org.uk/guidance/ph6/resources/behaviour-change-general-approaches-55457515717 [accessed 2016-02-18] [WebCite Cache ID 6fOXH6Jk6]
12. Bowen DJ, Kreuter M, Spring B, Cofta-Woerpel L, Linnan L, Weiner D, et al. How we design feasibility studies. Am J Prev Med 2009 May;36(5):452-457 [FREE Full text] [doi: 10.1016/j.amepre.2009.02.002] [Medline: 19362699]
13. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M, Medical Research Council Guidance. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ 2008;337:a1655 [FREE Full text] [Medline: 18824488]

14. NHS Health Scotland. Scottish Physical Activity Screening Question (Scot-PASQ). URL: http://www.paha.org.uk/Resource/scottish-physical-activity-screening-question-scot-pasq [accessed 2016-02-18] [WebCite Cache ID 6fOXMtWrZ]
15. Ellis T, Latham NK, DeAngelis TR, Thomas CA, Saint-Hilaire M, Bickmore TW. Feasibility of a virtual exercise coach to promote walking in community-dwelling persons with Parkinson disease. Am J Phys Med Rehabil 2013 Jun;92(6):472-81; quiz 482 [FREE Full text] [doi: 10.1097/PHM.0b013e31828cd466] [Medline: 23552335]
16. Busse M, Quinn L, Debono K, Jones K, Collett J, Playle R, Members of the COMMET-HD Management Group. A randomized feasibility study of a 12-week community-based exercise program for people with Huntington's disease. J Neurol Phys Ther 2013 Dec;37(4):149-158. [doi: 10.1097/NPT.0000000000000016] [Medline: 24232362]
17. Minns Lowe Catherine J, Barker KL, Holder R, Sackley CM. Comparison of postdischarge physiotherapy versus usual care following primary total knee arthroplasty for osteoarthritis: an exploratory pilot randomized clinical trial. Clin Rehabil 2012 Jul;26(7):629-641. [doi: 10.1177/0269215511427749] [Medline: 22180446]
18. Hayes S, Rye S, Battistutta D, Yates P, Pyke C, Bashford J, et al. Design and implementation of the Exercise for Health trial - a pragmatic exercise intervention for women with breast cancer. Contemp Clin Trials 2011 Jul;32(4):577-585. [doi: 10.1016/j.cct.2011.03.015] [Medline: 21463707]
19. BHF National Centre for Physical Activity and Health. Using the Functional Fitness MOT. URL: http://www.bhfactive.org.uk/older-adults-training-and-events-item/370/index.html [accessed 2016-02-18] [WebCite Cache ID 6fOXdM8i2]
20. Later Life Training (LLT). About Motivate Me. URL: http://www.laterlifetraining.co.uk/courses/motivate-me/about-motivate-me/ [accessed 2016-05-23] [WebCite Cache ID 6hiQFXuSM]
21. Rikli RE, Jones CJ. Functional fitness normative scores for community-residing older adults, ages 60-94. J Aging Phys Act 1999;7(2):162-181.
22. Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. Res Q Exerc Sport 1999 Jun;70(2):113-119. [doi: 10.1080/02701367.1999.10608028] [Medline: 10380242]
23. Jones CJ, Rikli RE, Max J, Noffal G. The reliability and validity of a chair sit-and-reach test as a measure of hamstring flexibility in older adults. Res Q Exerc Sport 1998 Dec;69(4):338-343. [doi: 10.1080/02701367.1998.10607708] [Medline: 9864752]
24. Liemohn W, Sharpe G, Wasserman J. Criterion Related Validity of the Sit-and-Reach Test. J Strength Cond Res 1994;8(2):91-94.
25. Rose DJ, Jones CJ, Lucchese N. Predicting the Probability of Falls in Community- Residing Older Adults Using the 8-Foot Up-and-Go: A New Measure of Functional Mobility. J Aging Phys Act 2002;10:466-475.
26. Skelton DA, Greig CA, Davies JM, Young A. Strength, power and related functional ability of healthy people aged 65-89 years. Age Ageing 1994 Sep;23(5):371-377. [Medline: 7825481]
27. Lin M, Hwang H, Hu M, Wu HI, Wang Y, Huang F. Psychometric comparisons of the timed up and go, one-leg stand, functional reach, and Tinetti balance measures in community-dwelling older people. J Am Geriatr Soc 2004 Aug;52(8):1343-1348. [doi: 10.1111/j.1532-5415.2004.52366.x] [Medline: 15271124]
28. El-Sobkey SB. Normative Values for One Leg Stance Balance Test in Population Based Sample of Community Dwelling Older People. Middle-East J Sci Res 2011;7(4):497-503.
29. Later Life Training (LLT). LLT Home Exercise Booklets. URL: http://www.laterlifetraining.co.uk/llt-home-exercise-booklets/ [accessed 2016-05-23] [WebCite Cache ID 6hiQYF9dF]
30. Stewart AL, Mills KM, King AC, Haskell WL, Gillis D, Ritter PL. CHAMPS physical activity questionnaire for older adults: outcomes for interventions. Med Sci Sports Exerc 2001 Jul;33(7):1126-1141. [Medline: 11445760]
31. The Scottish Government. Scottish Index of Multiple Deprivation 2012: A National Statistics Publication for Scotland. Edinburgh: The Scottish Government; 2012 Dec 18. URL: http://22fa0f74501b902c9f11-8b3fbddfa1e1fab453a8e75cb14f3396.r26.cf3.rackcdn.com/simd_448749_v7_20121217.pdf [accessed 2016-02-18] [WebCite Cache ID 6fOW1ZDqz]

Abbreviations

FFMOT: Functional Fitness MOT (Note: in the UK the abbreviation MOT refers to the annual test of vehicle safety and as such is generally recognized by the population. In the same vein, the Functional Fitness MOT is a battery of human physical fitness tests so participants recognize the term)
MSK: musculoskeletal
PA: physical activity
TI: technical instructor

Edited by G Eysenbach; submitted 22.02.16; peer-reviewed by E de Bruin; comments to author 28.03.16; revised version received 04.04.16; accepted 04.04.16; published 20.06.16.

Please cite as:
de Jong LD, Peters A, Hooper J, Chalmers N, Henderson C, Laventure RME, Skelton DA
The Functional Fitness MOT Test Battery for Older Adults: Protocol for a Mixed-Method Feasibility Study
JMIR Res Protoc 2016;5(2):e108
URL: http://www.researchprotocols.org/2016/2/e108/
doi:10.2196/resprot.5682
PMID:27324114

Protocol

Working Time Arrangements as Potential Risk Factors for Ischemic Heart Disease Among Workers in Denmark: A Study Protocol

Harald Hannerz[1*], MSc; Ann Dyreborg Larsen[1*], PhD; Anne Helene Garde[1*], PhD

National Research Centre for the Working Environment, Copenhagen, Denmark

[*]all authors contributed equally

Corresponding Author:
Harald Hannerz, MSc
National Research Centre for the Working Environment
Lersø Parkallé 105
Copenhagen, DK-2100
Denmark
Phone: 45 39 16 54 60
Fax: 45 39 16 52 01
Email: HHA@NRCWE.DK

Abstract

Background: It has long been suspected that a worker's risk of developing an ischemic heart disease (IHD) may be influenced by his or her working time arrangements. A multitude of studies have been performed, and special attention has been given to long working hours and nighttime work. The statistical powers of the individual studies have, however, generally been too low to either dismiss or confirm an actual relationship, and meta-analyses of underpowered studies are generally associated with publication bias. Hence, uncertainty remains and whether these factors indeed are related to IHD has yet to be settled.

Objective: This project will test whether the incidences of IHD and usage of antihypertensive drugs among employees in Denmark are independent of weekly working hours and nighttime work. The objective of this paper is to present the intended analyses.

Methods: We will link individual participant data from the Danish labor force survey, 1999–2013, to data on socioeconomic status, industry, emigrations, redeemed prescriptions, hospitalizations, and deaths from registers covering the entire population of Denmark. The study will include approximately 160,000 participants, who will be followed through the registers, from the time of the interview until the end of 2014, for first occurrence of IHD and for antihypertensive drug treatment. We will use Poisson regression to analyze incidence rates as a function of nighttime work and of weekly working hours.

Results: We expect results to be ready in mid-2017.

Conclusions: To our knowledge, this will be the largest study ever of its kind. It will, moreover, be free from hindsight bias, since the hypotheses, inclusion criteria, significance levels, and statistical models will be completely defined and published before we are allowed to link the exposure data to the outcome data.

(JMIR Res Protoc 2016;5(2):e130) doi:10.2196/resprot.5563

KEYWORDS

occupational health; prescription drugs; hospital treatment; night worker; long working hours

Introduction

Background

Our project will look at rates of ischemic heart disease (IHD) among Danish employees as a function of weekly working hours and nighttime work.

From the viewpoint of cardiovascular risk factors, there appear to be both advantages and disadvantages of long working hours and nighttime work.

One of the advantages of nighttime work is that it usually eliminates exposure to rush hour commuting stress, both to and from work; such stress has been associated with psychological strain [1,2], increased blood pressure [3], and increased rates of acute myocardial infarction [4,5]. Moreover, a survey of more than 400 people in United Kingdom indicated that 44% of people believed that rush hour traffic was the single most stressful part of their life [6]. Daytime workers may reduce their exposure to rush hour traffic, at least in one direction, by choosing to work long hours.

Another potential advantage of nighttime work and long working hours is that they can generate extra income, compared with ordinary daytime work, and thereby reduce the risk or intensity of financial strain. An increased income has been associated with a decreased risk of IHD [7], while financial strain has been associated with an increased risk of hypertension [8] and acute myocardial infarction [9].

The disadvantage of long working hours and nighttime or shift work is that they usually are associated with short sleep duration, mismatch of circadian rhythm, social disruption, and behavioral changes [10,11], which in turn are associated with an increased risk of IHD [12]. The mechanism may be related to disturbed regulation of inflammatory, metabolic, and cardiovascular processes. Thus, short-term sleep restriction increases heart rate [13] and blood pressure [14], changes immune function [13], increases C-reactive protein concentration [13], and decreases glucose tolerance and sympathetic nervous system activity [15].

The evidence of an association between night or shift work and IHD has been reviewed by Frost et al [16], Ha et al [17], and Vyas et al [18]. Frost et al [16] reviewed 14 research papers and concluded that “the available evidence concerning the influence of the type and duration of shift work, as well as sex, on the risk of IHD is too limited to permit any conclusions on these issues." In a meta-analysis that combined the results from 8 studies, Ha et al estimated the effect of night or shift work versus ordinary daytime work, first at a rate ratio (RR) equal to 1.17 (95% CI 1.00–1.37) and then, after adjustment for publication bias, at RR=1.12 (95% CI 0.94–1.33) [17].

Vyas et al [18] reviewed 35 research papers and used the results of the papers in meta-analyses, which estimated the RR of night or shift work versus ordinary daytime work at 1.24 (95% CI 1.10–1.39) for coronary events, 1.23 (95% CI 1.15–1.31) for acute myocardial infarction, and 1.05 (95% CI 1.01–1.09) for ischemic stroke. However, 87% (1,750,565/2,011,935) of the participants in the meta-analyses came from ecologic studies, which of course makes the estimates less certain than their confidence intervals imply.

Virtanen et al [19] investigated the relationship between long working hours and coronary heart disease in a systematic review and meta-analysis, which included results from 12 research papers. The RR for coronary heart disease among workers with “long" versus “normal" working hours was estimated at 1.80 (95% CI 1.42–2.29) when all studies were included and 1.39 (95% CI 1.12–1.72) when restricted to prospective studies. The cut points for long weekly working hours ranged from >40 to >65 hours.

The reviews by Vyas et al [18] and by Virtanen et al [19] suggested that the disadvantages of nighttime work and long working hours tend to outweigh the advantages of such work time arrangements. However, since the meta-analyses only included published studies, we cannot rule out publication bias. The risk of publication bias is especially high if the included studies are too small to be of interest unless the results are statistically significant [20], and this is definitely the case with the studies that Virtanen et al [19] included in their meta-analysis.

Kivimaki et al [21] conducted a more reliable meta-analysis of the relationship between long working hours and IHD, in which they mitigated the risk of publication bias by conducting and inserting a series of new and hitherto unpublished studies. By combining the results from the unpublished studies with corresponding results from published studies, they obtained the following RRs for long versus normal (35–40) working hours a week: 1.02 (95% CI 0.91–1.15) for 41–48 hours, 1.07 (95% CI 0.92–1.24) for 49–54 hours, and 1.08 (95% CI 0.92–1.24) for >54 working hours. These RRs are most probably the best estimates ever of the strength of association between long working hours and coronary heart disease. We should, however, keep in mind that meta-analyses that include published results never can be done blinded. The researchers often know the literature before they formulate inclusion criteria and, however systematic and objective they attempt to be, it can never be ruled out that the selection of papers as well as the selection of estimates within the papers might be influenced by their a priori expectations. From this viewpoint, it would be good to know whether the null finding by Kivimaki et al would be reproduced if it were tested in an equally sized blinded study, that is, a study in which the inclusion criteria, hypotheses, and statistical models were completely specified and published before any results were available.

Kivimaki et al [21] based their RRs on a total of 2481 new cases among 129,301 participants. Our project has access to person-based data on work time arrangements for approximately 160,000 employees with long or normal working hours, which, upon follow-up, we expect to yield approximately 3200 new cases of IHD. The exposure data of the project have not been linked to health data before, and this provides an opportunity to study the relationship between work time arrangements and subsequent IHD, with a remarkably high statistical power, completely blinded.

Aims and Hypotheses

We want to know whether the incidence of antihypertensive drug usage and the incidence of hospital treatment or death due to IHD are independent of weekly working hours and nighttime work among full-time employees in Denmark, and will address these research questions in a series of nested hypothesis tests (Textbox 1).

Textbox 1. Hypotheses to be tested.

1. The incidence of antihypertensive drug usage and the incidence of hospital treatment or death due to ischemic heart disease (IHD) among full-time employees in Denmark are prospectively independent of weekly working hours, as well as interaction between weekly working hours and each of the following variables: socioeconomic status, sex, and nighttime work.

1.1. The incidence of hospital treatment or death due to IHD is prospectively independent of weekly working hours, as well as interaction between weekly working hours and each of the following variables: socioeconomic status, sex, and nighttime work.

1.1.1. The prospective association between weekly working hours and incidence of hospital treatment or death due to IHD is independent of socioeconomic status.

1.1.2. The prospective association between weekly working hours and incidence of hospital treatment or death due to IHD is independent of sex.

1.1.3. The prospective association between weekly working hours and incidence of hospital treatment or death due to IHD is independent of nighttime work.

1.1.4. The incidence of hospital treatment or death due to IHD is prospectively independent of weekly working hours when we disregard interaction effects.

1.2. The incidence of antihypertensive drug usage is prospectively independent of weekly working hours, as well as interaction between weekly working hours and each of the following variables: socioeconomic status, sex, and nighttime work.

1.2.1. The prospective association between weekly working hours and incidence of antihypertensive drug usage is independent of socioeconomic status.

1.2.2. The prospective association between weekly working hours and incidence of antihypertensive drug usage is independent of sex.

1.2.3. The prospective association between weekly working hours and incidence of antihypertensive drug usage is independent of nighttime work.

1.2.4. The incidence of antihypertensive drug usage is prospectively independent of weekly working hours when we disregard interaction effects.

2. The incidence of antihypertensive drug usage and the incidence of hospital treatment or death due to IHD among full-time employees in Denmark is prospectively independent of nighttime work, as well as interaction between nighttime work and each of the variables socioeconomic status and sex.

2.1. The incidence of hospital treatment or death due to IHD is prospectively independent of nighttime work, as well as interaction between nighttime work and each of the variables socioeconomic status and sex.

2.1.1. The prospective association between nighttime work and incidence of hospital treatment or death due to IHD is independent of socioeconomic status.

2.1.2. The prospective association between nighttime work and incidence of hospital treatment or death due to IHD is independent of sex.

2.1.3. The incidence of hospital treatment or death due to IHD is prospectively independent of nighttime work when we disregard interaction effects.

2.2. The incidence of antihypertensive drug usage is prospectively independent of nighttime work, as well as interaction between nighttime work and each of the variables socioeconomic status and sex.

2.2.1. The prospective association between nighttime work and incidence of antihypertensive drug usage is independent of socioeconomic status.

2.2.2. The prospective association between nighttime work and incidence of antihypertensive drug usage is independent of sex.

2.2.3. The incidence of antihypertensive drug usage is prospectively independent of nighttime work when we disregard interaction effects.

We will set the overall significance level for the effect of weekly working hours at .05 and we will set the overall significance level for the effect of nighttime work at .05. We will solve the multiple testing problems by the following strategy:

- A null hypothesis at the first level will be rejected if either of its two second-level null hypotheses is rejected.
- A null hypothesis at the second level will be rejected if the *P* value of its statistical test is ≤.025.
- A null hypothesis at the third level will be rejected if (1) its associated second-level null hypothesis is rejected and (2) the *P* value of its statistical test is ≤.025.

Hospital treatment or death due to IHD is the primary outcome of the study, and a statically significant association with this outcome would afford direct statistical evidence of an association with IHD.

Hypertension plays an important role in the etiology of IHD [22], and relative rates of antihypertensive drug usage have been shown to be highly correlated with relative rates of IHD among occupational groups in Denmark [23,24]. We will therefore regard results obtained for antihypertensive drug usage as indirect statistical evidence of an association with IHD if they are statistically significant and show a similar pattern to the results obtained for hospital treatment or death due to IHD.

Methods

Ethics Approval

The study will comply with The Act on Processing of Personal Data, Denmark (Act No. 429 of May 31, 2000), which implements the European Union (EU) Directive 95/46/EC on the protection of individuals. The data usage is approved by the Danish Data Protection Agency, file number 2001-54-0180. The ethical aspect of the project was examined and approved by Statistics Denmark, account number 704291.

Data Material

The data base of the project will consist of interview data from the Danish Labour Force Survey 1999–2013, which are linked to data from the central person register [25], the employment classification module [26], the national patient register [27], the cause of death register [28], and the national prescription register [29]. The linkage will be based on the participants' personal identification numbers.

The Danish Labour Force Survey has been conducted since 1994, in accordance with EU directives, which apply to all member states of the EU. It is based on random samples of 15- to 74-year-old people in the Danish population. The samples are drawn quarterly and the participants are invited to be interviewed 4 times over a period of one and a half years. The structured interviews, which are done by telephone, cover various aspects of labor market participation, including specifications on working hours and work schedules [30]. The response rate is currently 65% [30].

The central person register contains information on sex, addresses, and dates of birth, death, and migrations for every person who is or has been an inhabitant of Denmark sometime between 1968 and the present. A person's socioeconomic status (SES), occupation, and industry have been registered annually in the employment classification module since 1975. The national hospital register has existed since 1977 and contains data from all public hospitals in Denmark (>99% of all admissions). From 1977 to 1994, the register only included inpatients, but from 1995 it has also covered outpatients and emergency ward visits. Since 1994, the diagnoses have been coded according to *International Classification of Diseases, Tenth Revision* (ICD-10) [31]. The national prescription register covers all redeemed prescriptions at pharmacies in Denmark since 1995, and the products are coded in accordance with the Anatomical Therapeutic Chemical Classification System (ATC).

Exposure Variables

The labor force surveys gather person-based information on weekly working hours, calculated by adding the hours worked in secondary jobs to the ones worked in a primary job. The participants are asked first how many hours they usually work and then how many hours they worked during the reference week (a predetermined work week, which occurred 1–4 weeks prior to the interview). They are also asked whether and to what extent they work at night. The questions used to gather this information have changed slightly with time. Before 2001, there was no mention of whether meal breaks should be counted as working hours. During 2001–2006, all participants were instructed to exclude meal breaks when they counted their work hours. As of 2007, the time used for meal breaks is to be counted if the person was paid while eating and is to be excluded otherwise. Another peculiarity that was introduced in 2007 is that the participants are asked whether the weekly working hours vary a lot or there are other reasons that make it difficult to provide a meaningful estimate of usual weekly working hours. If they answer "yes" to any of these questions, then "average working hours" is to be used as a proxy for "usual working hours."

Before 2001, the participants were simply asked whether they worked at night, but from 2001 onward the question has been whether they worked at night during the last 4 weeks. Until 2006 the response categories were "yes, regularly," "yes, occasionally," and "no, never". From 2007 onward the response categories were expanded to "yes, regularly" (ie, more than half of the working days in the last 4 weeks), "yes occasionally" (ie, at least once within the last 4 weeks, but less than half of the working days), and "no, not within the last 4 weeks."

We will disregard the changes in the data collection routines in the primary analyses of this project. We will define the exposure variables as follows.

Weekly Working Hours

In keeping with Kleppa et al [32] and Hannerz and Albertsen [33], we will treat working hours as a categorical variable, with 32–40 hours representing normal weekly working hours, 41–48 hours representing overtime work that lies within the limits of the European working time directive, and 49–100 hours representing overtime work beyond the threshold of the directive. We will base the categorization on the person's usual working hours.

Nighttime Work

Participants who responded with either "yes, regularly" or "yes, occasionally" to the question about nighttime work will be defined as being exposed and those who responded with "no..." will be defined as being unexposed to nighttime work.

Clinical End Points

The primary end point is hospital treatment or death, with IHD as the principal diagnosis or cause of death, respectively. The case definition includes the following ICD-10 codes: I20 angina pectoris, I21 acute myocardial infarction, I22 subsequent myocardial infarction, I23 certain current complications following acute myocardial infarction, I24 other acute IHDs, I25 chronic IHD. The secondary end point is redemption of a prescription for antihypertensive drugs. The following ATC codes are included: C02 antihypertensives, C03 diuretics, C07 alpha- and beta-blockers, C08 calcium channel blockers, and C09 angiotensin-converting enzyme inhibitors and angiotensin-II antagonists.

Follow-Up and Inclusion Criteria

The participants will be followed from the beginning of the calendar year that succeeds that of their baseline interview. The follow-up will end at the time the participant is diagnosed with IHD, emigrates, or dies, or the end of the study period (December 31, 2014), whichever comes first. To be eligible for inclusion, they should be between 21 and 59 years old at the start of the follow-up period and employed with ≥32 weekly working hours at the time of the interview. People who received hospital treatment for IHD during the calendar year of the interview will be excluded from the IHD analysis. People who redeemed a prescription for antihypertensive drugs during the calendar year of the interview will be excluded from the antihypertensive drug analysis.

Primary Analysis

We will use Poisson regression to analyze incidence rates of hospital treatment or death due to IHD as a function of weekly working hours (32–40, 41–48, or >48 hours/week), nighttime work (yes vs no), sex, age (10-year classes), calendar time (2000–2004, 2005–2009, or 2010–2014), time passed since start of follow-up (0–4, 5–9, or ≥10 years), employment in the health care industry (yes vs no), and SES (low, medium, high, or unknown). Age, calendar time, and time passed since start of follow-up will be treated as dynamic (time-varying) variables. The remaining variables will be fixed at baseline (the calendar year of the interview). The logarithm of person-years at risk will be used as offset. People who participated in more than one interview will be classified in accordance with the responses given in their first interview. Later interviews will be disregarded.

We will retrieve information on occupation and industry from the employment classification module, and refer it to the status during the calendar year of the baseline interview. Industries were coded in accordance with the Statistics Denmark classification DB93 [34] in 1999–2002, DB03 [35] in 2002–2007, and DB07 [36] in the calendar years 2008–2013. Occupations were coded in accordance with DISCO-88 (the Danish version of the International Standard Classification of Occupations, ISCO-88) [37] in the calendar years 1999–2009 and DISCO-08 (the Danish version of ISCO-08) [38] in the calendar years 2010–2013.

We will code the variable “employment in the health care industry" as “yes" if the 3-digit industrial code of DB93 or DB03 equals 851 or the 2-digit code of DB07 equals 86.

We will base SES on the participant’s occupation and will code it as “high," “medium," or “low" in accordance with the 3-class version of the European Socio-economic Classification (ESeC). The coding will be performed in accordance with the SAS (SAS Institute) programming statements shown in Textbox 2.

Textbox 2. SAS programming statements for occupations coded according to the Danish version of the International Standard Classification of Occupations (DISCO-88) and socioeconomic class (SES) coded according to the European Socio-economic Classification (ESeC).

```
/* SES classification (ESeC three class version) of employees by use of DISCO-88 */
if '1' le substr(DISCO_88, 1, 1) le '2' then SES = "High";
if '3' le substr(DISCO_88, 1, 1) le '4' then SES = "Medium";
if '5' le substr(DISCO_88, 1, 1) le '9' then SES = "Low";
if '31' le substr(DISCO_88, 1, 2) le '32' or substr(DISCO_88, 1, 3) in ('334', '342', '344', '345', '348', '521') then SES = "High";
if substr(DISCO_88, 1, 3) = '731' then SES = "Medium";
if substr(DISCO_88, 1, 3) in ('413', '414', '421', '422') then SES = "Low";
/* SES classification (ESeC three class version) of employees by use of DISCO-08 */
if '1' le substr(DISCO_08, 1, 1) le '2' then SES = "High";
if '3' le substr(DISCO_08, 1, 1) le '4' then SES = "Medium";
if '5' le substr(DISCO_08, 1, 1) le '9' then SES = "Low";
if substr(DISCO_08, 1, 3) in ('311', '312', '314', '315', '321', '322' '323') then SES = "High";
if substr(DISCO_08, 1, 3) in ('224', '742') then SES = "Medium";
if substr(DISCO_08, 1, 2) = '42' or substr(DISCO_08, 1, 3) = '432' then SES = "Low";
```

Statistical Models and Tests to Analyze Effects of Weekly Working Hours

The full model will include the following covariates: calendar time, time passed since start of follow-up, employment in the health care industry, age, sex, SES, nighttime work, working hours, working hours × sex, working hours × SES, and working hours × nighttime work. We will use the parameter estimates obtained with the full model to calculate RRs for incident use of antihypertensive drugs and for hospitalization or death due to IHD as a function of weekly working hours, by sex, SES, and nighttime work. We will consider the following contrasts: 41–48 versus 32–40 working hours/week, and >48 versus 32–40 working hours/week. The results will be presented as outlined in Table 1.

Table 1. Dummy table for reporting the RR[a] with 95% CI for incident use of antihypertensive drugs and hospitalization or death due to IHD[b] as a function of weekly working hours among Danish employees during 2000–2014, stratified by sex, socioeconomic status, and night shift status.

Worker subgroups	Weekly working hours	Antihypertensive drugs			Hospitalization or death due to IHD		
		Cases	RR	95% CI	Cases	RR	95% CI
Sex							
Male	>48						
	41–48						
	32–40		1.00	–		1.00	–
Female	>48						
	41–48						
	32–40		1.00	–		1.00	–
Socioeconomic status							
Low	>48						
	41–48						
	32–40		1.00	–		1.00	–
Medium	>48						
	41–48						
	32–40		1.00	–		1.00	–
High	>48						
	41–48						
	32–40		1.00	–		1.00	–
Unknown	>48						
	41–48						
	32–40		1.00	–		1.00	–
Nighttime work							
Yes	>48						
	41–48						
	32–40		1.00	–		1.00	–
No	>48						
	41–48						
	32–40		1.00	–		1.00	–

[a]RR: rate ratio.

[b]IHD: ischemic heart disease.

We will test hypotheses 1.1 and 1.2 by use of likelihood ratios comparing the full model with a model containing only the following covariates: calendar time, time passed since start of follow-up, employment in the health care industry, age, sex, SES, and nighttime work.

We will test hypotheses 1.1.1 and 1.2.1 by use of likelihood ratios comparing the full model with a model containing only the following covariates: calendar time, time passed since start of follow-up, employment in the health care industry, age, sex, SES, nighttime work, working hours, working hours × sex, and working hours × nighttime work.

We will test hypotheses 1.1.2 and 1.2.2 by use of likelihood ratios comparing the full model with a model containing only the following covariates: calendar time, time passed since start of follow-up, employment in the health care industry, age, sex, SES, nighttime work, working hours, working hours × SES, and working hours × nighttime work.

We will test hypotheses 1.1.3 and 1.2.3 by use of likelihood ratios comparing the full model with a model containing only the following covariates: calendar time, time passed since start of follow-up, employment in the health care industry, age, sex, SES, nighttime work, working hours, working hours × sex, and working hours × SES.

We will test hypotheses 1.1.4 and 1.2.4 by use of likelihood ratios comparing a model containing only the covariates calendar time, time passed since start of follow-up, employment in the health care industry, age, sex, SES, nighttime work, and working hours with a model containing only the covariates calendar time,

time passed since start of follow-up, employment in the health care industry, age, sex, SES, and nighttime work.

Statistical Models and Tests to Analyze Effects of Nighttime Work

The full model will include the following covariates: calendar time, time passed since start of follow-up, employment in the health care industry, age, sex, SES, working hours, nighttime work, nighttime work × sex, and nighttime work × SES. We will use the parameter estimates obtained with the full model to calculate RRs for incident use of antihypertensive drugs and hospitalization or death due to IHD as a function of nighttime work, by sex and SES. The results will be presented as outlined in Table 2.

Table 2. Dummy table for reporting the RR[a] with 95% CI for incident use of antihypertensive drugs and hospitalization or death due to IHD[b] as a function of nighttime work among Danish employees during 2000–2014, stratified by sex and socioeconomic status.

Worker subgroups	Nighttime work	Antihypertensive drugs			Hospitalization or death due to IHD		
		Cases	RR	95% CI	Cases	RR	95% CI
Sex							
Male	Yes						
	No		1.00	–		1.00	–
Female	Yes						
	No		1.00	–		1.00	–
Socioeconomic status							
Low	Yes						
	No		1.00	–		1.00	–
Medium	Yes						
	No		1.00	–		1.00	–
High	Yes						
	No		1.00	–		1.00	–
Unknown	Yes						
	No		1.00	–		1.00	–

[a]RR: rate ratio.

[b]IHD: ischemic heart disease.

We will test hypotheses 2.1 and 2.2 by use of likelihood ratios comparing the full model with a model containing only the following covariates: calendar time, time passed since start of follow-up, employment in the health care industry, age, sex, SES, and working hours.

We will test hypotheses 2.1.1 and 2.2.1 by use of likelihood ratios comparing the full model with a model containing only the following covariates: calendar time, time passed since start of follow-up, employment in the health care industry, age, sex, SES, nighttime work, working hours, and working hours × sex.

We will test hypotheses 2.1.2 and 2.2.2 by use of likelihood ratios comparing the full model with a model containing only the following covariates: calendar time, time passed since start of follow-up, employment in the health care industry, age, sex, SES, nighttime work, working hours, and working hours × SES.

We will test hypotheses 2.1.3 and 2.2.3 by use of likelihood ratios comparing a model containing the covariates calendar time, time passed since start of follow-up, employment in the health care industry, age, sex, SES, nighttime work, and working hours with a model containing only the covariates calendar time, time passed since start of follow-up, employment in the health care industry, age, sex, SES, and working hours.

Power Calculations

To estimate the statistical power of the hypothesis tests, we first needed to estimate the expected number of cases in the various exposure categories.

To obtain such estimates, we followed the entire population of 21- to 59-year-old employees in Denmark from January 1, 2000 and onward in the same registers that we will use to follow up the samples of this project. While discounting prevalent cases (those who had experienced the clinical end point of the study during the calendar year 1999), we noted all new cases that occurred and tabulated those against the time that had passed since the start of the follow-up. Table 3 gives the results, where the values for the first 13 years of IHD cases and the first 12 years of antihypertensive drug cases are based on actual data, whereas we extrapolated the values for the remaining years by use of a second-degree Taylor polynomial.

Table 3. Cumulative percentage of new cases among employees in Denmark aged 21–59 years at baseline, as a function of time passed since start of follow-up (January 1, 2000).

Years of follow-up	Hospitalization or death due to IHD[a]		Antihypertensive drugs	
	Men	Women	Men	Women
1	0.34	0.14	1.41	2.38
2	0.65	0.26	2.89	4.63
3	0.98	0.41	4.44	6.76
4	1.32	0.55	6.15	8.98
5	1.67	0.70	8.07	11.23
6	2.03	0.86	10.01	13.38
7	2.39	1.04	12.14	15.62
8	2.76	1.22	14.37	17.89
9	3.14	1.41	16.55	20.05
10	3.53	1.63	18.63	22.02
11	3.98	1.88	20.70	23.92
12	4.42	2.13	22.69	25.75
13	4.83	2.36	24.64	27.54
14	5.21	2.58	26.56	29.32
15	5.58	2.80	28.48	31.09

[a]IHD: ischemic heart disease.

Since the sample of participants who were interviewed in calendar year *n* will be followed for 2014– *n* years, the expected percentages of new cases in that sample can be found in the row headed by 2014– *n* years of follow-up, and so forth.

By relating the frequency distribution of the participants stratified by calendar year of interview, sex, and exposure category to the percentages given in Table 3, we finally obtained the expected numbers of cases that were needed to calculate the power (see Table 4).

Table 4. Expected number of new cases under the null hypothesis.

Type of exposure	Level	No. of participants	Expected no. of IHD[a] cases	Expected no. of antihypertensive drug cases
Night shifts	Yes	20,337	439	2924
	No	137,521	2786	21,068
Weekly working hours	>48	9734	210	1304
	41–48	15,872	297	2082
	32–40	132,252	2718	20,606

[a]IHD: ischemic heart disease.

Since our hypotheses will be evaluated by use of chi-square distributed likelihood ratio tests, we have chosen to depict the statistical power as a function of Cohen w, which is an effect size defined by equation (1) (Figure 1). Cohen classified w=0.1 as a small effect, w=0.3 as a medium effect and w=0.5 as a large effect [39].

Figure 2 shows the statistical power of hypotheses 1.1 and 1.2. Figure 3 shows the power of hypotheses 2.1 and 2.2. The calculations are based on the total number of expected cases and the noncentral chi-square distribution with 12 degrees of freedom for the effects of long working hours (hypotheses 1.1 and 1.2) and 5 degrees for the effects of nighttime work (hypotheses 2.1 and 2.2).

Figure 1. Equation (1): calculation of Cohen effect size w, where $p_{0\,i}$ and $p_{1\,i}$ are the expected proportions of cases that fall into exposure category i under the null hypothesis and the alternative hypotheses. Equation (2): calculation of expected rate ratio, E[RR], where RR_1 is the rate ratio for ischemic heart disease (IHD) among employees in the body mass index (BMI) category 25≤BMI<30 versus BMI<25 kg/m^2, RR_2 is the rate ratio for IHD among employees in the category BMI≥30 versus BMI<25 kg/m^2, and RR_3 is the rate ratio for IHD among smoking versus nonsmoking employees. The parameters p_1 and q_1 are the proportions of employees who belong to the category 25≤BMI<30 kg/m^2, p_2 and q_2 are the proportions of employees who belong to the category BMI≥30 kg/m^2, and p_3 and q_3 are the proportions of smokers among employees with and without nighttime work.

$$w = \sqrt{\sum_i \frac{(p_{1i} - p_{0i})^2}{p_{0i}}} \qquad (1)$$

$$E[RR] = \frac{1 + p_1(RR_1 - 1) + p_2(RR_2 - 1)}{1 + q_1(RR_1 - 1) + q_2(RR_2 - 1)} \times \frac{1 + p_3(RR_3 - 1)}{1 + q_3(RR_3 - 1)} \qquad (2)$$

Figure 2. Power to detect that the examined incidences depend on weekly working hours either as a general effect or as an effect of interaction with sex, socioeconomic status, or nighttime work, as a function of Cohen w. IHD: ischemic heart disease.

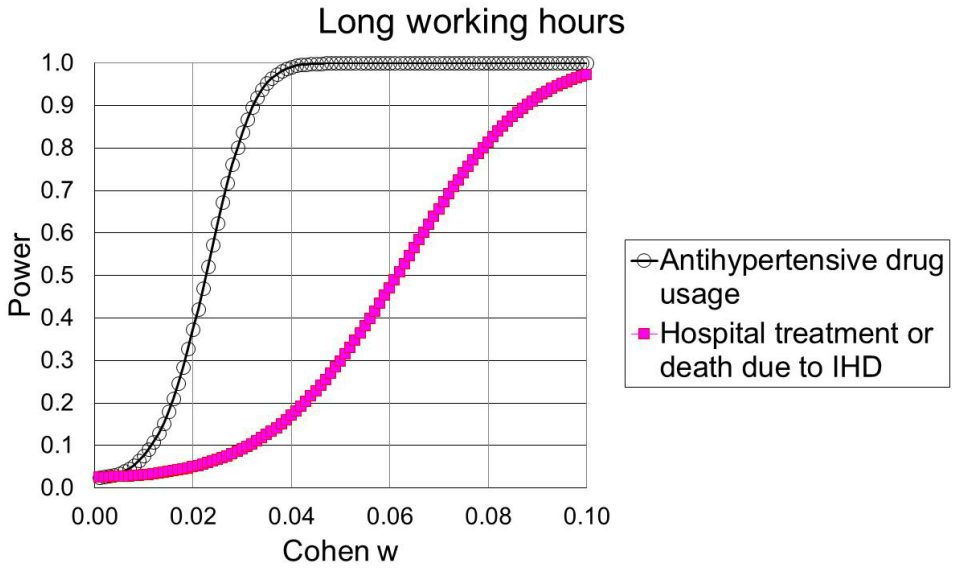
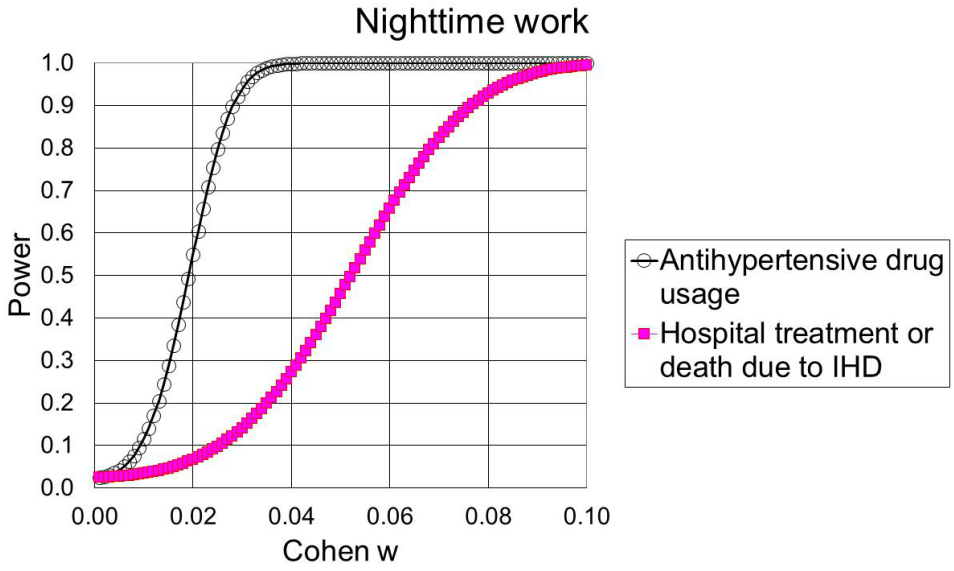


Figure 3. Power to detect that the examined incidences depend on nighttime work either as a general effect or as an effect of interaction with sex or socioeconomic status, as a function of Cohen w. IHD: ischemic heart disease.



Sensitivity Analysis 1

Since the questions used to obtain information about nighttime work and weekly working hours were revised in 2001 and then again in 2007, we will perform a sensitivity analysis with the results stratified by calendar period of interview (1999–2000, 2001–2006, and 2007–2013). The end point, covariates, and statistical model of the sensitivity analysis will be the same as the ones used to test hypotheses 1.1.4 and 2.1.3.

Sensitivity Analysis 2

To ascertain that an observed instance of hospital treatment during the follow-up is a new episode rather than a revisit in a course of treatment that was initiated before baseline, the primary analysis will exclude all workers who were treated for IHD sometime during the calendar year preceding baseline. It will, however, not exclude all former cases of IHD, and it is possible that the estimates of the primary analysis will be affected by nonexcluded workers who were treated for IHD more than 1 year earlier than baseline. We will address this issue with a sensitivity analysis, which will exclude all workers who received hospital treatment for IHD one or more times during a 5-year period prior to baseline. The analysis will include only those who were at least 20 years old and lived in Denmark throughout the 5-year period of interest. In all other respects, the design will be the same as the one used to test hypotheses 1.1.4 and 2.1.3.

Sensitivity Analysis 3

The actual working hours, that is, the hours worked during the reference week, constitute a well-defined quantity with minimal recall bias. The usual working hours are less well defined, and the way they are understood and remembered might vary between individuals. In spite of this drawback, we chose to base our analysis on the workers' usual rather than their actual working hours. We did so because some of the participants, by chance, would have worked less than usual during the reference week due to, for example, holidays, vacation, or sickness absence, while others would have worked more than usual due to, for example, a deadline or a temporary staff shortage. Since the usual working hours might be associated with recall bias, we will perform a sensitivity analysis in which we include only participants who belong to the same category according to their actual working hours as they do according to their usual working hours. In all other respects, the design will be the same as the one used to test hypotheses 1.1.4 and 2.1.3. Table 5 gives a -tabulation of the actual and usual working hours.

Table 5. Number of economically active 21- to 59-year-old participants, stratified by combinations of actual and usual weekly working hours.

Actual weekly working hours	Usual weekly working hours				
	0–31	32–40	41–48	>48	Total
Missing	187	56	16	19	278
0–31	31,094	32,748	2888	1545	68,275
32–40	2603	82,781	2762	788	88,934
41–48	462	10,981	8250	869	20,562
>48	413	5686	1956	6513	14,568
Total	34,759	132,252	15,872	9734	192,617

Statistics on Smoking, Overweight, and Obesity

It is recognized that the risk of IHD depends on a person's body mass index (BMI) and smoking habits. Among Danish employees, the RR for IHD has been estimated at 1.54 for current versus never smokers [40], at 1.41 for 25≤BMI<30 versus BMI<25, and at 2.69 for BMI≥30 versus BMI<25 kg/m^2[41].

Unfortunately, the Danish Labour Force Survey does not contain any information about the worker's weight and smoking habits, which makes us unable to control for these factors in our analyses. We therefore wanted to know in what direction and to what extent we can expect the estimates of the project to be influenced by differences in smoking habits and BMI. To shed some light on this issue, we compiled some descriptive statistics on the prevalence of smoking and high BMI in relation to long working hours and nighttime work among a random sample of employees in Denmark (Table 6,Table 7). The sample was drawn in 2010 and the data were collected by use of a mailed questionnaire. The response rate was 48% [42].

Table 6. Crude percentages of current smokers, persons with moderate overweight (25≤BMI[a]<30 kg/m^2), and persons with obesity (BMI≥30 kg/m^2), by working time arrangement, in a random sample of 20- to 59-year-old employees in Denmark, 2010.

Working time arrangements	Current smoker	25≤BMI<30	BMI≥30
	% (n/N)	% (n/N)	% (n/N)
32–40 working hours/week	22.4 (1205/5383)	33.8 (1821/5383)	12.9 (695/5383)
41–48 working hours/week	20.7 (255/1231)	36.1 (445/1231)	12.8 (157/1231)
>48 working hours/week	21.0 (141/671)	39.6 (266/671)	12.1 (81/671)
Without nighttime work	21.7 (1465/6766)	34.5 (2335/6766)	12.7 (858/6766)
With nighttime work	26.2 (136/519)	38.0 (197/519)	14.5 (75/519)

[a]BMI: body mass index.

Table 7. Age (10-year classes) and sex standardized percentages of current smokers, persons with moderate overweight (25≤BMI[a]<30 kg/m^2), and persons with obesity (BMI≥30 kg/m^2), by working time arrangement, in a random sample of 20- to 59-year-old employees in Denmark, 2010.

Working time arrangement	Current smoker		25≤BMI<30		BMI≥30	
	%	95% CI	%	95% CI	%	95% CI
32–40 working hours/week	22.6	21.5–23.7	34.7	33.4–35.9	12.9	12.1–13.9
41–48 working hours/week	21.0	18.8–23.5	34.8	32.2–37.5	12.5	10.7–14.5
>48 working hours/week	21.3	18.0–25.2	35.3	31.6–39.5	10.8	8.5–13.7
Without nighttime work	21.6	20.7–22.6	34.5	33.4–35.6	12.7	11.9–13.5
With nighttime work	25.8	22.3–30.0	38.4	34.5–42.8	15.4	12.5–19.0

[a]BMI: body mass index.

Table 7 suggests that the prevalence of smoking, overweight, and obesity tend to be higher among employees who work at night than among those who don't. To get an idea of the extent to which such differences may influence the RR of IHD between employees with and without nighttime work, we calculated an expected rate ratio, E[RR], under the assumption that the groups are equal in all respects other than the smoking and BMI distributions, using equation (2) (Figure 1).

Our calculations imply that a failure to control for smoking, overweight, and obesity (in a study population in which the prevalences are equal to those given in Table 7) would increase E[RR] of IHD between employees with and without nighttime work by a factor of 1.07.

Results

We expect results to be ready in mid-2017.

Discussion

This study protocol provides a detailed description of the hypotheses, inclusion criteria, significance levels, and statistical models of a project designed to estimate prospective associations between different types of work time arrangements and IHD in the general working population of Denmark.

Statistics Denmark randomly sampled the participants in the study from the target population and we have strengthened the prospective design by the strategy to exclude prevalent cases.

For nighttime work and long working hours, the statistical power is sufficient (compare [43]), and the nested hypothesis testing ensures that the probability that statistically significant findings will arise by chance alone is <5%.

Since the design of the project is being peer reviewed and published before the exposure data are linked to health data, we have eliminated hindsight and within-study selection bias. We have also eliminated bias from missing follow-up data, since

the clinical end points are ascertained through registers that cover the entire target population.

It has previously been shown that the incidence of IHD is highly dependent on age [44], sex [44], and SES [23,45,46] It has, moreover, been suggested that employment in the health care sector is associated with referral and prescription bias [23,47,48] Our statistical models will mitigate the bias from these factors, by incorporating them as control variables. We can, however, not rule out the possibility of bias due to factors that we cannot control for. For example, the EU Working Time Directive stipulates that night workers are entitled to a free health assessment, prior to their assignment and at regular intervals thereafter, and such a stipulation might be associated with detection bias [49].

Another drawback is that the definition of “night worker" that we use in this project differs from the legal definition that is used in the EU Working Time Directive. According to the Danish implementation of the directive, “nighttime" means any period of at least 7 hours, which includes the period between midnight and 5:00 AM, while “night worker" means “any worker, who, during nighttime, work at least three hours of his daily working time as a normal course" or “any worker who is likely to work at nighttime at least 300 hours during a period of twelve months" [50]. In contrast, our project classifies a participant as a night worker if she or he worked at night either regularly or occasionally during the 4-week period preceding the interview. Prior to 2007, the questionnaire did not specify how to interpret the response categories, but from 2007, “regularly" meant “more than half of the working days in the last 4 weeks," while “occasionally" meant “at least once within the last 4 weeks, but less than half of the working days." Hence, some of the night workers in this project would probably not qualify as night workers in a strictly legal sense.

In conclusion, this is an observational study, which cannot be used to confirm etiological hypotheses. It may, however, confirm that long working hours or nighttime work, or both, are predictors for IHD and thereby lend support to the hypothesis of a causal relationship.

Acknowledgments

The project was initiated by Otto Melchior Poulsen, former research director at the National Research Centre for the Working Environment (NRCWE). It is funded by the Danish taxpayers, through the Danish Work Environment Research Foundation, grant number 20130069288. The data of the project were and will be supplied by Statistics Denmark. Jesper Møller Pedersen and Simone Visbjerg Møller, NRCWE, helped us with project administration and data management.

We would like to thank the members of our advisory committee: Hermann Burr, Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA); Karen Albertsen, Team Working Life, Denmark; Martin Lindhart Nielsen, Bispebjerg Hospital, Denmark; Jan Hyld Pejtersen, Danish National Centre for Social Research; and Hans Bay, NRCWE.

We would also like to thank Mette Andersen Nexø, Elsa Bach, Elizabeth Bengtsen, Rikke Nilsson, Pia Gøtterup, Tina Norlén Thomsen, and Bodil Holst, NRCWE, for valuable advice and discussions.

Conflicts of Interest

None declared.

References

1. Evans G, Wener R, Phillips D. The morning rush hour, predictability and commuter stress. Environ Behav 2002;34:521-530.
2. Kluger A. Commute variability and strain. J Organiz Behav 1998;19:147-165.
3. Novaco RW, Stokols D, Campbell J, Stokols J. Transportation, stress, and community psychology. Am J Community Psychol 1979 Aug;7(4):361-380. [Medline: 495580]
4. Peters A, von Klot S, Heier M, Trentinaglia I, Hörmann A, Wichmann HE, Cooperative Health Research in the Region of Augsburg Study Group. Exposure to traffic and the onset of myocardial infarction. N Engl J Med 2004 Oct 21;351(17):1721-1730. [doi: 10.1056/NEJMoa040203] [Medline: 15496621]
5. Peters A, von Klot S, Mittleman MA, Meisinger C, Hörmann A, Kuch B, et al. Triggering of acute myocardial infarction by different means of transportation. Eur J Prev Cardiol 2013 Oct;20(5):750-758. [doi: 10.1177/2047487312446672] [Medline: 22544548]
6. BBC. BBC News. 2000 Nov 01. Commuting is 'Biggest Stress' URL: http://news.bbc.co.uk/2/hi/health/999961.stm [accessed 2016-06-10] [WebCite Cache ID 6gXak1EKF]
7. Andersen I, Osler M, Petersen L, Grønbaek M, Prescott E. Income and risk of ischaemic heart disease in men and women in a Nordic welfare country. Int J Epidemiol 2003 Jun;32(3):367-374 [FREE Full text] [Medline: 12777421]
8. Steptoe A, Brydon L, Kunz-Ebrecht S. Changes in financial strain over three years, ambulatory blood pressure, and cortisol responses to awakening. Psychosom Med 2005;67(2):281-287. [doi: 10.1097/01.psy.0000156932.96261.d2] [Medline: 15784795]
9. Rosengren A, Hawken S, Ounpuu S, Sliwa K, Zubaid M, Almahmeed WA, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. Lancet 2004;364(9438):953-962. [doi: 10.1016/S0140-6736(04)17019-0] [Medline: 15364186]

10. Akerstedt T. Shift work and disturbed sleep/wakefulness. Occup Med (Lond) 2003 Mar;53(2):89-94 [FREE Full text] [Medline: 12637592]
11. Laugsand LE, Vatten LJ, Platou C, Janszky I. Insomnia and the risk of acute myocardial infarction: a population study. Circulation 2011 Nov 8;124(19):2073-2081 [FREE Full text] [doi: 10.1161/CIRCULATIONAHA.111.025858] [Medline: 22025601]
12. Cappuccio FP, Cooper D, D'Elia L, Strazzullo P, Miller MA. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. Eur Heart J 2011 Jun;32(12):1484-1492 [FREE Full text] [doi: 10.1093/eurheartj/ehr007] [Medline: 21300732]
13. van Leeuwen WM, Lehto M, Karisola P, Lindholm H, Luukkonen R, Sallinen M, et al. Sleep restriction increases the risk of developing cardiovascular diseases by augmenting proinflammatory responses through IL-17 and CRP. PLoS One 2009;4(2):e4589 [FREE Full text] [doi: 10.1371/journal.pone.0004589] [Medline: 19240794]
14. Haack M, Serrador J, Cohen D, Simpson N, Meier-Ewert H, Mullington JM. Increasing sleep duration to lower beat-to-beat blood pressure: a pilot study. J Sleep Res 2013 Jun;22(3):295-304 [FREE Full text] [doi: 10.1111/jsr.12011] [Medline: 23171375]
15. Spiegel K, Leproult R, Van CE. Impact of sleep debt on metabolic and endocrine function. Lancet 1999 Oct 23;354(9188):1435-1439. [doi: 10.1016/S0140-6736(99)01376-8] [Medline: 10543671]
16. Frost P, Kolstad HA, Bonde JP. Shift work and the risk of ischemic heart disease - a systematic review of the epidemiologic evidence. Scand J Work Environ Health 2009 May;35(3):163-179 [FREE Full text] [Medline: 19387517]
17. Ha J, Kim S, Paek D, Park J. The Magnitude of Mortality from Ischemic Heart Disease Attributed to Occupational Factors in Korea - Attributable Fraction Estimation Using Meta-analysis. Saf Health Work 2011 Mar;2(1):70-82 [FREE Full text] [doi: 10.5491/SHAW.2011.2.1.70] [Medline: 22953190]
18. Vyas MV, Garg AX, Iansavichus AV, Costella J, Donner A, Laugsand LE, et al. Shift work and vascular events: systematic review and meta-analysis. BMJ 2012;345:e4800 [FREE Full text] [Medline: 22835925]
19. Virtanen M, Heikkilä K, Jokela M, Ferrie JE, Batty GD, Vahtera J, et al. Long working hours and coronary heart disease: a systematic review and meta-analysis. Am J Epidemiol 2012 Oct 1;176(7):586-596 [FREE Full text] [doi: 10.1093/aje/kws139] [Medline: 22952309]
20. Thornton A, Lee P. Publication bias in meta-analysis: its causes and consequences. J Clin Epidemiol 2000 Feb;53(2):207-216. [Medline: 10729693]
21. Kivimäki M, Jokela M, Nyberg ST, Singh-Manoux A, Fransson EI, Alfredsson L, IPD-Work Consortium. Long working hours and risk of coronary heart disease and stroke: a systematic review and meta-analysis of published and unpublished data for 603,838 individuals. Lancet 2015 Oct 31;386(10005):1739-1746 [FREE Full text] [doi: 10.1016/S0140-6736(15)60295-1] [Medline: 26298822]
22. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009;338:b1665 [FREE Full text] [Medline: 19454737]
23. Hannerz H, Dalhoff K, Burr H, Latza U. Correlation between relative rates of hospital treatment or death due to ischaemic heart disease (IHD) and of IHD-related medication among socio-occupational and economic activities groups in Denmark, 1996-2005. Int J Occup Med Environ Health 2014 Aug;27(4):536-546 [FREE Full text] [doi: 10.2478/s13382-014-0276-6] [Medline: 25008851]
24. Latza U, Rossnagel K, Hannerz H, Burr H, Jankowiak S, Backé E. Association of perceived job insecurity with ischemic heart disease and antihypertensive medication in the Danish Work Environment Cohort Study 1990-2010. Int Arch Occup Environ Health 2015 Nov;88(8):1087-1097 [FREE Full text] [doi: 10.1007/s00420-015-1030-5] [Medline: 25731852]
25. Pedersen CB. The Danish Civil Registration System. Scand J Public Health 2011 Jul;39(7 Suppl):22-25. [doi: 10.1177/1403494810387965] [Medline: 21775345]
26. Petersson F, Baadsgaard M, Thygesen LC. Danish registers on personal labour market affiliation. Scand J Public Health 2011 Jul;39(7 Suppl):95-98. [doi: 10.1177/1403494811408483] [Medline: 21775363]
27. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scand J Public Health 2011 Jul;39(7 Suppl):30-33. [doi: 10.1177/1403494811401482] [Medline: 21775347]
28. Helweg-Larsen K. The Danish Register of Causes of Death. Scand J Public Health 2011 Jul;39(7 Suppl):26-29. [doi: 10.1177/1403494811399958] [Medline: 21775346]
29. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. Scand J Public Health 2011 Jul;39(7 Suppl):38-41. [doi: 10.1177/1403494810394717] [Medline: 21775349]
30. Statistics Denmark. Arbejdskraftundersøgelsen. 2015. URL: http://www.dst.dk/da/statistik/dokumentation/statistikdokumentation/arbejdskraftundersoegelsen [accessed 2016-06-16] [WebCite Cache ID 6gXb0sUA8]
31. World Health Organization. International Statistical Classification of Diseases and Related Health Problems, 10th revision, edition 2010. Volume 2: Instruction Manual. Geneva: WHO; 2011. URL: http://www.who.int/classifications/icd/ICD10Volume2_en_2010.pdf [WebCite Cache ID 6gXbIvwq5]
32. Kleppa E, Sanne B, Tell GS. Working overtime is associated with anxiety and depression: the Hordaland Health Study. J Occup Environ Med 2008 Jun;50(6):658-666. [doi: 10.1097/JOM.0b013e3181734330] [Medline: 18545093]

33. Hannerz H, Albertsen K. Long working hours and subsequent use of psychotropic medicine: a study protocol. JMIR Res Protoc 2014;3(3):e51 [FREE Full text] [doi: 10.2196/resprot.3301] [Medline: 25239125]
34. Statistics Denmark. Dansk Branchekode 1993, udgave 2. 1996. URL: http://www.dst.dk/da/Statistik/Publikationer/VisPub?cid=4829 [accessed 2016-06-10] [WebCite Cache ID 6gXbVnZrB]
35. Statistics Denmark. Dansk branchekode 2003 - DB03. 2002. URL: http://www.dst.dk/Site/Dst/Udgivelser/GetPubFile.aspx?id=5132&sid=forside [accessed 2016-06-10] [WebCite Cache ID 6gXbcPhQg]
36. Statistics Denmark. Dansk branchekode 2007 - DB07. 2007. URL: http://www.dst.dk/Site/Dst/Udgivelser/GetPubFile.aspx?id=11119&sid=helepubl [WebCite Cache ID 6gXbqjRSv]
37. Statistics Denmark. DISCO-88 - Danmarks Statistiks Fagklassifikation. 1996. URL: http://www.dst.dk/da/Statistik/dokumentation/Nomenklaturer/DISCO-88 [WebCite Cache ID 6gvys9Mxb]
38. Statistics Denmark. DISCO-08 - Danmarks Statistiks Fagklassifikation. 2011. URL: https://www.dst.dk/Site/Dst/Udgivelser/GetPubFile.aspx?id=16711&sid=disco [accessed 2016-06-10] [WebCite Cache ID 6gvyaioQD]
39. Cohen J. Statistical Power Analysis for the Behavioral Sciences. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.
40. Møller S. [A Follow-up Study of Sedentary Work and Ischemic Heart Disease]. Copenhagen: University of Copenhagen; 2013. URL: https://figshare.com/articles/New_draft_item/3187753 [WebCite Cache ID 6gvzEyrG1]
41. Hannerz H, Holtermann A. Heavy lifting at work and risk of ischemic heart disease: protocol for a register-based prospective cohort study. JMIR Res Protoc 2014;3(3):e45 [FREE Full text] [doi: 10.2196/resprot.3270] [Medline: 25164612]
42. Bach E, Andersen L, Bjørner J, Borg V, Clausen T, Flyvholm M, et al. Arbejdsmiljø og Helbred i Danmark 2010. Resumé og Resultater. Copenhagen: National Research Centre for the Working Environment; 2011. URL: http://www.arbejdsmiljoforskning.dk/~/media/Forside/Arbejdsmiljoedata/Arbejdsmiljo-og-helbred-2010/Samlet-rapport-Arbejdsmiljoe-og-helbred-i-DK-2010.pdf [accessed 2016-06-10] [WebCite Cache ID 6gvzNGcXc]
43. Pejtersen JH, Burr H, Hannerz H, Fishta A, Hurwitz EN. Update on work-related psychosocial factors and the development of ischemic heart disease: a systematic review. Cardiol Rev 2015;23(2):94-98. [doi: 10.1097/CRD.0000000000000033] [Medline: 24979202]
44. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, American Heart Association Statistics Committee Stroke Statistics Subcommittee. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation 2015 Jan 27;131(4):e29-322. [doi: 10.1161/CIR.0000000000000152] [Medline: 25520374]
45. Avendano M, Kunst AE, Huisman M, Lenthe FV, Bopp M, Regidor E, et al. Socioeconomic status and ischaemic heart disease mortality in 10 western European populations during the 1990s. Heart 2006 Apr;92(4):461-467 [FREE Full text] [doi: 10.1136/hrt.2005.065532] [Medline: 16216862]
46. Tüchsen F, Endahl LA. Increasing inequality in ischaemic heart disease morbidity among employed men in Denmark 1981-1993: the need for a new preventive policy. Int J Epidemiol 1999 Aug;28(4):640-644 [FREE Full text] [Medline: 10480690]
47. Soll-Johanning H, Hannerz H, Tüchsen F. Referral bias in hospital register studies of geographical and industrial differences in health. Dan Med Bull 2004 May;51(2):207-210. [Medline: 16009057]
48. Tüchsen F, Andersen O, Olsen J. Referral bias among health workers in studies using hospitalization as a proxy measure of the underlying incidence rate. J Clin Epidemiol 1996 Jul;49(7):791-794. [Medline: 8691230]
49. European Parliament, Council of the European Union. Directive 2003/88/EC of The European Parliament and of The Council of 4 November 2003 concerning certain aspects of the organisation of working time. Official J Eur Union 2003;299:9-19.
50. Beskæftigelsesministeriet. Bekendtgørelse af lov om gennemførelse af dele af arbejdstidsdirektivet. Lov nr. 258 af 8/4/2003. [The Act on Implementation of Parts of the Working Time Directive. Act no. 258 af 8/4/2003]. [In Danish]. 2003. URL: https://www.retsinformation.dk/forms/r0710.aspx?id=30093 [accessed 2016-06-10] [WebCite Cache ID 6iANBaY5h]

Abbreviations

ATC: Anatomical Therapeutic Chemical Classification System
BMI: body mass index
DISCO-88: Danish version of the International Standard Classification of Occupations
E[RR]: expected rate ratio
ESeC: European Socio-economic Classification
EU: European Union
ICD-10: International Classification of Diseases, Tenth Revision
IHD: ischemic heart disease
ISCO-88: International Standard Classification of Occupations
RR: rate ratio
SES: socioeconomic status

Edited by G Eysenbach; submitted 25.01.16; peer-reviewed by JA Lie, K Albertsen; comments to author 02.03.16; revised version received 21.04.16; accepted 21.04.16; published 22.06.16.

Please cite as:
Hannerz H, Larsen AD, Garde AH
Working Time Arrangements as Potential Risk Factors for Ischemic Heart Disease Among Workers in Denmark: A Study Protocol
JMIR Res Protoc 2016;5(2):e130
URL: http://www.researchprotocols.org/2016/2/e130/
doi:10.2196/resprot.5563
PMID:27335284

Protocol

Early Monitoring of Response (MORE) to Golimumab Therapy Based on Fecal Calprotectin and Trough Serum Levels in Patients With Ulcerative Colitis: A Multicenter Prospective Study

Attyla Drabik[1], MD; Andreas Sturm[2], PhD, MD; Margit Blömacher[3], PhD; Ulf Helwig[4], Phd, MD

[1]Clinical Trial Support, Münster, Germany

[2]DRK Kliniken Berlin Westend, Department of Gastroenterology, Berlin, Germany

[3]Kompetenznetz Darmerkrankungen e. V., Kiel, Germany

[4]Medical Practice for Internal Medicine Oldenburg, Oldenburg, Germany

Corresponding Author:
Ulf Helwig, Phd, MD
Medical Practice for Internal Medicine Oldenburg
Neue Donnerschweer Straße 30
Oldenburg, 26123
Germany
Phone: 49 441 361 3150
Fax: 49 441 382 744
Email: helwig@internisten-ol.de

Abstract

Background: The treatment of ulcerative colitis (UC) patients with moderate to severe inflammatory activity with anti-tumor necrosis factor alpha (TNFα) antibodies leads to a clinical remission rate of 10% after 8 weeks of therapy. However, it must be taken into account that patient selection in clinical trials clearly influences both response and remission rates. An unsatisfactory response to anti-TNFα medication after week 12 often leads to a discontinuation of treatment. The early prediction of clinical response could therefore help optimize therapy and potentially avoid ineffective treatments.

Objective: The aim of this study is to develop an algorithm for optimizing golimumab administration in patients with moderate to severe UC by calculating the probability of clinical response in Week 26 based on data from Week 6.

Methods: The study is designed as a prospective, single-arm, multicenter, non-interventional observational study with no interim analyses and a sample size of 58 evaluable patients. The primary outcome is the prediction of clinical response in Week 26 based on a 50% reduction in fecal calprotectin and a positive golimumab trough level in Week 6.

Results: Enrollment started in October 2014 and was still open at the date of submission. The study is expected to finish in December 2016.

Conclusions: The early identification of patients who are responding to an anti-TNFα antibody is therapeutically beneficial. At the same time, patients who are not responding can be identified earlier. The development of a therapeutic algorithm for identifying patients as responders or non-responders can thus help prescribing physicians to both avoid ineffective treatments and adjust dosages when necessary. This in turn promotes a higher degree of treatment tolerance and patient safety in the case of anti-TNFα antibody administration.

ClinicalTrial: German Clinical Trials Register, Deutsches Register Klinischer Studien DRKS00005940; https://drks-neu.uniklinik-freiburg.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00005940 (Archived by WebCite at http://www.webcitation.org/6i4Xoo1sH)

(JMIR Res Protoc 2016;5(2):e124) doi:10.2196/resprot.5791

KEYWORDS

ulcerative colitis; golimumab; fecal calprotectin; tumor necrosis factor alpha

Introduction

Background

The treatment of ulcerative colitis (UC) patients with moderate to severe inflammatory activity with anti-tumor necrosis factor alpha (TNFα) antibodies leads to a clinical remission rate of 10% (ULTRA1 study, 80/40 mg adalimumab) [1] to 39% (ACT1 study, infliximab 5 mg/kg body weight [2] and SUCCESS study [3]) after 8 weeks of therapy. However, it must be taken into account that patient selection in clinical trials clearly influences both response and remission rates. In addition, the results of these studies are not consistent with those of observational trials with a high degree of target population representativeness. International guidelines therefore recommend that the success of an anti-TNFα therapy beyond the 12-week mark must be predicted as soon as possible in order to adjust or discontinue treatment depending on the clinical situation [1,4-6]. An unsatisfactory response to anti-TNFα medication after Week 12 often leads to a discontinuation of treatment. The early prediction of clinical response could therefore help to optimize therapy and potentially avoid ineffective treatments [7].

In this regard, the PURSUIT study showed that the administration of the new human anti-TNFα immunoglobulin G1 monoclonal antibody golimumab to subjects with moderately to severely active UC induced clinical response in Week 6 after two injections (Weeks 0 and 2) in 51.0-54.9% of patients in a randomized clinical trial, whereas placebo response was 30.3% (P<.001) [8].

After 6 weeks, responders in the golimumab group were randomized again to receive either placebo or 50 or 100 mg golimumab doses every 4 weeks for a further 54 weeks. The analysis of clinical response in this trial showed a statistically significant response for golimumab 50 mg versus placebo (P<.001) after 54 weeks (47.0% and 31.2% respectively) [9].

Study Objective

This early Monitoring of Response (MORE) study (DRKS00005940) seeks to achieve a more thorough understanding of therapeutic development in patients with moderate to severe ulcerative colitis receiving regular doses of golimumab. The aim is to develop an algorithm for optimizing golimumab administration in patients with moderate to severe ulcerative colitis by calculating the probability of clinical response in Week 26 based on data from Week 6.

Methods

Trial Design

The study is carried out in conformity with the German Medicinal Products Act (Arzneimittelgesetz, AMG) and is a non-interventional study in accordance with the Medicinal Products Act (§ 4 section 23 p. 3 AMG). The study is designed as a prospective, single-arm, multicenter, non-interventional observational study with no interim analyses and a sample size of 58 evaluable patients, for which 61 patients must be recruited.

Outcomes

Primary

The primary outcome is the prediction of clinical response in Week 26 based on a 50% reduction in fecal calprotectin and a positive golimumab trough level of >2.5 µg/ml in Week 6.

Our definition of a clinical response is a reduction in the partial Mayo score by 2 points between baseline and Week 6, or a partial Mayo score of ≤1 in Week 6.

Secondary

In addition to the primary study goal, the following secondary outcomes are analyzed:

1. At which point in time is a 50% reduction in fecal calprotectin a reliable predictor of response?

2. How strong is the correlation between antibody towards golimumab (ATG) level and fecal calprotectin level?

3. How strong is the correlation between ATG and the partial Mayo score?

4. How strong is the correlation between golimumab trough level and fecal calprotectin?

5. How strong is the correlation between golimumab trough level and the partial Mayo score?

6. Do the following parameters exert any influence on clinical response?

   a) C-reactive protein (CRP)

   b) white blood cells (WBC) count

   c) hemoglobin

   d) platelet count

   e) ferritin

7. Frequency of adverse reactions

Statistics

Analysis

Our aim is to study the detection of a positive trough level of golimumab of >2.5 µg/ml and a significant reduction in fecal calprotectin of 50% from baseline in Week 6 as a reliable predictor for clinical response in Week 26 during long-term treatment with golimumab. In this connection, a level between 2.5 µg/ml and 4.3 µg/ml is regarded as being associated with a therapeutic effect of golimumab [8,9].

Statistical analysis is mainly carried out with descriptive methods such as frequency tables, and statistical parameters such as mean, standard deviation, and quantiles. Bar graphs are used for qualitative data and box-and-whisker plots for quantitative data. In addition, inferential statistical analysis is carried out with relevant significance tests and confidence intervals. Missing data are not imputed.

In order to evaluate the primary outcome, the test problem presented in the section on statistical hypotheses is formulated and solved. The test is carried out with a power of 80% and a

two-tailed significance level of alpha=.05. Analysis is carried out with a logistic regression model based on the percentage change of fecal calprotectin and golimumab trough levels. In addition, secondary parameters (eg, ATGs, CRP, WBC) are also analyzed to identify further correlations between the data of Week 6 and therapy outcome in Week 26. The aim is to identify further constraints to the statistical model in order to take into account all relevant parameters in the final version of the algorithm. Secondary outcomes are assessed in an explorative way, that is, no pre-formulated hypotheses are tested. The *P* values obtained are thus interpreted according to Fisher's method: a *P* value is considered a metric value, and the smaller the *P* value, the larger the significance of the corresponding effect. No interim analyses are planned. Data analysis is carried out only once, at the end of the study.

Hypotheses

The following two-tailed test problem is used for the primary outcome:

Hypothesis 0: beta1=0 versus Hypothesis 1: beta1≠0, where beta1 is the coefficient of the logistic regression model, and null hypothesis: H0. There is no correlation between a significant reduction in fecal calprotectin of 50% from baseline in Week 6 and clinical response to therapy with golimumab in Week 26.

Therefore, our research hypothesis, H1, is that there is a correlation between a significant reduction in fecal calprotectin of 50% from baseline in Week 6 and clinical response to therapy with golimumab in Week 26.

Sample Size

Rationale

Sample size is planned based on data from studies researching a correlation between fecal calprotectin and response to an anti-TNFα therapy.

De Vos et al [10] describe response rates as: "After 10 weeks anti-TNFα therapy induced endoscopic remission in 63% (confidence interval: 47–78%) of patients". Molander et al [11] describe the correlation between the predictive quality of fecal calprotectin and the remission rate. The results are displayed in Table 1.

Table 1. Cross classification of fecal calprotectin predictive quality and remission.

	Fecal calprotectin decline		Total
	Yes	No	
Remission			
Yes	30	3	33
No	6	21	27
Total	36	24	60

Based on these results, the odds ratio (OR) is calculated as OR (30*21) / (6*3)=35. It should be noted that for the above study the cut-off point for fecal calprotectin decline was a reduction of >75% from baseline. Lower cut-off points, for example, a 50% reduction, would lead to smaller OR, as the number of patients with neither decline nor response is described as being almost constant in the above-mentioned literature: "Absence of decrease in calprotectin levels at week 6 identified patients resistant to the treatment" [11]. It is therefore assumed for sample size calculation that 80% of the patients will have a "fecal calprotectin decline." Table 2 summarizes the scenarios that have been taken into consideration.

Table 2. Sample size rationale: Response rates and their effect on resulting OR for 9 different scenarios.

Scenario	Response rate (%)	OR
1	40	10
2	40	20
3	40	30
4	50	10
5	50	20
6	50	30
7	60	10
8	60	20
9	60	30

Calculation

Sample size calculation is carried out with the statistical analysis software SAS. Table 3 shows the required number of evaluable patients for each scenario. It is expected that 5% of the intention-to-treat principle population will be excluded. Sample size is inversely proportional to the OR and the response rate.

Table 3. Sample size calculation: Number of evaluable subject and total number of subjects considering dropouts for 9 different scenarios.

Scenario	Response rate, %	OR	Evaluable subjects, n	Subjects including potential dropouts, total n
1	40	10	58	61
2	40	20	40	42
3	40	30	34	36
4	50	10	50	53
5	50	20	34	36
6	50	30	29	31
7	60	10	45	48
8	60	20	31	33
9	60	30	26	28

To prevent study failure due to an underpowered study, a worst case scenario with a response rate of 40% and an OR of 10 is used as a basis for sample size. A total of 58 evaluable subjects are therefore necessary for the trial, thus 61 patients must be recruited.

Study Population

The evaluation of primary and secondary outcomes is carried out according to the intention-to-treat principle. The corresponding population comprises all patients included in the study regardless of possible protocol violations (eg, dropouts). In addition to intention-to-treat analysis, sensitivity analysis according to the per-protocol principle is carried out. Relevant protocol violations leading to exclusion from the per-protocol group are defined in the statistical analysis plan.

Selection of Study Centers

All study centers are part of the German Inflammatory Bowel Disease (IBD) Study Group and are chosen according to their main area of focus and their experience in the treatment of UC. By signing the investigator agreement, each study center selected confirms its fulfilment of all formal requirements for inclusion in the study and guarantees its compliance with data privacy laws and any other regulations pertaining to the execution of this observational study.

Participant Criteria

The inclusion criteria for the study include (1) clinically and endoscopically confirmed diagnosis of UC, (2) study-independent treatment with golimumab according to current medical practices, (3) age ≥18 years, (4) sufficient German language communication skills, (5) ability of the patient to understand the nature, significance, and scope of the clinical trial and make an independent decision based on this knowledge, and (6) elevated calprotectin levels (≥100 mg/L or ≥100 mg/kg) within 3 weeks prior to inclusion.

Our exclusion criteria include (1) infectious colitis, (2) off-label treatment with golimumab, or (3) treatment with golimumab within the previous 3 months.

Study-Specific Interventions

No medical interventions are carried out in the course of the study other than those required by standard medical procedure. When taking routine blood samples, golimumab serum levels and ATG levels should also be monitored if possible. Only the natural progress of the disease in UC patients is monitored and evaluated.

Schedule of Visits

There are no defined study visits. In the course of the study, the only clinical and laboratory data recorded are those corresponding to standard medical procedure. Data are recorded in the following observational weeks: baseline, 2, 6, 14, 22, and 26. Deviations of +/- 3 days from this documentation schedule fall within the scope of the study protocol. The period until the next examination is subsequently shortened or lengthened accordingly in order to compensate for deviations and maintain the examination rhythm.

The following data are recorded at the initial screening/baseline examination: date of consent, screening date, inclusion and exclusion criteria, personal information (date of birth, sex, height, weight), date of initial diagnosis, information regarding prior anti-TNFα medication, partial Mayo score, laboratory tests (hemoglobin, WBC, platelet, ferritin, CRP, fecal calprotectin, and ATG), and medication (dose of golimumab, cortisone, and azathioprine).

The following data are recorded during each subsequent examination (week 2, 6, 14, 22, and 26) in the course of the study: partial Mayo score, laboratory tests (hemoglobin, WBC, platelet, ferritin, CRP, and fecal calprotectin), and medication (dose of golimumab, cortisone, and azathioprine). In addition, in Weeks 2 and 6, golimumab trough serum levels and ATG are measured.

Documentation

Data are recorded using case report forms (CRF). The investigator is responsible for the timely, correct, complete, and legible recording of study data in the CRF and confirms recording by signature. CRF are completed with a black ballpoint pen. Corrections are documented as follows. The wrong entry is crossed out with a single line, and corrections

are entered next to the crossed-out text and verified by date and initials, stating the reason for the change if necessary. Instructions for use (entry and corrections) are included in each CRF. Source data according to the ICH E6 guideline on good clinical practice (GCP) are original documents in patient files, as well as doctors' letters, certified copies of original records, and laboratory printouts. In addition, all patient questionnaires (self-reporting) are also considered source data. Study data are to be recorded from patient files.

Patient Identification

All patient data are pseudonymized. Each patient will be clearly identified by a patient identification number assigned at each study center. The investigator will keep a patient identification list documenting the patient identification number with the patient's full name, date of birth, sex, and date of informed consent.

The patient identification list is part of the investigator file and will remain at the clinic. The patient identification number consists of a 2-digit clinic number, a hyphen, and a running 3-digit number of recruited patients per study center.

Trial

Start of Patient Participation

Any patient with a clinically and endoscopically confirmed diagnosis of UC and qualified for golimumab treatment according to routine medical practice is a potential study candidate. All potential candidates who come to the attention of the investigator will be informed regarding the possibility of participating in the study. Potential candidates interested in participating in the study will be promptly informed about the study in order to obtain their informed consent in accordance with the section "Patient Information and Informed Consent".

End of Patient Participation

The observation of each patient ends according to the schedule with the last study visit. A patient's participation in the study will be terminated prematurely if at least one of the following criteria is met: (1) withdrawal of informed consent, (2) termination of golimumab treatment, (3) lack of medical justification for further participation in the study, (4) premature termination of the complete trial, or (5) subsequent discovery that not all inclusion criteria are met and/or that any exclusion criteria are met.

Trial Duration/End of Trial

The recruiting phase has a planned duration of 18 months. The observational phase has a planned duration of 26 weeks. The complete trial is considered to have ended after all queries from the study coordination center have been answered by each individual study center, but at the latest 4 months after the last visit of the last patient.

Study centers that grossly violate the AMG, data protection regulations, or the GCP guidelines can be excluded from the further recruitment and observation of study patients. Premature termination of the study as a whole will be taken into consideration if ethical or scientific justification for the trial is compromised or no longer valid, errors or violations significantly compromise the scientific integrity of the data collected for the study with regard to the study aims, or the requirements for a successful execution of the study are no longer fulfilled for other reasons.

The principal investigator will consult the corresponding biometrician regarding any possible premature termination of the trial. The minutes of the aforementioned consultation meeting will be recorded and subjected to the approval of both parties. Any decision regarding the premature termination of the trial will be taken jointly by the principal investigator and the corresponding biometrician.

Data Quality Assurance

Upon receipt at the study coordination center, CRF will be checked for completeness and consistency (in-house review). Queries will be generated for missing or implausible entries and sent to the corresponding study centers. After the clarification of implausible entries and completion of missing data, CRF will be handed over to the corresponding data management department for data entry.

Quality Control and Assurance

Quality control in the study is ensured by the possibility of monitoring the study centers involved. For each monitoring visit, a monitoring report is generated documenting the progress of the observational study and describing any problems that may have arisen. The exact nature and extent of the monitoring activities are described in a separate monitoring manual. All investigators declare their consent to regular visits of study monitors to the study centers. In addition, they must provide direct access to all necessary study documents, including original patient documents relevant to the study. The principal investigator and/or auditors designated by the principal investigator are entitled to conduct audits at the study centers and any other facilities participating in the study. They are entitled to inspect and review all study-relevant documents. This right also applies to regulatory inspectors.

Ethical and Regulatory Aspects

The study is conducted in compliance with the current version of the Declaration of Helsinki (10/2013, Fortaleza, Brazil). This study cannot begin before approval has been obtained from the corresponding ethics committee. Prior to inclusion in the study, the investigator will inform each patient about the nature, significance, risks, and scope of the study, as well as the patient's right to withdraw from the study at any time without prejudice. An informed consent form is handed to the patient describing the study in non-scientific and generally understandable language. Each patient must consent to study participation in writing. The patient must be provided with ample time to make a decision and given the opportunity to ask any questions before the consent form is signed. In accordance with AMG, § 40 Abs. 2a, patients are informed that the data related to their disease will be stored with a pseudonym and analyzed for scientific purposes. Patients must consent to the use of their pseudonymized data in writing. Informed consent forms are to be signed and dated by the patient and the treating physician.

This clinical study is carried out in conformity with the requirements of the current German Medicinal Products Act, as well as all applicable legal provisions regarding data protection and the GCP guidelines. The general notification requirement as per § 67 AMG will be complied with.

Results

Enrollment started in October 2014 and was still open at the date of submission. The study is expected to finish in December 2016.

Discussion

Rationale for the Trial

The early identification of patients who are responding well to an anti-TNFα-antibody is therapeutically beneficial. At the same time, patients who are not responding can be identified earlier. The development of a therapeutic algorithm for identifying patients as responders or non-responders can help prescribing physicians both to avoid ineffective treatments and to adjust dosages when necessary. This in turn would promote a higher degree of treatment tolerance and patient safety in the case of anti-TNFα antibody administration.

There is a clear association between detectable trough levels of anti-TNFα inhibitors and clinical therapeutic response. On the other hand, the detection of anti-drug antibodies is associated with a poor response.

Fecal calprotectin levels reflect mucosal inflammation status. The strong correlation between high fecal calprotectin and mucosal inflammation has been widely described. Furthermore, it is also clear that fecal calprotectin levels decrease if there is therapeutic response.

A regular question among IBD patients is how long they will have to take their medication in total. Yet there is currently insufficient data regarding optimal treatment length with TNFα inhibitors. In view of the elevated costs and possible side effects associated with this type of treatment, it is desirable to clearly define a patient population for which continued therapy is justifiable.

Justifications for Trial Design

This study is prospective, as the aim is to use the data from trial Week 6 to calculate the probability of clinical response in Week 26. Only one study cohort is required to answer this question, and no comparison group is necessary.

In order to achieve a higher degree of representativeness of the results for the intended population, the trial is carried out throughout Germany and at multiple centers specifically chosen for this purpose. Treatment, including diagnosis and monitoring, does not follow a predefined study protocol and is carried out exclusively in accordance with current medical practices. The aim of this non-interventional approach is to ensure a high degree of representativeness of the study results for daily medical practice.

Conclusion

This early Monitoring of Response (MORE) study aims to achieve a more thorough understanding of therapeutic development in patients with moderate to severe ulcerative colitis receiving regular doses of golimumab by developing an algorithm for optimizing golimumab administration in patients with moderate to severe ulcerative colitis.

Acknowledgments

This study is supported by MSD Sharp & Dohme GmbH (Haar, Germany) and the German IBD Study Group (Kiel, Germany).

The authors are grateful to all parties involved in the study, the study coordinating center German IBD Study Group, the sites, and the participants.

Authors' Contributions

All authors contributed to design of the study protocol, revision of draft article, and final approval of version to be published.

Conflicts of Interest

UH has received a Lecture/Advisory board honorarium from MSD; AbbVie, Falk Foundation, Takeda, Mundipharma, Hospira, Ferring. AS has received a Lecture/Advisory board honorarium from Falk Foundation, Recordati, Astellas, Hospira, Mundipharma, MSD, Takeda, Jannsen.

References

1. Reinisch W, Sandborn WJ, Hommes DW, D'Haens G, Hanauer S, Schreiber S, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut 2011 Jun;60(6):780-787. [doi: 10.1136/gut.2010.221127] [Medline: 21209123]
2. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005 Dec 8;353(23):2462-2476. [doi: 10.1056/NEJMoa050516] [Medline: 16339095]

3. Panaccione R, Ghosh S, Middleton S. ECCO meeting 2011. Infliximab, azathioprine or infliximab + azathioprine for treatment of moderate to severe ulcerative colitis: The UC SUCCESS trial URL: https://www.ecco-ibd.eu/publications/congress-abstract-s/abstracts-2011/item/13.html [accessed 2016-06-01] [WebCite Cache ID 6hw8WAZVB]
4. Reinisch W, Sandborn W, Kumar A. 52-week clinical efficacy with adalimumab in patients with moderately to severely active ulcerative colitis who failed corticosteroids and/or immunosuppressants. J Crohns Colitis 2011;5:10-15. [doi: 10.1097/MIB.0b013e318281f2b7] [Medline: 23665965]
5. Dignass A, Lindsay JO, Sturm A, Windsor A, Colombel J, Allez M, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. J Crohns Colitis 2012 Dec;6(10):991-1030 [FREE Full text] [doi: 10.1016/j.crohns.2012.09.002] [Medline: 23040451]
6. Sandborn WJ, van AG, Reinisch W, Colombel J, D'Haens G, Wolf DC, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2012 Feb;142(2):257-265.e1. [doi: 10.1053/j.gastro.2011.10.032] [Medline: 22062358]
7. Cornillie F, Hanauer SB, Diamond RH, Wang J, Tang KL, Xu Z, et al. Postinduction serum infliximab trough level and decrease of C-reactive protein level are associated with durable sustained response to infliximab: a retrospective analysis of the ACCENT I trial. Gut 2014 Nov;63(11):1721-1727 [FREE Full text] [doi: 10.1136/gutjnl-2012-304094] [Medline: 24474383]
8. Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2014 Jan;146(1):85-95; quiz e14. [doi: 10.1053/j.gastro.2013.05.048] [Medline: 23735746]
9. Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, PURSUIT-Maintenance Study Group. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2014 Jan;146(1):96-109.e1. [doi: 10.1053/j.gastro.2013.06.010] [Medline: 23770005]
10. De VM, Dewit O, D'Haens G, Baert F, Fontaine F, Vermeire S, et al. Fast and sharp decrease in calprotectin predicts remission by infliximab in anti-TNF naïve patients with ulcerative colitis. J Crohns Colitis 2012 Jun;6(5):557-562. [doi: 10.1016/j.crohns.2011.11.002] [Medline: 22398050]
11. Molander P, af Björkesten BC, Mustonen H, Haapamäki J, Vauhkonen M, Kolho K, et al. Fecal calprotectin concentration predicts outcome in inflammatory bowel disease after induction therapy with TNFα blocking agents. Inflamm Bowel Dis 2012 Nov;18(11):2011-2017. [doi: 10.1002/ibd.22863] [Medline: 22223566]

Abbreviations

AMG: Arzneimittelgesetz, German Medicinal Products Act
ATG: antibody towards golimumab
CRF: case report form
CRP: C-reactive protein
DRKS: Deutsches Register Klinischer Studien, German Clinical Trials Register
GCP: good clinical practice
GLM: golimumab
IBD: inflammatory bowel disease
ICH: International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
OR: odds ratio
TNFα: tumor necrosis factor alpha
UC: ulcerative colitis
WBC: white blood cells

Edited by G Eysenbach; submitted 23.03.16; peer-reviewed by G Rydzewska, M Löwenberg, A Strik; comments to author 23.04.16; revised version received 06.05.16; accepted 06.05.16; published 28.06.16.

Please cite as:
Drabik A, Sturm A, Blömacher M, Helwig U
Early Monitoring of Response (MORE) to Golimumab Therapy Based on Fecal Calprotectin and Trough Serum Levels in Patients With Ulcerative Colitis: A Multicenter Prospective Study
JMIR Res Protoc 2016;5(2):e124
URL: http://www.researchprotocols.org/2016/2/e124/
doi:10.2196/resprot.5791
PMID:27352964

Original Paper

The SmokefreeTXT (SFTXT) Study: Web and Mobile Data Collection to Evaluate Smoking Cessation for Young Adults

Linda Squiers[1], MA, PhD; Derick Brown[2], BS; Sarah Parvanta[2], MPH, PhD; Suzanne Dolina[2], MPH; Bridget Kelly[3], MPH, PhD; Jill Dever[3], PhD; Brian G Southwell[2], MA, PhD; Amy Sanders[4], MA; Erik Augustson[5], MPH, PhD

[1]RTI International, Center for Communication Science, Rockville, MD, United States

[2]RTI International, Research Triangle Park, NC, United States

[3]RTI International, Washington, DC, United States

[4]ICF International, Rockville, MD, United States

[5]National Cancer Institute, Division of Cancer Control and Population Sciences, Rockville, MD, United States

Corresponding Author:
Linda Squiers, MA, PhD
RTI International
Center for Communication Science
6110 Executive Boulevard, Suite 902
Rockville, MD, 20852-3907
United States
Phone: 1 919 597 5128
Fax: 1 301 260 0605
Email: lsquiers@rti.org

Abstract

Background: Text messaging (short message service, SMS) has been shown to be effective in delivering interventions for various diseases and health conditions, including smoking cessation. While there are many published studies regarding smoking cessation text messaging interventions, most do not provide details about the study's operational methods. As a result, there is a gap in our understanding of how best to design studies of smoking cessation text messaging programs.

Objective: The purpose of this paper is to detail the operational methods used to conduct a randomized trial comparing three different versions of the National Cancer Institute's SmokefreeText (SFTXT) program, designed for smokers 18 to 29 years of age. We detail our methods for recruiting participants from the Internet, reducing fraud, conducting online data collection, and retaining panel study participants.

Methods: Participants were recruited through website advertisements and market research online panels. Screening questions established eligibility for the study (eg, 18 to 29 years of age, current smoker). Antifraud measures screened out participants who could not meet the study requirements. After completing a baseline survey, participants were randomized to one of three study arms, which varied by type and timing of text message delivery. The study offered US $20 gift cards as incentives to complete each of four follow-up surveys. Automated email reminders were sent at designated intervals to increase response rates. Researchers also provided telephone reminders to those who had not completed the survey after multiple email reminders. We calculated participation rates across study arms and compared the final sample characteristics to the Current Population Survey to examine generalizability.

Results: Recruitment methods drove 153,936 unique visitors to the SFTXT Study landing page and 27,360 began the screener. Based on the screening questions, 15,462 out of 27,360 responders (56.51%) were eligible to participate. Of the 15,462 who were eligible, 9486 passed the antifraud measures that were implemented; however, 3882 failed to verify their email addresses or cell phone numbers, leaving 5604 who were invited to complete the baseline survey. Of the 5604 who were invited, 4432 completed the baseline survey, but only 4027 were retained for analysis because 405 did not receive the intervention.

Conclusions: Although antifraud measures helped to catch participants who failed study requirements and could have biased the data collected, it is possible that the email and cell phone verification check excluded some potentially eligible participants from the study. Future research should explore ways to implement verification methods without risking the loss of so many potential participants.

ClinicalTrial: Clinical Trials.gov NCT01885052; https://clinicaltrials.gov/ct2/show/NCT01885052; (Archived by WebCite at http://www.webcitation.org/6iWzcmFdw)

(JMIR Res Protoc 2016;5(2):e134) doi:10.2196/resprot.5653

KEYWORDS

tobacco use cessation; text messaging; clinical trial; survey methods; cell phones; telemedicine

Introduction

Text messaging (short message service, SMS) has been shown to be effective in delivering interventions for various diseases and health conditions, including smoking cessation. There are many similarities in the design of existing text-based cessation interventions. Kong et al [1] conducted a narrative review of 15 text-based smoking cessation interventions and found that all based their motivational messages in cognitive behavioral and social cognitive theories focused on self-efficacy, with roughly half of the interventions tailoring the message content according to baseline questionnaire responses. All studies recruited participants who indicated that they were willing to quit smoking, and seven of the programs recruited young adults 18 to 29 years of age. The reviewed interventions varied in duration and format. All interventions included text messages to participants during the active quit phase, which ranged from 1 to 13 weeks; 10 interventions also included a preparation phase (ranging from 1 to 4 weeks) before the participant reached his or her quit date, and 8 included a maintenance phase during which the number of text messages received decreased over time. Similarly, the number of text messages varied by intervention, from nine messages per day to three per week, with increased frequency during the active quit period. Eleven of the interventions reviewed specifically offered or informed participants about other cessation treatments, including support through email, websites, self-help booklets, and medication, to supplement the text messaging intervention.

When developing smoking cessation studies, researchers also look to previous studies to answer questions pertaining to how study participants should be recruited, what type of data collection strategy would work best for a smoking cessation text messaging program, how frequently the data should be collected, what kind of incentive (if any) should be used, what type of antifraud methods should be used, how long recruitment should last, what response and retention rates can be anticipated, and what level of follow-up is required to retain participants through all data collection activities.

While the review by Kong et al provided details about the key elements of text messaging programs, it did not provide clear answers to these specific issues; however, it did synthesize the general methods used in the 15 studies that were reviewed. This review indicated that recruitment strategies for text-based cessation interventions most frequently used online venues (eg, Google, Facebook, Craigslist; [2-4]), although Free et al [5] reported use of a wide variety of recruitment methods, including radio, billboards, newspapers, and cessation service providers. Kong et al found that data collection tended to be conducted online [3-5] with secondary options including phone [5] and text message [4]. Very few studies reported offering a financial incentive for data collection efforts. Ybarra et al [4] offered US $10 to $20 for completion of post-quit follow-up surveys, but they did not discuss fraud that may have occurred as a result of this financial incentive. Reviews and individual studies often do not provide the details about the operational methods used, and do not highlight the lessons learned from using these methods, resulting in a gap in our understanding of how best to design studies of smoking cessation text messaging programs.

Study Objective

While some studies provide a general description of study methods, most do not provide the details about operational methods used to conduct a study. The purpose of this paper is to detail the operational methods we used to conduct a randomized trial comparing three different versions of National Cancer Institute's (NCI) SmokefreeText (SFTXT) program (Clinical Trials.gov NCT01885052). In particular, we detail our methods for recruiting participants from the Internet, reducing fraud, conducting online data collection, and maintaining the panel of over 4000 study participants.

Rationale for the Study

This study was developed to compare three different versions of NCI's SFTXT program, which is designed for smokers 18 to 29 years of age. The current SFTXT program (available at NCI's smokefree.gov website [6]) is an 8-week text messaging program that includes 2 weeks of preparatory messages before a participant's quit date and 6 weeks of motivational support messages after a participant's quit date. For this study, we assigned a quit date 2 weeks post-baseline, as opposed to the real-life application of SFTXT that allows users to choose their own quit date. Program data indicated that 34.1% of participants dropped out of the program within one week after their chosen quit date. Given these data, NCI was interested in determining whether a modified program focusing only on preparatory messages and quit-day support messages would be as effective as the full program. NCI also wanted to determine how these high-intensity motivational messaging programs compared with a low-intensity program that provided only quit date reminders and smoking status check-in messages. Three different versions of the SFTXT program were tested using a randomized three-arm longitudinal study design. The number of texts received varied by study arm, with Arm 1 participants receiving 11, Arm 2 participants receiving 40, and those in Arm 3 receiving a total of 127 text messages. Participants received a variety of types of texts depending on their group assignment. Examples of the types of texts included quit date reminders, tips on staying smoke-free, motivational messages, facts about smoking cessation, mood assessments, and others. The authors can be contacted for a full description of the study, including

details about the intervention components of all three SFTXT programs tested.

Methods

Recruitment Goal and Power

To determine the sample size needed to conduct this study, we performed a power analysis [7] assuming a 32% predicted smoking abstinence rate and a 60% wave-to-wave attrition rate. The analytic goal was to detect a 5% difference between any two arms within the experimental design with 80% power and a two-sided test. This power analysis yielded a conservative baseline recruitment size of 4248 (1416 per arm) and a minimum sample size of 435 participants per arm to complete all five surveys.

Recruitment Methods

Advertisements

SFTXT Study participants were recruited from June 26, 2013, through January 8, 2014, using a series of online strategies. Advertisements were posted on Facebook, Craigslist, and Pandora, along with search ads on Google, Yahoo!, and Bing. Additionally, market research firms emailed announcements about the study to their online panel members who smoked, and were within the eligible age group. Individuals who clicked on an SFTXT Study advertisement were directed to a 10-question screener to determine study eligibility.

Eligibility Criteria

To be eligible to participate in the study, individuals had to (1) be aged 18 to 29, (2) live in the United States, (3) have smoked on at least 5 of the past 30 days, (4) be at least moderately interested in stopping smoking within the next 30 days, and (5) not be seeking cessation services elsewhere. Given that all study communication was conducted via email or by text message, participants needed to have an active email address and agree to receiving up to 130 messages over 8 weeks on their mobile phones. Only one family member per household was eligible to participate in the study, as determined by a question on the screener questionnaire, and verified using an automated Internet Protocol (IP) address duplication check. Participants could not have a close friend who was already participating in the study. Finally, to be eligible, individuals had to be willing to share their contact information.

Eligible individuals completed an online consent form and were required to provide their email address (entered twice) and mobile phone number, and give permission for the study team to use the email and phone number to send surveys and leave reminder messages. Eligible individuals were also asked for an alternate phone number, but could participate in the study without providing one. Ineligible individuals were asked to complete a four-question exit survey that included demographic questions about sex, race/ethnicity, and education level.

Email and Text Verification

To confirm contact information, participants responded to an email verification request and a text message verification request before receiving the baseline survey. This procedure also verified that a participant could receive both emails and text messages for the study.

Incentives

To keep participants engaged in the study, we initially offered a choice of an Amazon or iTunes electronic gift card as an incentive for completing each of the five surveys. We conducted an initial pilot study for 2 weeks in July, 2012. Within the first few days of this pilot, we noticed that similar email addresses were being used to enroll participants. For example, an enrollee might have entered Jane.Doe@gmail.com, and shortly thereafter we would find a similar email address, such as JDoe@gmail.com. Upon investigation, we discovered that the system we created to check for duplicate emails or phone numbers was not working properly. To verify that the second case was associated with the first, we examined the IP addresses from the two cases to see if they were identical. We identified 105 duplicate or fraudulent enrollees, and these cases were notified by email that they were terminated from the study. We stopped the study for 16 days to fix the system for duplication checks, and added more antifraud measures, which are described below. We also decided to stop incentivizing the baseline survey. Instead, we only incentivized the four follow-up surveys at US $20 per survey.

Antifraud Measures

To ensure the integrity of the SFTXT Study sample, multiple antifraud measures were implemented within the screener instrument to prevent two types of behaviors: (1) eligible participants enrolling multiple times in the SFTXT Study (presumably) to obtain multiple incentives (US $20 for completion of each of the four follow-up surveys), and (2) previously ineligible individuals reenrolling and changing their responses to be within the eligibility criteria.

Our antifraud process included the following measures:

- *CAPTCHA*. CAPTCHA is a technique used to verify that a person, and not a computer, is accessing the website. A common type of CAPTCHA asks a user to type letters or numbers that appear in a distorted image on the screen. This task is very difficult for a computer to perform, making it an effective way to verify that a person is on the other end of the transaction.
- *Honesty pledge.* An honesty pledge can be implemented at the start of a survey to attempt to improve data quality. Users are asked to acknowledge that they intend to answer the survey truthfully. Results from a recent study presented at the American Association of Public Opinion Reporting (AAPOR) suggested that these types of pledges can help reduce the occurrence of straightlining, question skipping, and other types of fraud [8].
- *Hosting the survey on a secure site*. With a secure site, only those with a password can gain access. This mechanism reduces the likelihood that a participant could tell their friends to take the survey to collect incentives. To access each survey, participants needed to enter the username and password that was sent to them with the link to the follow-up surveys.

- *Conducting rigorous data cleaning*. The cleaning process looked for straightlining, anyone completing the survey in an extremely short amount of time, and other such indicators.
- *Duplication checks*. The antifraud process included automated duplication checks of phone numbers, email addresses, and IP addresses. If duplicates were detected, the individual was excluded from the study. To ensure that no lapses occurred in antifraud prevention, retroactive duplication checks were implemented by linking cases to one another through the contact information and IP addresses, which helped to ensure the sample's validity.

Data Collection

Once participants completed the verification process, they were invited to participate in the study. Study data were collected at five time points: baseline, 3 weeks post-baseline (7 days post-quit date), 8 weeks post-baseline (6 weeks post-quit date), 20 weeks post-baseline (18 weeks post-quit date), and 32 weeks post-baseline (30 weeks post-quit date). Additionally, upon completion of the baseline survey, participants were randomly assigned to one of the three study arms. A quit date was set at 2 weeks after completion of the baseline survey for all study participants.

Participants were invited to complete each survey via an email with a link to the study website. Participants could complete the survey at one time or could save their partial responses and complete the survey later. Participants were required to take the baseline and 3-week follow-up survey within 14 days of the initial email invitation and within 36 days for the 8-week, 20-week, and 32-week surveys, and were classified as survey non-respondents if they did not do so. These participants, however, remained in the study and were invited to complete the remaining questionnaires. Participants who had not completed a survey were emailed reminders on the third, fourth, fifth, sixth, and tenth day after the invitation was sent. If a participant still had not completed a survey, a staff member telephoned them as a final reminder before expiration of the 2-week window for taking the survey.

Panel Support and Maintenance

To support the study, project team members answered participants' questions about the study via email and telephone. The majority of participant questions focused on the verification process, missing login information, and requests to have incentive gift codes re-sent. This process enabled participants to update their contact information and receive answers to questions regarding existing survey invitations and incentives, which helped to ensure that the intervention was implemented as designed.

Participants were allowed to withdraw from all or parts of the SFTXT Study at any time, including the 2-week period before the assigned quit date. Participants who texted "STOP" in the 2 weeks before the assigned quit date were opted out of the study entirely and received no future text messages or follow-up survey invitations, as they would not have received the intervention. Participants who texted "STOP" after the assigned quit date no longer received the text messages but continued to receive follow-up survey invitations and were still considered study participants. These individuals could still opt out entirely if they contacted the study director to leave the study completely.

Statistical Analysis

To be considered a study participant, an individual needed to meet all eligibility criteria, complete the verification process, and complete the baseline survey. Individuals were defined as *verified* if they provided informed consent, pledged to give honest responses, provided an email address and phone number, and verified their contact information. For the baseline survey to be considered complete, individuals needed to respond to essential questions (eg, smoking history, demographics). To assess differences between arms for response and retention rates, we conducted significance testing based on a chi-squared test for differences between Arms 1 and 2, Arms 1 and 3, and Arms 2 and 3. To calculate the response rate for the baseline survey, we used the AAPOR [9] RR6 formula with *noncontact* and *other* set to zero.

Results

Participant Recruitment

Participants were recruited over 196 days. Figure 1 presents the steps involved in recruiting and determining the eligibility of study participants, and the number retained and excluded at each step, beginning with initial visits to the SFTXT landing page where the study screener was located. There were 153,936 unique visitors to the landing page, or 785 visits per day on average.

Of those 153,936 unique visitors, 27,360 (17.77%) began the screener. Based on their responses to the screener, 15,462 of 27,360 visitors (56.51%) met the study's eligibility requirements. Failure to provide informed consent excluded 3428 of the 15,462 eligible participants (22.17%). Antifraud measures excluded 2548 of 12,034 participants who provided informed consent (21.17%): 576 (4.79%) refused the honesty pledge, 1312 (10.90%) did not provide contact information, and 660 (5.48%) failed the duplication checks, leaving 9486 of the 15,462 eligible participants (61.35%) who had both consented and passed the antifraud measures. Another 3882 of 9486 (40.92%) eligible participants were sent a verification code; however, they failed to verify their email address and phone number and were excluded based on this requirement.

The remaining 5604 respondents were sent an invitation to complete the baseline survey; 1172 of 5604 respondents (20.91%) did not complete this survey and were excluded from the study. Participants (405 of 4432, 9.14%) were also excluded if they did not receive the intervention. For example, 233 of 4432 faced technical difficulties (eg, undelivered text messages). Participants who texted "STOP" at any point *before* their quit date (n=150) were excluded because they had not received an essential part of the intervention (ie, messages on their quit date) and, depending on the study arm, may have received less than half of the text messages. A small number of participants (n=22) opted out of the study entirely by notifying the project team, typically via email. Those who texted "STOP" after the quit date were retained in the analytic sample.

Final Sample

A total of 4,027 participants were retained for analysis, including participants who texted STOP *after* their quit date (n=236), as they had received the essential quit date messages and most of the intervention at that point. The frequency of texting "STOP" messages sent after the quit date was significantly higher in Arm 3 (153/236) than in Arm 1 (54/236) or Arm 2 (29/236) and significantly higher in Arm 1 than in Arm 2. Of these participants, 41 responded to a survey question asking why they opted out of receiving further text messages, with the majority (51%, 21/41) reporting that there were too many texts or that the texts were bothersome. Others stated that the texts did not help them quit smoking (10/41), or that they had stopped trying to quit (6/41).

Response and Retention Rates

Verified and consented individuals (5604 of 9486 eligible participants) were invited to take the SFTXT baseline survey, and 4027 participants subsequently completed it and were retained for analysis (see Table 1). This sample size, which excludes participants who completed the baseline survey but were ultimately dropped from the analytic sample, equates to a response rate of 71.86% (using the AAPOR RR5 formula [8]).

Table 1. Response rates by recruitment stage and study arm (n=153,936).

Response rate for recruitment stage	Overall		Arm 1		Arm 2		Arm 3	
	n	%	n	%	n	%	n	%
Unique visits to project websites	153,936		—		—		—	
Initiated screener/initiation rate	27,630	17.77	—		—		—	
Completed screener/screener rate	26,057	94.31	—		—		—	
Eligible	15,462	59.34	5041	32.60	5307	34.32	5114	33.07
Verified (baseline survey invitation)	5604	36.24	1828	32.62	1902	33.94	1874	33.44
Completed baseline survey[a,b]	4027	71.86	1313	32.60	1400	34.77	1314	32.63

[a]An AAPOR [9] RR6 formula was used for the calculation, with *noncontact* and *other* set to zero.

[b]Includes all cases retained for analysis.

Retention rates for each follow-up survey were calculated for the analytic sample (n=4027; Table 2). Approximately 56.67% (2282/4027) of participants completed all four follow-up surveys, and 19.99% (805/4027) did not complete any of the follow-up surveys. Within each study arm and across arms, retention rates tended to decline as the weeks between baseline and follow-up increased. For example, the retention rate for the 3-week follow-up survey was 74.72% (3009/4027), whereas the retention rate for the 32-week follow-up survey declined to 64.64% (2603/4027). The lowest retention rates in the 3-week and 8-week follow-up surveys were in Arm 1, whereas the lowest retention rates in the 20-week and 32-week follow-up surveys were in Arm 3.

For the 3-week follow-up, Arm 2 had a significantly higher retention rate than Arm 1 (P=.01). There were no significant differences between arms at the 8-week and 20-weeks follow-ups. For the 32-week follow-up, Arm 2 had a significantly higher retention rate than Arm 3 (P=.03). Arm 1 was significantly more likely than Arm 2 not to complete any follow-up surveys (P=.01). Arm 2 was significantly more likely than Arm 3 to complete all follow-up surveys (P=.05).

Table 2. Retention rates (n=4027).

Follow-up survey	Overall (n=4027)		Arm 1 (n=1313)		Arm 2 (n=1400)		Arm 3 (n=1314)	
	n	%	n	%	n	%	n	%
3-week	3009	74.72	949	72.28	1071	76.50	989	75.27
8-week	2881	71.54	925	70.45	1024	73.14	932	70.93
20-week	2675	66.42	866	65.96	957	68.36	852	64.84
32-week	2603	64.64	846	64.43	933	66.64	824	62.71
Completed no follow-up surveys	805	19.99	292	22.23	256	18.29	257	19.56
Completed all follow-up surveys	2282	56.67	746	56.82	818	58.43	718	54.64

The proportion of participants who completed each survey on the day the invitation was emailed was highest for the baseline survey (56.16%, 3147/5604) and lowest at the 32-week follow-up survey (22.80%, 918/4027), as shown in Table 3. Email and telephone reminders boosted the response rate for all five surveys.

Table 3. Percentage of the overall sample completing survey by prompt and data collection point (n=4027).

Percent complete	Baseline	3-week	8-week	20-week	32-week
Day invitation sent	56.2	30.9	31.8	24.1	22.8
Day after invitation sent	5.6	8.9	9.0	8.0	7.9
Single email reminder[a]	1.1–2.1	3.8–7.9	1.4–4.7	2.5–5.6	2.3–7.0
Single phone reminder	0.8	3.0	2.6	3.2	2.9

[a]Four email reminders were sent for each survey.

Representativeness of the Sample

Multimedia Appendix 1 presents the demographic and smoking history characteristics for the SFTXT analytic sample compared with population estimates from the January, 2011 Current Population Survey (CPS), the most recent survey data available with detailed cigarette smoking information [10]. CPS data are weighted, so counts are not displayed. To create the SFTXT population within CPS, the CPS data were subset down to individuals 18 to 29 years of age who smoked five or more cigarettes per day. The SFTXT sample was predominately female (70.15%, 2825/4027), whereas the CPS population had a more equal distribution of females and males. Compared with the CPS population, the SFTXT sample included more highly educated participants (25.4% vs. 17.3% with a college degree or more), but fewer participants that were employed full-time (39.7% vs. 62.1%). Household income and race/ethnicity characteristics were similar between SFTXT and CPS. In terms of smoking history, the SFTXT sample contained a higher proportion of individuals who tried to quit smoking at least once in the past year (73.8%) compared with the CPS population (60.9%). Average scores on the Heaviness of Smoking Index were higher in the SFTXT sample than in the CPS population, indicating higher nicotine dependence levels among SFTXT participants. Multimedia Appendix 1 also displays demographic and smoking history characteristics within each study arm of the SFTXT sample. These characteristics did not differ significantly by study arm.

Discussion

Principal Findings

When designing this study, we reviewed past studies of smoking cessation text messaging interventions to determine what methods had been successfully used in the past. Unfortunately, few studies provided details about study implementation and the effectiveness of strategies that were used to recruit, retain, and manage study participants and reduce fraudulent entry into the study. Our results help to fill these gaps.

Through online advertising, this smoking cessation study resulted in 153,936 visits to the study's landing page, of whom 27,360 screeners initiated, and 4027 participants were recruited. Antifraud measures prevented, at a minimum, 2448 people from enrolling. Another 3882 respondents were excluded from participating because they did not validate both their email and phone number when sent the verification requests. Of the 4027 participants recruited, 64.64% (2603/4027) were retained across four follow-up waves that extended to 32-weeks post-intervention. Results from our examination of the effectiveness of the enrollment, data collection, and antifraud methods used in this study can be used to inform the methods and procedures developed for future studies. Although the effectiveness of every procedure we used cannot be quantified, we offer the following suggestions based on experience conducting this study.

First, the online advertising and other recruiting efforts were effective in driving more than 150,000 people to the study website, with over half meeting the eligibility criteria. When compared with CPS data, a higher proportion of our sample was female and had higher levels of educational attainment. However, study participants were heavier smokers and had previously tried to quit in the past year, likely because of our eligibility requirement that participants must be at least moderately interested in quitting.

While the total sample was slightly smaller than our target goal of 4248, our retention rates were higher than anticipated, with 56.67% (2282/4027) completing all four follow-up surveys. We had initially planned for approximately 60% attrition over the four waves of follow-up, for a total of 40% completing the final follow-up survey.

The reason for this higher than expected retention rate may have been the incentive of the US $20 Amazon or iTunes gift cards offered for completion of each follow-up survey. Future studies could use smaller incentive amounts to see if they would be equally effective in retaining the sample. We recommend incentivizing only follow-up surveys; offering an incentive for a baseline survey that is recruiting participants through online advertising seemed to invite people to attempt to enter the study more than one time so they could get additional gift cards.

Retention rates differed by arm, with Arm 2 having higher retention rates than Arm 1; this result is not entirely unexpected because Arm 2 received significantly more text messages than Arm 1. However, the amount of communication received does not solely explain differences in retention rates by arm, as Arm 3 received significantly more messages than Arm 2. This finding may indicate a threshold for the amount of messaging that keeps participants engaged in both the intervention and the study. In this case, Arm 1 may have been below that threshold while Arm 3 exceeded that threshold.

Multiple email reminders to encourage participants to complete each survey may have positively affected completion rates for each survey. While we are unable to disentangle the effect of these reminders from the effect of the incentives, our findings suggest that the additional email reminders and the single phone

reminder resulted in a small percentage of participants completing a survey, especially for the 32-week follow-up survey, while a single email reminder appears to have prompted 7.0% of the sample to complete that survey. We recommend that researchers who are conducting longitudinal online surveys use multiple email reminders over time to encourage participants to complete each survey.

To receive an invitation to complete each survey, having a correct email address for each participant was necessary. For studies such as this one, we recommend requiring participants to enter their email address two times and programming the data collection instrument to continue only if both email addresses match. However, additional procedures may be needed to ensure that those who are eligible do not have any other barriers to participation. In the overall recruitment process, the largest number of potential participants lost was during phone number and email verification. This number represented a large proportion of the otherwise eligible sample (40.92%, 3882/9486) and, although we sent an email reminding participants to complete the verification process, if their email address was problematic, they would not have received the reminder. Future studies could use both phone and text-based reminders, and should explore other ways to prevent such loss. Without additional research, it is difficult to know all of the possible reasons for so many unverified cases. It is plausible that potential participants did not receive or notice the verification email and/or text, or felt it was too burdensome to go through that process. Others may simply have forgotten. Regardless of the reasons for their dropout, these individuals were known to be eligible and had provided contact information. Additional research could help to determine whether email or phone information is inaccurate, or if reminders to verify (or instructions emphasizing the simplicity of the verification procedures) can help to reduce the number of participants who do not complete the process. In addition, researchers should be mindful of such instances during the recruitment phase, because this type of sample loss incurs unnecessary costs to the recruitment effort.

Previous Internet studies of smoking cessation have found some respondents to be fraudulent [2]. The antifraud procedures we established allowed us to identify more than 5000 cases that would have been included in the dataset otherwise. Thus, we were able to screen out participants who may have continued to provide bad or duplicate data, and enhance the overall quality of the dataset. The results of this study add further evidence to growing literature that suggests antifraud measures can help deter some respondents who otherwise might have provided less complete or invalid data [8].

Limitations

Compared with CPS data, our sample was more likely to be female, younger, more educated, heavier smokers, and more likely to have tried quitting in the last year than the general population of smokers 18 to 29 years of age. CPS data did not ask how motivated smokers were to quit, leaving us unable to determine if our sample was more motivated than the general population of smokers 18 to 29 years of age; being moderately interested in quitting was a study requirement. Consequently, the results cannot be generalized beyond this specific sample. Our findings are limited, because we did not design our study to determine the effectiveness of individual study procedures (eg, email reminders, phone reminder, incentives) in retaining participants. Future studies could be designed to conduct experiments to compare these methods.

Comparison with Prior Work

Our results detail specific methods used to conduct an online longitudinal study of a text-based smoking cessation intervention. Other studies have reported on outcomes, but to date, no other studies provide detailed information about the effectiveness of the operational methods used to conduct the studies.

Conclusions

The methods described here helped the project team to recruit an overall sample of more than 4000 smokers for the study. Antifraud measures helped to catch participants who tried to collect multiple incentives or were unable to verify their phone numbers or email addresses. This step may have resulted in loss of potentially eligible sample members, but may have contributed to higher retention rates than we originally projected. This tradeoff is a lesson for future studies. Additional research should explore more efficient ways to conduct such verification without risking the loss of so many potential respondents.

Acknowledgments

Janice Tzeng, Sidney Holt, Marjorie Margolis, and Brittany Zulkiewicz (all with RTI International) helped manage the day-to-day operations of the study, select and track antifraud measures, and manage data collection and documenting implementation of the study. Venkat Yetekuri programmed all data collection instruments, developed and implemented antifraud measures and study processes, and managed data collection.

Authors' Contributions

Authors (in alphabetical order) all reviewed this manuscript. Erik Augustson (NCI) was the project officer for the study, which RTI International conducted in collaboration with, and on behalf of, NCI. He was responsible for determining the study design, reviewing all data collection instruments, and reviewing the draft and final versions of the manuscript. Derick Brown (RTI International) conducted quality assurance checks of all data, conducted all analyses, and wrote parts of the methods and results sections. Jill Dever (RTI International) oversaw the development and write-up of the study methods and data analyses, and wrote sections of the introduction. Suzanne Dolina (RTI International) wrote the introduction section, parts of the methods section, and

reviewed and provided feedback on all other sections of the manuscript. Bridget Kelly (RTI International) wrote parts of the methods section, the discussion section, and reviewed and provided feedback on all other sections of the manuscript. Sarah Parvanta (RTI International) wrote the abstract, study objectives, and parts of the results. She reviewed and provided feedback on all other sections of the manuscript. Brian Southwell (RTI International) served as a senior advisor on the project and reviewed and provided feedback on the manuscript. Linda Squiers (RTI International) directed the study and coordinated writing, reviewing, and editing of all sections of the manuscript, as well as creation of tables and figures. She also wrote parts of the introduction, methods, results, and discussion sections. Amy Sanders was responsible for overseeing the recruitment of subjects, working with the text messaging vendor, and reviewing the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Demographics of SFTXT analytic sample compared with Census estimates, overall and by study arm (n=4027).

[PDF File (Adobe PDF File), 45KB - resprot_v5i2e134_app1.pdf]

References

1. Kong G, Ells DM, Camenga DR, Krishnan-Sarin S. Text messaging-based smoking cessation intervention: a narrative review. Addict Behav 2014 May;39(5):907-917 [FREE Full text] [doi: 10.1016/j.addbeh.2013.11.024] [Medline: 24462528]
2. Abroms LC, Boal AL, Simmens SJ, Mendel JA, Windsor RA. A randomized trial of Text2Quit: a text messaging program for smoking cessation. Am J Prev Med 2014 Sep;47(3):242-250. [doi: 10.1016/j.amepre.2014.04.010] [Medline: 24913220]
3. Buller DB, Borland R, Bettinghaus EP, Shane JH, Zimmerman DE. Randomized trial of a smartphone mobile application compared to text messaging to support smoking cessation. Telemed J E Health 2014 Mar;20(3):206-214 [FREE Full text] [doi: 10.1089/tmj.2013.0169] [Medline: 24350804]
4. Ybarra ML, Holtrop JS, Prescott TL, Rahbar MH, Strong D. Pilot RCT results of stop my smoking USA: a text messaging-based smoking cessation program for young adults. Nicotine Tob Res 2013 Aug;15(8):1388-1399 [FREE Full text] [doi: 10.1093/ntr/nts339] [Medline: 23348969]
5. Free C, Knight R, Robertson S, Whittaker R, Edwards P, Zhou W, et al. Smoking cessation support delivered via mobile phone text messaging (txt2stop): a single-blind, randomised trial. Lancet 2011 Jul 2;378(9785):49-55 [FREE Full text] [doi: 10.1016/S0140-6736(11)60701-0] [Medline: 21722952]
6. Smokefree. 2015. URL: http://smokefree.gov [accessed 2015-08-10] [WebCite Cache ID 6hSYv6YU2]
7. Cohen J. Statistical power analysis. Current Directions in Psychol Sci 1992 Jun;1(3):98-101. [doi: 10.1111/1467-8721.ep10768783]
8. Burdein I. The Pledge Test Encouraging Accurate Reporting. 2011 May 12 Presented at: American Association of Public Opinion Reporting; May 12, 2011; Phoenix, AZ.
9. American Association of Public Opinion Research. Standard definitions: final disposition of case codes and outcome rates for surveys. Ann Arbor, MI: American Association of Public Opinion Research (AAPOR); 2011. URL: https://www.esomar.org/uploads/public/knowledge-and-standards/codes-and-guidelines/ESOMAR_Standard-Definitions-Final-Dispositions-of-Case-Codes-and-Outcome-Rates-for-Surveys.pdf [accessed 2015-05-21] [WebCite Cache ID 6YgNkhpCl]
10. U.S. Census Bureau, Current Population Survey. DataFerret online database URL: http://dataferrett.census.gov/LaunchDFA.html [accessed 2016-01-03] [WebCite Cache ID 6eGmXdSrX]
11. Heatherton TF, Kozlowski LT, Frecker RC, Rickert W, Robinson J. Measuring the heaviness of smoking: using self-reported time to the first cigarette of the day and number of cigarettes smoked per day. Br J Addict 1989 Jul;84(7):791-799. [Medline: 2758152]

Abbreviations

AAPOR: American Association for Public Opinion Research
CPS: Current Population Survey
IP: Internet Protocol
NCI: National Cancer Institute
SFTXT: SmokefreeText
SMS: short message service

Edited by G Eysenbach; submitted 15.02.16; peer-reviewed by S Cutrona, A Marcon; comments to author 28.03.16; revised version received 12.04.16; accepted 13.04.16; published 27.06.16.

Please cite as:
Squiers L, Brown D, Parvanta S, Dolina S, Kelly B, Dever J, Southwell BG, Sanders A, Augustson E
The SmokefreeTXT (SFTXT) Study: Web and Mobile Data Collection to Evaluate Smoking Cessation for Young Adults
JMIR Res Protoc 2016;5(2):e134
URL: http://www.researchprotocols.org/2016/2/e134/
doi:10.2196/resprot.5653
PMID:27349898

Original Paper

Using Nonexperts for Annotating Pharmacokinetic Drug-Drug Interaction Mentions in Product Labeling: A Feasibility Study

Harry Hochheiser[1,2], PhD; Yifan Ning[1], MS; Andres Hernandez[1,3], MS; John R Horn[4], PharmD; Rebecca Jacobson[1,2], MS, MD; Richard D Boyce[1], PhD

[1]Department of Biomedical Informatics, School of Medicine, University of Pittsburgh, Pittsburgh, PA, United States

[2]Intelligent Systems Program, University of Pittsburgh, Pittsburgh, PA, United States

[3]Center for Bioinformatics and Computational Biology, BIOS, Manizales, Colombia

[4]Department of Pharmacy, School of Pharmacy and University of Washington Medicine, Pharmacy Services, University of Washington, Seattle, WA, United States

Corresponding Author:
Harry Hochheiser, PhD
Department of Biomedical Informatics
School of Medicine
University of Pittsburgh
5607 Baum Blvd
Suite 523
Pittsburgh, PA,
United States
Phone: 1 412 648 9300
Fax: 1 412 624 5310
Email: harryh@pitt.edu

Abstract

Background: Because vital details of potential pharmacokinetic drug-drug interactions are often described in free-text structured product labels, manual curation is a necessary but expensive step in the development of electronic drug-drug interaction information resources. The use of nonexperts to annotate potential drug-drug interaction (PDDI) mentions in drug product label annotation may be a means of lessening the burden of manual curation.

Objective: Our goal was to explore the practicality of using nonexpert participants to annotate drug-drug interaction descriptions from structured product labels. By presenting annotation tasks to both pharmacy experts and relatively naïve participants, we hoped to demonstrate the feasibility of using nonexpert annotators for drug-drug information annotation. We were also interested in exploring whether and to what extent natural language processing (NLP) preannotation helped improve task completion time, accuracy, and subjective satisfaction.

Methods: Two experts and 4 nonexperts were asked to annotate 208 structured product label sections under 4 conditions completed sequentially: (1) no NLP assistance, (2) preannotation of drug mentions, (3) preannotation of drug mentions and PDDIs, and (4) a repeat of the no-annotation condition. Results were evaluated within the 2 groups and relative to an existing gold standard. Participants were asked to provide reports on the time required to complete tasks and their perceptions of task difficulty.

Results: One of the experts and 3 of the nonexperts completed all tasks. Annotation results from the nonexpert group were relatively strong in every scenario and better than the performance of the NLP pipeline. The expert and 2 of the nonexperts were able to complete most tasks in less than 3 hours. Usability perceptions were generally positive (3.67 for expert, mean of 3.33 for nonexperts).

Conclusions: The results suggest that nonexpert annotation might be a feasible option for comprehensive labeling of annotated PDDIs across a broader range of drug product labels. Preannotation of drug mentions may ease the annotation task. However, preannotation of PDDIs, as operationalized in this study, presented the participants with difficulties. Future work should test if these issues can be addressed by the use of better performing NLP and a different approach to presenting the PDDI preannotations to users during the annotation workflow.

(JMIR Res Protoc 2016;5(2):e40) doi:10.2196/resprot.5028

KEYWORDS

crowdsourcing; natural language processing; drug interactions, drug product labeling, structured product labels

Introduction

Exposure to interacting drug combinations can lead to patient harm. Recent estimates indicate that between 5.3% and 14.3% of hospital patients in the United States experience a clinically meaningful alteration in the exposure or response of one drug occurring as a result of coadministration of another drug [1]. Fortunately, such harm can often be avoided by employing appropriate management strategies [2]. Toward that goal, US federal regulations require the mention of known, clinically relevant potential drug-drug interactions (PDDIs) in prescription drug labeling [3,4].

Structured product labels (SPLs) are mandated by the US Food and Drug Administration. The labels, produced by pharmaceutical manufacturers, are presented in a standardized format [5] and approved by regulators. As detailed descriptions subject to regulatory approval, SPLs play a vital role in disseminating drug information. However, the structure in these documents is only in the form of high-level sections such as *Description*, *Indications and Usage*, *Contraindications*, and *Warnings*. Specific PDDI details are given in plain text, tables, and figures within the *Drug Interactions* section or other locations throughout the label. Although future efforts may lead to more structured and therefore more computable labels, the regulatory importance of the SPLs and the legacy labels of more than 16,000 drugs make the labels key resources for drug-drug interaction information.

Unfortunately, product labeling is incomplete. A study of drugs that interact with the narrow therapeutic range drug warfarin found PDDI information deficiencies in 15% of relevant product labels [6]. A broader study of drugs sold in the United States, United Kingdom, and Germany found that a warning about a critical drug interaction was missing from the label of one of the interacting drugs at least 40% of the time [7]. Although publicly available PDDI information sources can serve as useful adjuncts to product label information, these collections are often far from complete. Our recent analysis of 14 collections of PDDI information found significant divergence, with overlap between pairs of sources usually less than 50% [8]. Addressing the issue of missing product label PDDI information is important to better meet the information needs of drug experts, clinicians, and patients.

We hypothesize that a computable representation of PDDIs present in product labels and other high-quality sources will enable novel methods for drug information retrieval that will in turn provide researchers and clinicians with improved capabilities for finding complete and current DDI information. Testing this hypothesis requires an efficient means of generating computable representations of PDDI mentions.

In prior work, we developed a prototype system that used simple named entity recognition (NER) and Semantic Web Linked Data [9] to link claims about PDDIs from publicly available external resources to the *Drug Interactions* section of the product label [10]. Experiments found that our system linked at least one potentially novel interaction (ie, not mentioned in the label) to the *Drug Interactions* section of product labeling for 20 antidepressants. Moreover, there were several cases where all of the PDDI mentions linked to the *Drug Interactions* section for an antidepressant were potentially novel and would complement product label information. For example, an interaction between escitalopram and tapentadol mentioned in the National Drug File-Reference Terminology [11,12] was potentially novel to all 20 escitalopram product labels.

While promising, the simple NER approach often missed potentially important links between the label and other sources. Sophisticated natural language processing (NLP) methods might prove to be more complete, accurate, and scalable than simple NER. However, there is reason to believe that even the best NLP methods would not perform well enough to guarantee automatic identification of all PDDI mentions across all drug product labels. The PDDI NLP algorithm that performed best against the 2013 SemEval Challenge text corpus had a sentence-level recall of 0.81 and a precision of 0.86 (F_1 =0.84)[13]. An algorithm we developed in prior work focusing specifically on NLP identification of pharmacokinetic PDDI mentions within product label sections had a document level recall of 0.84 and a precision of 0.88 (F_1=0.86) [14] (sentence-level performance was not evaluated).

Based on these findings, we have concluded that the involvement of human curators is necessary for the task of generating computable representations of PDDIs present in product labels and other high-quality sources. The use of semiautomatic curation is relatively common in biomedicine [15]. Unfortunately, the high cost of expert annotation is a major potential barrier to further progress. New approaches are needed to increase the scale and quality of data curation.

Replacing experts with nonexpert crowds (crowdsourcing) can increase the feasibility of large-scale annotation tasks for biomedical data [16-18]. Initial efforts at crowdsourcing for the annotation of medical text have found the method to be effective when the workflow is properly managed [16]. Results can be comparable in quality to those obtained via more traditional and expensive expert annotation methods [17]. Crowdsourcing is particularly attractive for obtaining results faster and at a lower cost than other participant recruitment schemes [17]. The Informatics for Integrating Biology and the Bedside (i2b2) 2010 workshop assessment found that a well-selected group of nonexperts could perform extraction of drug information from clinical reports [19]. Other biomedical efforts have applied crowdsourcing to gene-mutation mentions in the biomedical literature [20] and for clinical trial announcements [21]. A study of the feasibility of using people recruited through Amazon's Mechanical Turk to annotate medication indications found that nonexperts could achieve accuracy of greater than 95% on the binary question of whether a medication is an indication for a disease mentioned in the medication's drug label [22]. Similar approaches have been used to engage communities of experts in tackling challenges such as linking medications and problems

in clinical texts from electronic medical records [23,24] and developing mappings between institutional procedure descriptions and Logical Observation Identifiers Names and Codes (LOINC) [25,26].

Our experience with NLP methods for extracting PDDI annotations suggests the possibility of using NLP annotation to provide suggestions to human annotators. Previous efforts have explored the possibility of using such preannotation. Hanauer et al [27] found that iterative alternation between human annotation and model building facilitated rapid creation of NLP models. Some comparative studies have shown that preannotation can improve annotator performance relative to unassisted annotation [28-30], but other studies have seen no difference [31].

The goal of this study was to assess the potential feasibility of using persons who are not drug experts in the task of annotating PDDIs mentioned in drug product labels. A secondary goal was to test the influence of NLP assistance on the annotation quality of both experts and nonexperts.

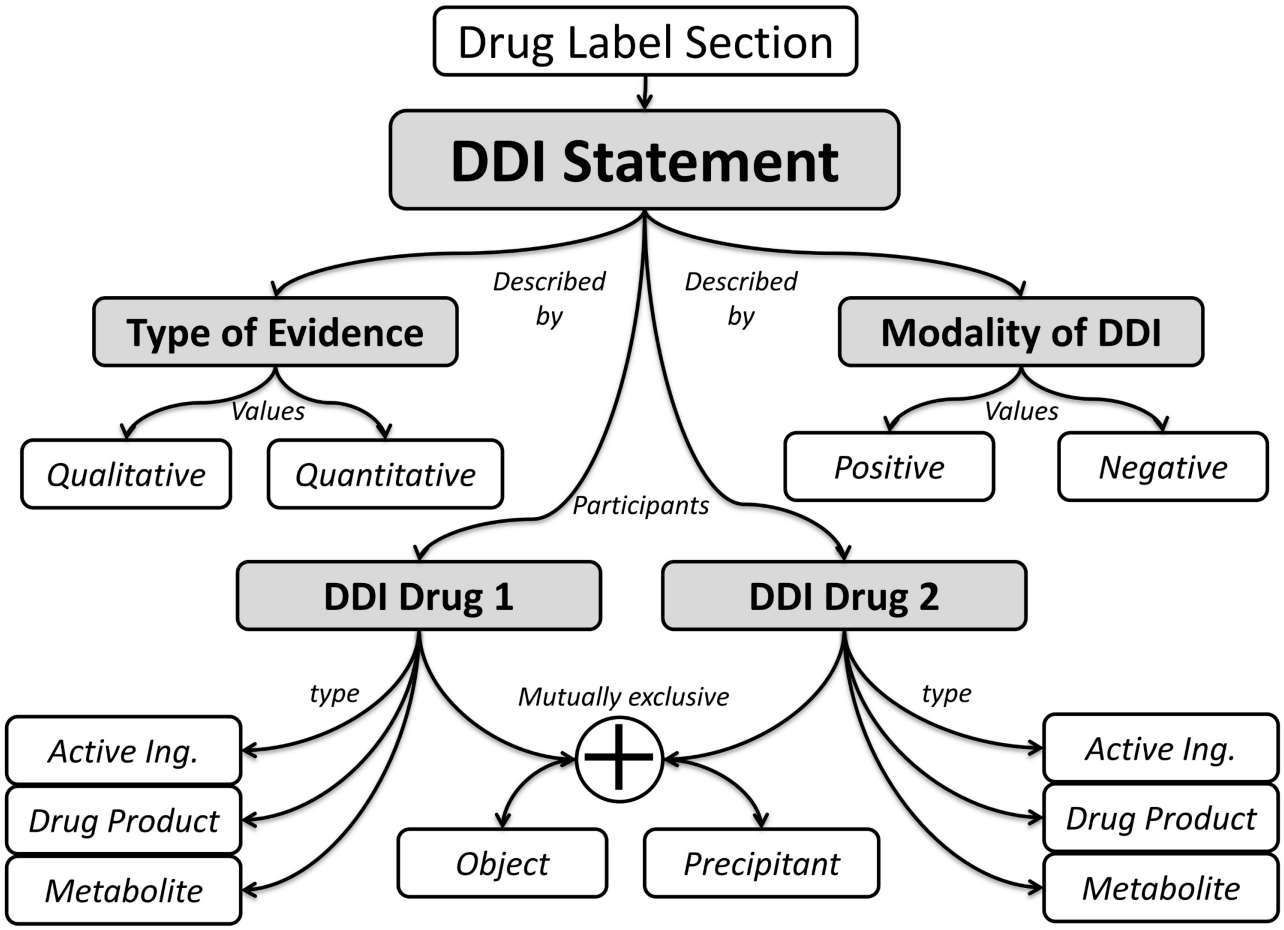
Methods

The Annotation Model

PDDI annotation requires a data model that describes the types of information that must be collected. The PDDI data model used in this study is given in Figure 1. Each PDDI mention is extracted from a span of sentences present within a product label and can include four features:

- Type of evidence (active ingredient, metabolite, or drug product): an active ingredient is a pharmacologically active chemical component used in a drug product. A metabolite is a biochemical entity produced as a result of drug metabolism. A drug product is a packaging of an active ingredient for sale or distribution, often identified by a brand name. Throughout this paper, we use the generic term “drug” to mean any of these three types.
- Role (object or precipitant): the role that each drug plays within the interaction. In pharmacokinetic PDDIs the precipitant drug affects an enzyme that regulates the absorption, distribution metabolism, or excretion of the object drug.
- Statement (quantitative or qualitative): an indication of whether the PDDI mention describes the pharmacokinetic effect of a DDI in quantitative terms (50% increase) or qualitative terms (increase or decrease) with no indication of magnitude.
- Modality (positive or negative): whether the PDDI mention is making a positive or negative claim. A positive claim is one that supports the existence of the interaction. A negative claim is one that explicitly states that no interaction exists between the drugs in question.

Figure 1. Data model used in this study for PDDIs mentioned within drug product labels.

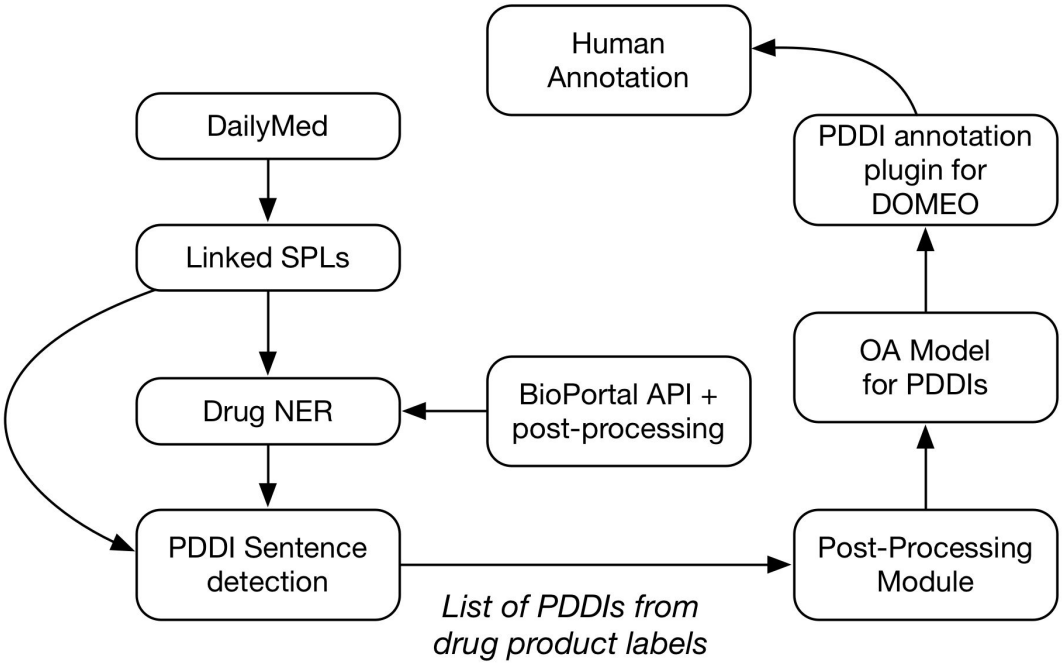


Natural Language Processing Pipeline and Postprocessing Module

In prior work, we developed algorithms for extracting drug named entities and pharmacokinetic PDDI mentions from drug product labels [14]. We integrated our NLP algorithms into a preannotation pipeline (Figure 2). The pipeline used the following steps:

1. The NLP process applies NER to each product label section [32]. The NER algorithm uses the National Center for Biomedical Ontology BioPortal Annotator to extract drug mentions and synonyms from the RxNorm and MeSH terminologies [33]. The results are postprocessed to improve recall and precision by filtering out entities that are not active ingredients, drug products, or metabolites based on entity relationships provided by RxNorm and WordNet [34].
2. Output from the NER process is then processed by an NLP algorithm for identifying pharmacokinetic PDDI mentions [14]. For each product label section, the PDDI extraction algorithm outputs a table of sentence spans labeled as to whether they include a pharmacokinetic PDDI (true or false). Spans including PDDI mentions are also labeled to indicate the modality of the mention (positive or negative). Output of the NLP algorithm is passed to a postprocessing module designed to increase the process's precision and recall (Figure 2). This module uses RxNorm relationships and exact case-insensitive matching to map drug product mentions to unique identifiers of the sole active ingredients.
3. The PDDI mentions present in the corpus are transformed into a machine-readable annotation schema using the Open Annotation data model [35], necessary for subsequent loading into the study annotation tool.
4. Finally, the resulting preannotated named entities and PDDI mentions are loaded into the study annotation tool.

Figure 2. Pipeline for extraction of pharmacokinetic PDDIs from drug labels sections.



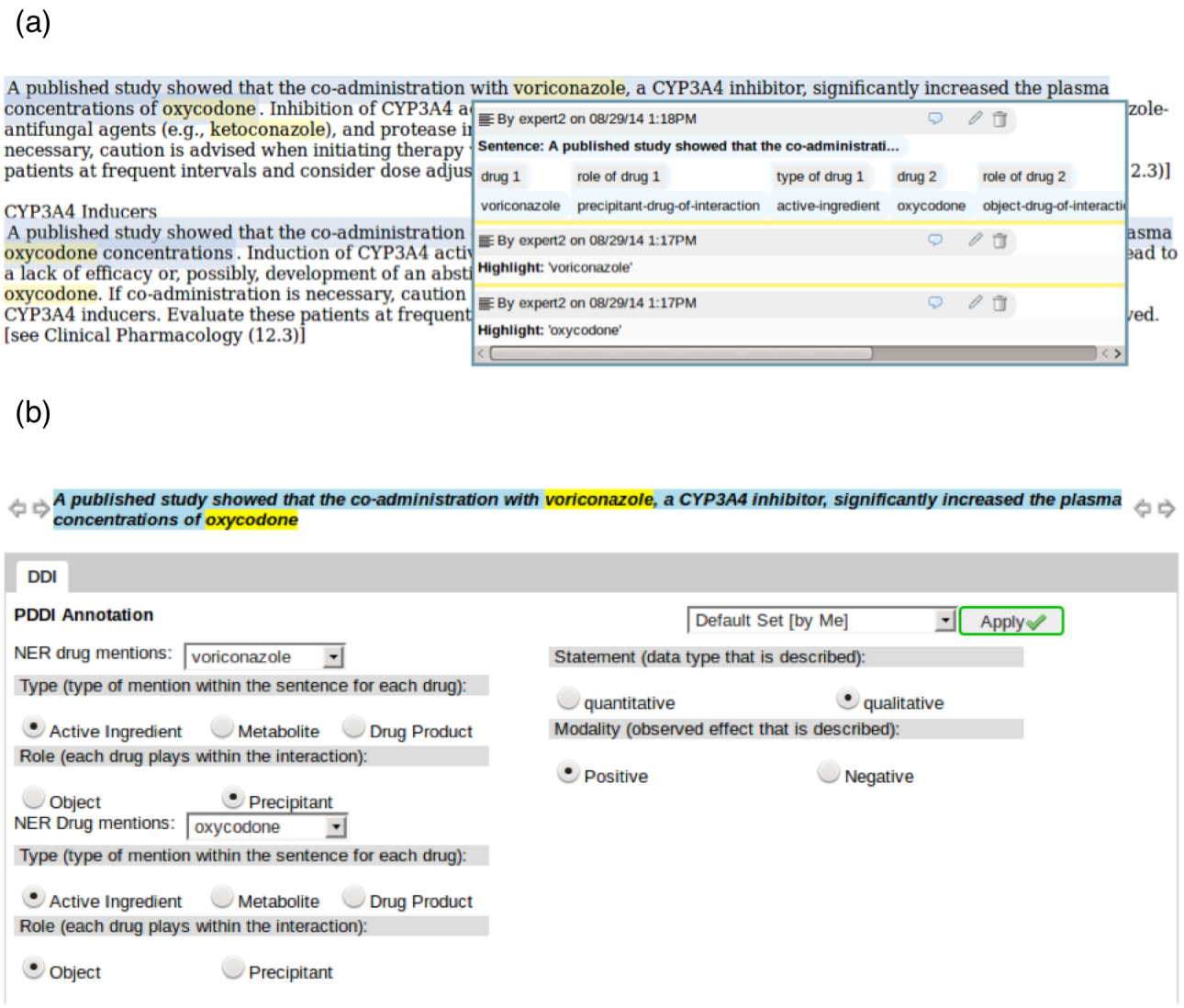
Reference Standard

In an earlier study, we developed a corpus of 208 annotated PDDI statements from SPLs. Two experts in drug information used the data model described above to annotate these sections, with subsequent discussions used to develop a consensus model. The resulting corpus contains 607 pharmacokinetic PDDI mentions along with 3351 active ingredients, 234 drug products, and 201 metabolite mentions [14]. These sections were used in the current study, with the consensus annotations acting as a gold standard.

Drug-Drug Interaction Annotation Tool

Participants used a custom-designed user interface (Figure 3) based on the DOMEO Web-based system [36] to annotate PDDI mentions. DOMEO is an extensible Web application that supports scalable Web-based annotation necessary for crowdsourcing efforts [37]. We extended DOMEO with a plugin that can be used to link text in drug label sections with details of the PDDI data model (Figure 1) [38]. To complete a PDDI annotation task, users would view a product label section and select one or more sentences from the section that discusses the PDDI. They would then use our PDDI annotation plugin to provide values in a Web form indicating the two drugs involved in the interaction, the type and role for each drug, the type of PDDI mention (quantitative or qualitative), and the modality of the mention (positive or negative).

Figure 3. Screenshots of the DOMEO PDDI annotation plugin: (a) product label excerpt with text selected by an annotator as being relevant to a PDDI and (b) form with the fields that the annotator must complete in order to describe the PDDI using the data model described in Figure 1.



Annotation Scenarios

We explored four annotation scenarios aimed at assessing the impact of different approaches to NLP preannotation. The 208 product label sections from our reference standard [14] were distributed across four scenarios so that each scenario had roughly the same number of long and short sections:

- Scenario 1 (no assistance) consisted of 52 label sections with no NLP assistance for annotation. Annotators had to read and highlight all drugs and PDDI mentions within the assigned drug label sections.
- Scenario 2 (drug mentions) consisted of 52 drug label sections with preannotations for drug mentions but not PDDI mentions. Annotators had to correct preannotated drug mentions, identify any drug mentions that the NLP missed, and highlight all PDDIs mentioned in the label sentences.
- Scenario 3 (drug mention plus PDDIs) consisted of 53 label sections preannotated with both drug and PDDI mentions. The annotator had to edit and correct NLP preannotations and add any mentions missed by the NLP.
- Scenario 4 (no assistance, second time), a second completely unassisted scenario, was included with the intent of measuring any learning effects associated with the completion of the NLP-assisted tasks. This scenario consisted of 48 drug label sections.

Each participant completed all four scenarios in order. Three of the 208 sections were reserved for training purposes to familiarize participants with the annotation tool and process, leaving 205 sections to be annotated by each participant.

Participants

A drug expert was defined as a professional in pharmacy or related field with a Doctor of Pharmacy degree or equivalent and more than five years' experience in drug-drug interaction research. A drug nonexpert was defined as an undergraduate or graduate student with some basic training in chemistry. Both expert and nonexpert participants were recruited from personal contacts of the investigative team. All participants were compensated for participating in this study. The University of Pittsburgh Institutional Review Board approved the study protocol as exempt.

Annotator Guidelines and Training

Annotators were provided with guidelines describing the annotation task. Guidelines were written based on assumption of college-level formal training in chemistry (eg, general chemistry) for both groups. The complete guidelines are provided in Multimedia Appendix 1. Participants attended a half-day training session that introduced the goal of the annotation task and provided the annotation guidelines.

Annotation Tasks

Each participant completed all of the four scenarios in the order given above. For each task, the annotators were asked to read the entire content of the relevant drug label sections, identify all drug and PDDI mentions, and record information about the PDDI corresponding to the PDDI annotation model. They were also asked to self-report the amount of time it took to completely annotate each section. The results of each training task were verified to ensure that each annotator completed each scenario according to the study requirements. A short questionnaire completed at the end of each scenario included closed- and open-ended questions about the participant's perception of the usability and effectiveness of the annotation tool and NLP preannotation.

Annotation Performance Metrics

Performance metrics were calculated by comparing the PDDIs in each participant's results with the reference standard described above [14]. User's annotations were considered true positives if they (a) matched the precipitant, object, and modality of the reference standard and (b) used sentences that either partially or exactly overlapped the sentences used in the reference standard. Metrics were computed by label and then averaged by scenario.

We supplemented the standard metrics of precision, recall, and F_1 with additional metrics to gain more insight into the effect of NLP preannotation on the PDDI annotation task. Specifically, for Scenario 3 (ie, the full NER plus NLP preannotation), we evaluated how often participants decided to change NLP annotations and whether those NLP annotations agreed or disagreed with the reference standard.

Results

Two experts and 4 nonexperts were recruited into the study. One expert left the study after experiencing too many difficulties with the PDDI annotation user interface. One nonexpert left the study because of not having time to complete annotations due to work and school commitments. The remaining participants completed the annotation task for all scenarios.

Annotation performances measured in F_1 score relative to the reference standard [14] indicate relatively strong performance (F_1>0.7) for all participants for the first two scenarios, with a drop in performance for the last two scenarios. (Figure 4 and Table 1; full recall and precision results in Multimedia Appendix 2). The performance of the entire NLP pipeline is included for each scenario for comparison even though participants were only provided PDDI preannotations in Scenario 3.

Tables 2 and 3 summarize self-reported task completion times and subjective feedback across the first three scenarios. As Scenario 4 was conducted solely to assess learning effects, task completion time and subjective responses were not collected. Participants differed in their reports of time required, ranging from Nonexpert 1 reporting times comparable to those of the expert to Nonexpert 3 reporting more than 5 hours spent completing Scenario 3 (Table 2).

Results from the subjective question assessing ease of use are given in Table 3. Users agreed that the PDDI annotation interface was moderately difficult when full preannotation assistance was enabled and also agreed that the PDDI annotation plugin without NLP assistance or using a lower level of assistance is relatively easy to use. Full questionnaires and results are given in multimedia appendices 3-7.

Tables 4 and 5 illustrate the agreement between the participants, NLP, and reference standard in the scenario with NLP and preannotation assistance (Scenario 3). Table 4 addresses performance on the 151 PDDI annotations found in the reference standard, while Table 5 summarizes false positives—mentions extracted in the NLP or by users that were not found in the reference standard.

Though exploratory because of the very small sample size, success in detecting true-positive PDDI mentions missed by the NLP was similar between the expert and nonexperts (Table 4, column 2). The expert also had slightly more false negatives than the nonexpert participants irrespective of whether spans were found by NLP (Table 4, columns 1 and 3). False-positive rates for the expert were comparable to those of the nonexperts (Table 5, column 1). Nonexperts also seemed to be slightly more likely to agree with false-positive mentions extracted by the NLP (Table 5, columns 2 and 3).

Table 1. F_1 measures for all participants and NLP system across all scenarios and overall.

Annotator	Scenario 1[a]	Scenario 2[b]	Scenario 3[c]	Scenario 4[d]	Overall
Expert	0.80	0.79	0.54	0.66	0.68
Nonexpert 1	0.79	0.83	0.59	0.53	0.66
Nonexpert 2	0.76	0.68	0.57	0.70	0.67
Nonexpert 3	0.74	0.62	0.53	0.62	0.61
NLP	0.58	0.40	0.41	0.46	0.46

[a]No assistance.

[b]Preannotation of drug mentions.

[c]Preannotation of drug mentions and PDDIs.

[d]No assistance.

Table 2. Participant self-reported task completion times.

Participant	Scenario	<1 hour	1-3 hours	3-5 hours	>5 hours
Expert					
	1	X			
	2	X			
	3	X			
Nonexpert 1					
	1	X			
	2	X			
	3	X			
Nonexpert 2					
	1		X		
	2	X			
	3	X			
Nonexpert 3					
	1			X	
	2			X	
	3				X

Table 3. Usability questionnaire results. All results reported on a 5-point scale (1=*very difficult* to 5=*very easy*).

Participant	Scenario 1	Scenario 2	Scenario 3	Mean
Expert	2	4	2	2.67
Nonexpert 1	4	5	2	3.67
Nonexpert 2	4	5	2	3.67
Nonexpert 3	3	3	2	2.67
Mean	3.25	4.25	2	—

Table 4. Comparison of agreement between the participants, NLP preannotation, and PDDI annotations (N=151) in the reference standard during the scenario with NER and NLP preannotation assistance (Scenario 3).

NLP Result	No mention found		Mention	
Participant	No mention	Mention[a]	No mention[b]	Mention
	NLP FN[f] User FN n (%)	NLP FN User TP n (%)	NLP TP[c] User FN n (%)	NLP TP User TP n (%)
Expert	59 (39.1)	50 (33.1)	23 (15.2)	19 (12.6)
Nonexpert 1	46 (30.5)	63 (41.7)	11 (7.3)	31 (20.5)
Nonexpert 2	43 (28.5)	66 (43.7)	11 (7.3)	31 (20.5)
Nonexpert 3	49 (32.5)	60 (39.7)	13 (8.6)	29 (19.2)

[a]Indicates case where the user corrected an NLP error.

[b]Indicates cases where the NLP was correct and the user was incorrect.

[c]FN: false negative

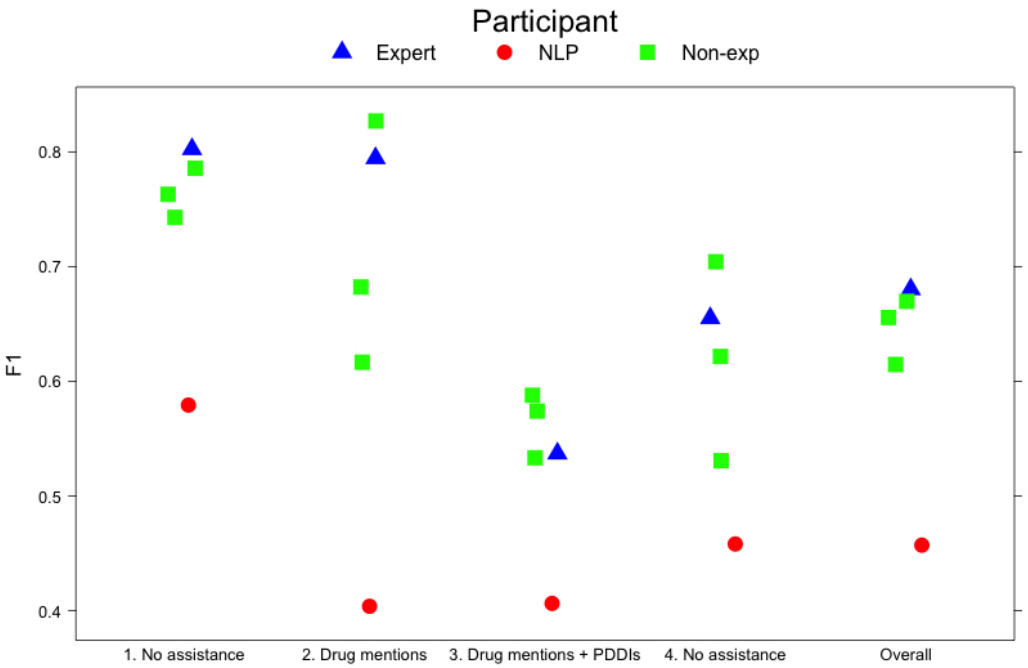
[d]TP: true positive

Table 5. Analysis of user and NLP false positives relative to the reference standard for Scenario 3.

NLP result	No mention	Mention (n=93)	
Participant	Mention[a]	No mention[b]	Mention
	NLP TN User FP n	NLP FP User TN n (%)	NLP FP User FP n (%)
Expert	25	93 (100)	0 (0)
Nonexpert 1	16	88 (94.6)	5 (5.4)
Nonexpert 2	37	86 (92.5)	7 (7.5)
Nonexpert 3	24	88 (94.6)	5 (5.4)

[a]Indicates cases where the user identified spans that were not identified by the NLP. [b]Indicates cases where the NLP identified spans that the participant did not annotate.

Figure 4. Annotator and NLP performance (F1 scores) for each of the four scenarios and overall performance across all four scenarios.



Discussion

Overview

Our long-term goal is to develop tools that will deliver computable representations of reliable, accurate PDDI information to clinicians, facilitating decision support and hopefully reducing adverse events. The number of drugs that might need to be addressed (more than 16,000) and the complexity of the content in the SPLs make this a daunting task. Our experience in building NLP tools for the extraction of PDDI information [10,14] illustrated some of the difficulty and led us to the conclusion that some amount of manual involvement in the process was required.

Our goal in this study was to address two key questions in the development of human-assisted processes for curating PDDI information. Specifically, who should conduct the annotation and what sort of assistance should they receive? Although pharmacists and other domain experts familiar with drug information presumably have the background and training necessary to interpret SPLs, annotation by experts is often prohibitively difficult. Thus, we set out to gain some preliminary insight into the practicality of asking participants not specifically trained in drug information to annotate this data. Second, we were interested in understanding what level of assistance might be helpful for users. If our NLP tools were found to speed completion of annotation tasks without reducing accuracy, this would decrease the cost of PDDI annotation even for nonexperts.

Is It Possible for Nonexperts to Produce Reliable PDDI Annotations From Drug Labels?

Annotation results from the nonexpert group were relatively strong in every scenario and better than the performance of the NLP pipeline (Figure 4). These findings suggest that nonexperts might be able to produce reliable PDDI annotations from drug labels with accuracy levels similar to those of experts and that crowdsourcing might be a feasible option for annotating PDDIs across a broader range of drug product labels. Our results are consistent with earlier demonstrations of the feasibility of applying crowdsourcing to related problems in annotation of biomedical texts [19-22].

Ensuring the success of nonexpert annotations of PDDI mentions will likely require greater attention to two keys issues: the usability of the annotation tools and the selection of the annotators.

Although self-reported task completion times (Table 2) indicated that two of the nonexperts were able to complete all tasks in times comparable to those of the expert, one nonexpert (Nonexpert 3) needed substantially more time. Differences in F_1 scores (Table 1) suggest that annotations provide by Nonexpert 3 were of slightly lower quality than those of the other two nonexperts. The combination of increased task-completion time and lower F_1 scores suggest that Nonexpert 3 may have struggled more than the other participants with the annotation task. In addition, difficulties with the annotation interface prevented one expert user from completing the annotation tasks.

Despite these difficulties, responses to the usability questions (Table 3) were generally positive, suggesting that usability concerns should not be insurmountable. The small sample size and self-reported time results limit our ability to develop a nuanced understanding of specific issues that might have led to increased task completion times or dissatisfaction with the user interface. Observational user studies, including think-aloud feedback from participants, would likely provide insight into usability problems, potential opportunities for redesign [39], and any difficulties associated with the longer task completion times and lower performance of Nonexpert 3.

Results from the repeated no assistance scenario (Scenario 4) do not appear to show any learning effect based on the previous three scenarios. Exposure to the preannotations in scenarios 2 and 3 may have confused participants, pointing out complexities in interpretation of the labels that might have negatively impacted performance.

Identification of individuals who are likely to produce high-quality results will be a key challenge for successful nonexpert annotation results. Although our nonexpert participants all had relevant educational backgrounds and computer experience, variations in the task completion times and F_1 scores suggest that some participants might find PDDI annotations more approachable than others. Future nonexpert PDDI annotation recruitment might draw on experience from prior efforts in crowdsourcing which have found that appropriate screening and training of participants can help improve outcomes [40,41].

What Is the Influence of NLP Assistance on Annotation Quality?

Most participants perceived PDDI annotation to be easier when NER preannotation was provided. However, the full NLP assistance (Scenario 3: drug mention plus PDDI preannotations) was associated with lower levels of perceived usability for both expert and nonexpert participants (Table 2). Complaints about deleting false positives were commonly expressed in the questionnaire data. These results suggest that the performance of the NLP algorithm and the presentation of NLP preannotated PDDIs might have adversely impacted participant performance. Participants suggested several possible improvements, including preannotating with NER and then presenting NLP preannotations only after a section is annotated. The purpose then would be to highlight possibly missed interactions. We think this approach would depend on an NLP algorithm with much better sentence-level performance than the algorithm used in this study.

Although exploratory, the comparison of the agreement between users, NLP preannotations, and the reference standard (tables 4 and 5) suggests several questions for future study. The expert was slightly less likely than the nonexperts to correct NLP false negatives (Table 4, column 1), possibly because the expert might have inappropriately used knowledge of the domain or applied an overly strict interpretation of the PDDI identification guidelines. The expert user was also more likely to reject a correct NLP interpretation (Table 4, column 3) and more likely to reject an incorrect NLP assertion (Table 5, column 2) suggesting that the expert user's thought processes were somehow different than those of the nonexperts. It is also possible that the nonexpert agreement with NLP false positives might be associated with greater trust in NLP on the part of the nonexpert participants. Of course, given the small size of this study, it is entirely possible that these participant-level observations are not statistically significant. Subsequent studies involving more participants and including investigation of user thought processes—perhaps via think-aloud protocols or retrospective interviews—would be needed to understand these phenomena.

Limitations

The generalizability of this study is limited by the small sample size; a larger study would be needed to more accurately characterize the differences between nonexperts, experts, and the NLP annotation. Another potential limitation of our study is that we could not evaluate the characteristics of label sections that might be more difficult to read and annotate by nonexperts. The experimental design attempted to address this concern by balancing the number of sections across each scenario to minimize the effect of differences in difficulty level. The study results might have been influenced by the accuracy of the NLP algorithm and the reliability and usability of the annotation user interface. Interface revisions based on usability might lead to improved performance for experts and nonexperts. Finally, as we did not conduct any debriefing interviews or otherwise assess participant mental states, we are only able to speculate as to factors that might contribute to differences in task performance.

Conclusions

Our goal was to explore of use of nonexperts to annotate PDDI mentions in drug product labels. Our results suggest that nonexperts could produce reliable PDDI annotations from drug labels with efficiency comparable to that of an expert annotator with training in pharmacy or pharmaceutics, indicating that the task of extracting PDDIs from drug product labeling might be suitable for crowdsourcing. Although NER preannotation was found useful to both experts and nonexperts, NLP preannotation as implemented in this study seemed to present an obstacle to all participants. A high performance NLP algorithm might still be helpful if NLP preannotations are shown to annotators after a section is annotated, if only to highlight possibly missed interactions. Improvements in the usability of the annotation tool and screening of potential annotators might further increase performance.

Acknowledgments

Research reported in this paper was partially supported by the Fogarty International Center of Global Health of the National Institutes of Health under grant number 1D43TW008443-01, National Institute on Aging grant K01AG044433, and National Library of Medicine grant 1R01LM011838-01. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. We also thank Paolo Ciccarese and Tim Clark for their advice on the development of the PDDI annotation plugin for DOMEO.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Annotation guidelines provided to study participants.

[PDF File (Adobe PDF File), 2MB - resprot_v5i2e40_app1.pdf]

Multimedia Appendix 2

Full precision, recall and F1 results for all participants and for the NLP pipeline in each of the four scenarios.

[PDF File (Adobe PDF File), 64KB - resprot_v5i2e40_app2.pdf]

Multimedia Appendix 3

Subjective questionnaires.

[PDF File (Adobe PDF File), 44KB - resprot_v5i2e40_app3.pdf]

Multimedia Appendix 4

Subjective responses, Scenario 1.

[XLSX File (Microsoft Excel File), 26KB - resprot_v5i2e40_app4.xlsx]

Multimedia Appendix 5

Subjective responses, Scenario 2.

[XLSX File (Microsoft Excel File), 29KB - resprot_v5i2e40_app5.xlsx]

Multimedia Appendix 6

Subjective responses, Scenario 3.

[XLSX File (Microsoft Excel File), 35KB - resprot_v5i2e40_app6.xlsx]

Multimedia Appendix 7

Subjective responses, Scenario 4.

[XLSX File (Microsoft Excel File), 25KB - resprot_v5i2e40_app7.xlsx]

References

1. Magro L, Moretti U, Leone R. Epidemiology and characteristics of adverse drug reactions caused by drug-drug interactions. Expert Opin Drug Saf 2012 Jan;11(1):83-94. [doi: 10.1517/14740338.2012.631910] [Medline: 22022824]
2. Hansten PD. Drug interaction management. Pharm World Sci 2003 Jun;25(3):94-97. [Medline: 12840961]
3. Dal-Ré R, Pedromingo A, García-Losa M, Lahuerta J, Ortega R. Are results from pharmaceutical-company-sponsored studies available to the public? Eur J Clin Pharmacol 2010 Nov;66(11):1081-1089. [doi: 10.1007/s00228-010-0898-y] [Medline: 20844869]
4. Code of Federal Regulations Title 21. Washington DC: US Food and Drug Administration URL: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.57 [accessed 2015-06-10] [WebCite Cache ID 6ZBdCKzvJ]
5. Guidance for industry: indexing structured product labeling. Washington DC: US Food and Drug Admininstration URL: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072317.pdf [accessed 2015-11-25] [WebCite Cache ID 6dJGbbaTV]
6. Hines LE, Ceron-Cabrera D, Romero K, Anthony M, Woosley RL, Armstrong EP, et al. Evaluation of warfarin drug interaction listings in US product information for warfarin and interacting drugs. Clin Ther 2011 Jan;33(1):36-45. [doi: 10.1016/j.clinthera.2011.01.021] [Medline: 21397772]
7. Pfistermeister B, Saß A, Criegee-Rieck M, Bürkle T, Fromm MF, Maas R. Inconsistencies and misleading information in officially approved prescribing information from three major drug markets. Clin Pharmacol Ther 2014 Nov;96(5):616-624. [doi: 10.1038/clpt.2014.156] [Medline: 25062063]
8. Ayvaz S, Horn J, Hassanzadeh O, Zhu Q, Stan J, Tatonetti NP, et al. Toward a complete dataset of drug-drug interaction information from publicly available sources. J Biomed Inform 2015 Jun;55:206-217 [FREE Full text] [doi: 10.1016/j.jbi.2015.04.006] [Medline: 25917055]

9. Marshall MS, Boyce R, Deus HF, Zhao J, Willighagen EL, Samwald M, et al. Emerging practices for mapping and linking life sciences data using RDF: a case series. Web Semantics: Science, Services and Agents on the World Wide Web 2012 Jul;14(4):2-13. [doi: 10.1016/j.websem.2012.02.003]
10. Boyce RD, Horn JR, Hassanzadeh O, Waard AD, Schneider J, Luciano JS, et al. Dynamic enhancement of drug product labels to support drug safety, efficacy, and effectiveness. J Biomed Semantics 2013;4(1):5 [FREE Full text] [doi: 10.1186/2041-1480-4-5] [Medline: 23351881]
11. Brown SH, Elkin PL, Rosenbloom ST, Husser C, Bauer BA, Lincoln MJ, et al. VA National Drug File Reference Terminology: a cross-institutional content coverage study. Stud Health Technol Inform 2004;107(Pt 1):477-481. [Medline: 15360858]
12. Olvey EL, Clauschee S, Malone DC. Comparison of critical drug-drug interaction listings: the Department of Veterans Affairs medical system and standard reference compendia. Clin Pharmacol Ther 2010 Jan;87(1):48-51. [doi: 10.1038/clpt.2009.198] [Medline: 19890252]
13. Bui Q, Sloot PM, van Mulligen EM, Kors JA. A novel feature-based approach to extract drug-drug interactions from biomedical text. Bioinformatics 2014 Dec 1;30(23):3365-3371 [FREE Full text] [doi: 10.1093/bioinformatics/btu557] [Medline: 25143286]
14. Boyce R, Gardner G, Harkema H. Using natural language processing to identify pharmacokinetic drug-drug interactions described in drug package inserts. 2012 May 07 Presented at: Proceedings of the Workshop on Biomedical Natural Language Processing; 2012; Montreal, Quebec, Canada p. 206-213 URL: https://dl.acm.org/citation.cfm?id=2391151
15. Rzhetsky A, Shatkay H, Wilbur WJ. How to get the most out of your curation effort. PLoS Comput Biol 2009 May;5(5):e1000391 [FREE Full text] [doi: 10.1371/journal.pcbi.1000391] [Medline: 19461884]
16. Good BM, Su AI. Crowdsourcing for bioinformatics. Bioinformatics 2013 Aug 15;29(16):1925-1933 [FREE Full text] [doi: 10.1093/bioinformatics/btt333] [Medline: 23782614]
17. MacLean DL, Heer J. Identifying medical terms in patient-authored text: a crowdsourcing-based approach. J Am Med Inform Assoc 2013;20(6):1120-1127 [FREE Full text] [doi: 10.1136/amiajnl-2012-001110] [Medline: 23645553]
18. Khare R, Good BM, Leaman R, Su AI, Lu Z. Crowdsourcing in biomedicine: challenges and opportunities. Brief Bioinform 2016 Jan;17(1):23-32. [doi: 10.1093/bib/bbv021] [Medline: 25888696]
19. Uzuner O, Solti I, Xia F, Cadag E. Community annotation experiment for ground truth generation for the i2b2 medication challenge. J Am Med Inform Assoc 2010;17(5):519-523 [FREE Full text] [doi: 10.1136/jamia.2010.004200] [Medline: 20819855]
20. Burger JD, Doughty E, Khare R, Wei C, Mishra R, Aberdeen J, et al. Hybrid curation of gene-mutation relations combining automated extraction and crowdsourcing. Database (Oxford) 2014 [FREE Full text] [doi: 10.1093/database/bau094] [Medline: 25246425]
21. Zhai H, Lingren T, Deleger L, Li Q, Kaiser M, Stoutenborough L, et al. Web 2.0-based crowdsourcing for high-quality gold standard development in clinical natural language processing. J Med Internet Res 2013;15(4):e73 [FREE Full text] [doi: 10.2196/jmir.2426] [Medline: 23548263]
22. Khare R, Burger JD, Aberdeen JS, Tresner-Kirsch DW, Corrales TJ, Hirchman L, et al. Scaling drug indication curation through crowdsourcing. Database (Oxford) 2015 [FREE Full text] [doi: 10.1093/database/bav016] [Medline: 25797061]
23. McCoy AB, Wright A, Krousel-Wood M, Thomas EJ, McCoy JA, Sittig DF. Validation of a Crowdsourcing Methodology for Developing a Knowledge Base of Related Problem-Medication Pairs. Appl Clin Inform 2015;6(2):334-344. [doi: 10.4338/ACI-2015-01-RA-0010] [Medline: 26171079]
24. McCoy AB, Wright A, Laxmisan A, Ottosen MJ, McCoy JA, Butten D, et al. Development and evaluation of a crowdsourcing methodology for knowledge base construction: identifying relationships between clinical problems and medications. J Am Med Inform Assoc 2012;19(5):713-718 [FREE Full text] [doi: 10.1136/amiajnl-2012-000852] [Medline: 22582202]
25. Vreeman DJ, Hook J, Dixon BE. Learning from the crowd while mapping to LOINC. J Am Med Inform Assoc 2015 Nov;22(6):1205-1211. [doi: 10.1093/jamia/ocv098] [Medline: 26224334]
26. Dixon BE, Hook J, Vreeman DJ. Learning from the crowd in terminology mapping: the LOINC experience. Lab Med 2015;46(2):168-174. [doi: 10.1309/LMWJ730SVKTUBAOJ] [Medline: 25918199]
27. Hanauer D, Aberdeen J, Bayer S, Wellner B, Clark C, Zheng K, et al. Bootstrapping a de-identification system for narrative patient records: cost-performance tradeoffs. Int J Med Inform 2013 Sep;82(9):821-831. [doi: 10.1016/j.ijmedinf.2013.03.005] [Medline: 23643147]
28. Gobbel GT, Garvin J, Reeves R, Cronin RM, Heavirland J, Williams J, et al. Assisted annotation of medical free text using RapTAT. J Am Med Inform Assoc 2014;21(5):833-841 [FREE Full text] [doi: 10.1136/amiajnl-2013-002255] [Medline: 24431336]
29. Lingren T, Deleger L, Molnar K, Zhai H, Meinzen-Derr J, Kaiser M, et al. Evaluating the impact of pre-annotation on annotation speed and potential bias: natural language processing gold standard development for clinical named entity recognition in clinical trial announcements. J Am Med Inform Assoc 2014;21(3):406-413 [FREE Full text] [doi: 10.1136/amiajnl-2013-001837] [Medline: 24001514]

30. Fort K, Sagot B. Influence of pre-annotation on POS-tagged corpus development. 2010 Presented at: Proceedings of the Fourth Linguistic Annotation Workshop; 7/15/2010; Uppsala, Sweden p. 56-63 URL: http://www.aclweb.org/anthology/W10-1807
31. South BR, Mowery D, Suo Y, Leng J, Ferrández Ã, Meystre SM, et al. Evaluating the effects of machine pre-annotation and an interactive annotation interface on manual de-identification of clinical text. J Biomed Inform 2014 Aug;50:162-172 [FREE Full text] [doi: 10.1016/j.jbi.2014.05.002] [Medline: 24859155]
32. Boyce R, Guzman R, Gardner G. SPL Drug Name Entity Recognizer. URL: https://github.com/dbmi-pitt/u-of-pitt-SPL-drug-NER [accessed 2015-06-09] [WebCite Cache ID 6ZAD5y4tT]
33. Shah NH, Bhatia N, Jonquet C, Rubin D, Chiang AP, Musen MA. Comparison of concept recognizers for building the Open Biomedical Annotator. BMC Bioinformatics 2009;10 Suppl 9:S14 [FREE Full text] [doi: 10.1186/1471-2105-10-S9-S14] [Medline: 19761568]
34. Miller GA. WordNet: a lexical database for English. Commun. ACM 1995;38(11):39-41. [doi: 10.1145/219717.219748]
35. World Wide Web Consortium (W3C). W3C Open Annotation Data Model URL: http://www.openannotation.org/spec/core/ [accessed 2015-06-11] [WebCite Cache ID 6ZD4c1fEe]
36. Ciccarese P, Shotton D, Peroni S, Clark T. CiTO + SWAN: The web semantics of bibliographic records, citations, evidence and discourse relationships. Semantic Web 2012:1-28 [FREE Full text]
37. Ciccarese P, Ocana M, Garcia Castro LJ, Das S, Clark T. An open annotation ontology for science on web 3.0. J Biomed Semantics 2011;2 Suppl 2:S4 [FREE Full text] [doi: 10.1186/2041-1480-2-S2-S4] [Medline: 21624159]
38. Ning Y, Hernandez A, Hochheiser H, Ciccarese P, Boyce R. DOMEO Client Drug-drug Interaction Plugin. URL: https://github.com/rkboyce/DomeoClient [accessed 2015-06-10] [WebCite Cache ID 6ZBq8SVE0]
39. Lazar J, Feng J, Hochheiser H. Research Methods in Human-Computer Interaction. London: Wiley; 2009.
40. Downs J, Holbrook M, Sheng S, Cranor L. Are your participants gaming the system? Screening Mechanical Turk workers. 2010 Presented at: Proceedings of the SIGCHI Conference on Human Factors in Computing Systems; April 10-15, 2010; Atlanta, GA p. 2399-2402. [doi: 10.1145/1753326.1753688]
41. Mitra T, Hutto C, Gilbert E. Comparing person- and process-centric strategies for obtaining quality data on Amazon Mechanical Turk. 2015 Presented at: Proceedings of the 33rd Annual ACM Conference on Human Factors in Computing Systems; 2015; Seoul, Republic of Korea p. 1345-1354. [doi: 10.1145/2702123.2702553]

Abbreviations

NER: named entity recognizer
NLP: natural language processing
SPL: structured product label
PDDI: potential drug-drug interactions

Edited by G Eysenbach; submitted 17.08.15; peer-reviewed by K Doing-Harris, P Schulz; comments to author 12.11.15; revised version received 25.11.15; accepted 19.12.15; published 11.04.16.

Please cite as:
Hochheiser H, Ning Y, Hernandez A, Horn JR, Jacobson R, Boyce RD
Using Nonexperts for Annotating Pharmacokinetic Drug-Drug Interaction Mentions in Product Labeling: A Feasibility Study
JMIR Res Protoc 2016;5(2):e40
URL: http://www.researchprotocols.org/2016/2/e40/
doi:10.2196/resprot.5028
PMID:27066806

Original Paper

Cardiac Rhythm Monitoring After Acute Decompensation for Heart Failure: Results from the CARRYING ON for HF Pilot Study

Emilio Vanoli[1], MD PhD; Andrea Mortara[2], MD; Paolo Diotallevi[3], MD; Giuseppe Gallone[2], MD; Barbara Mariconti[4], MD; Edoardo Gronda[5], MD; Alessandra Gentili[6], MS; Silvia Bisetti[7], MS; Giovanni Luca Botto[4], MD

[1]Dept Molecular Medicine, University of Pavia, Italy, Sesto San Giovanni, Milano,, Italy
[2]Policlinico di Monza, Cardiovascular Department, Monza, Italy
[3]Clinica San Gaudenzio, Novara, Italy
[4]Azienda Ospedaliera S.Anna, Como, Italy
[5]IRCCS Multimedica, Sesto San Giovanni, Milano, Italy
[6]Medtronic Regional Clinical Center, Roma, Italy
[7]Medtronic Italia, Milano, Italy

Corresponding Author:
Emilio Vanoli, MD PhD
Dept Molecular Medicine, University of Pavia, Italy
IRCCS MultiMedica, Via Milanese 300,
Sesto San Giovanni, Milano,, 20099
Italy
Phone: 39 3482638297
Fax: 39 0224209335
Email: emivano@gmail.com

Abstract

Background: There's scarce evidence about cardiovascular events (CV) in patients with hospitalization for acute heart failure (HF) and no indication for immediate device implant.

Objective: The CARdiac RhYthm monitorING after acute decompensatiON for Heart Failure study was designed to assess the incidence of prespecified clinical and arrhythmic events in this patient population.

Methods: In this pilot study, 18 patients (12 (67%) male; age 72±10; 16 (89%) NYHA II-III), who were hospitalized for HF with low left ventricular ejection fraction (LVEF) (<40%) and no immediate indication for device implant received an implantable loop recorder (ILR) before hospital discharge. Follow-up visits were scheduled at 3 and 6 months, and at every 6 months until study closure; device data were remotely reviewed monthly. CV mortality, unplanned CV hospitalization, and major arrhythmic events during follow-up were analyzed.

Results: During a median follow-up of 593 days, major CV occurred in 13 patients (72%); of those, 7 patients had at least 1 cardiac arrhythmic event, 2 had at least a clinical event (CV hospitalization or CV death), and 4 had both an arrhythmic and a CV event. Six (33%) patients experienced 10 major clinical events, 5 of them (50%) were HF related. During follow-up, 2 (11%) patients died due to a CV cause and 3 (16%) patients received a permanent cardiac device.

Conclusions: After an acute HF hospitalization, patients with LVEF<40% and who are not readily eligible for permanent cardiac device implant have a known high incidence of major CV event. In these patients, ILR allows early detection of major cardiac arrhythmias and the ability to react appropriately in a timely manner.

Trial Registration: ClinicalTrials.gov NCT01216670; https://clinicaltrials.gov/ct2/show/NCT01216670

(JMIR Res Protoc 2016;5(2):e62) doi:10.2196/resprot.4380

KEYWORDS

continuous cardiac monitoring; implantable loop recorder; acute heart failure; arrhythmias

Introduction

Acute heart failure (AHF) episodes that induce hospitalizations represent one of the largest causes of health status deterioration [1]. About 45% of patients hospitalized with AHF will be rehospitalized at least once (and 15% at least twice) within 12 months [2]. Estimates of the risk of death or rehospitalization within 60 days of admission vary from 30% to 60%, depending on the population studied [2-8]. A significant proportion of heart failure (HF) patients do not undertake any device implant strategy since they do not meet the guidelines criteria [2]. Very little, if any, monitored information exists in those patients experiencing AHF with modest left ventricle impairment or with HF with preserved left ventricular ejection fraction (LVEF). Timely information might allow interventions that then avoid major cardiovascular (CV) events and possible progressive worsening of the disease leading to hospitalization. The availability of implantable devices to continuously monitor cardiac trends may provide early warning of changes in cardiac status, which would then allow early clinical management and possibly reduce the number of HF hospitalizations. The CARdiac RhYthm monitorING after acute decompensatiON for Heart Failure (CARRYING ON for HF) trial was designed to assess the efficacy of implantable loop recorders (ILRs) in the early detection of prespecified clinical and arrhythmic events in this patient population.

Methods

Study Design and Patient Population

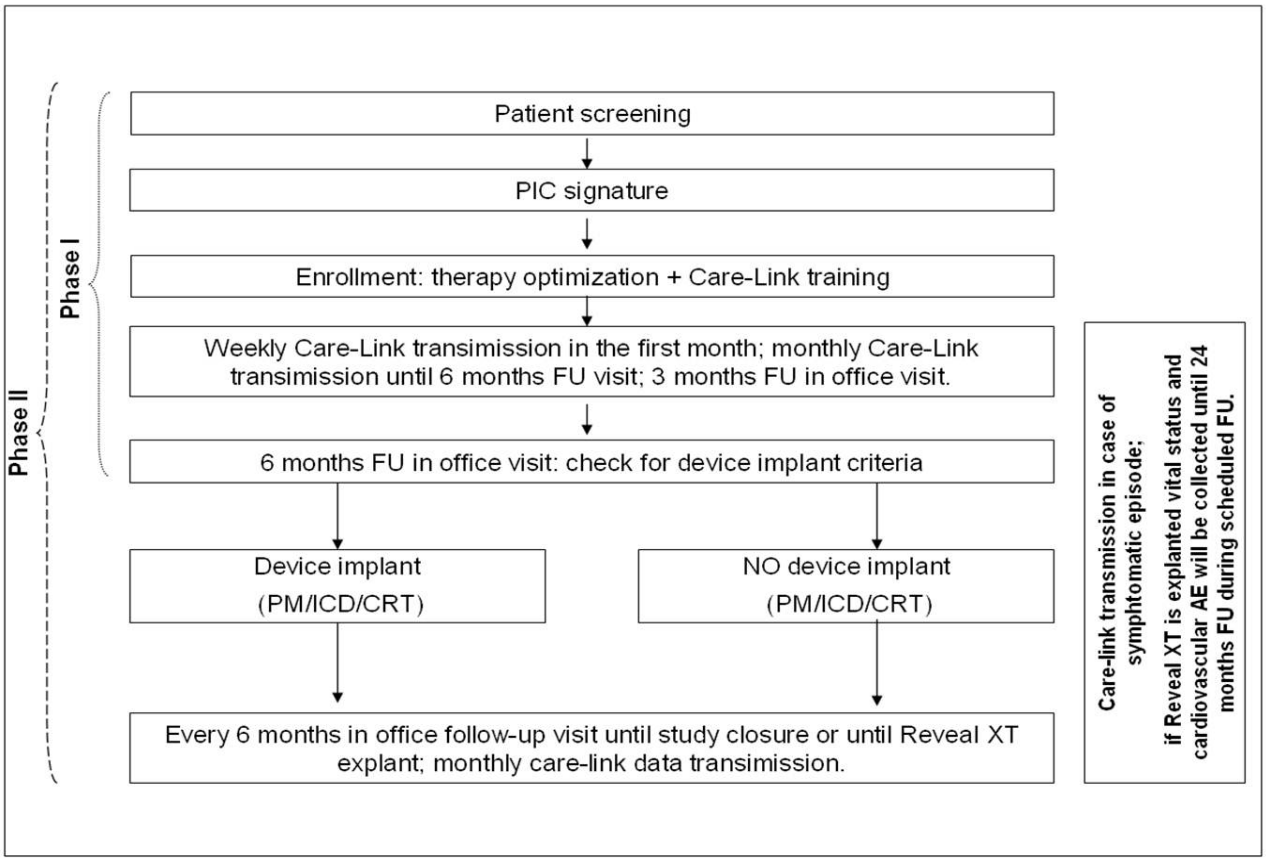
In this prospective pilot study, patients who were hospitalized for AHF, had an LVEF <40% but no immediate indication for device implant, and received an ILR before hospital discharge were enrolled.

Clinical follow-up visits were scheduled at 3 and 6 months and every 6 months thereafter. Device data were reviewed monthly through the Care-Link remote monitoring system or at any time the patients had symptoms (ClinicalTrials.gov; Identifier: NCT01216670). CARRYING-ON for HF Study design is reported in Figure 1.

Informed consent was obtained from each enrolled patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the local ethics committee.

The aim of the study was to assess the capability of loop recording to recognize early signs of prespecified clinical and arrhythmic events in this cohort of patients. Prespecified events were: (1) CV mortality or unplanned CV hospitalization and (2) any cardiac arrhythmic event detected by the implanted device (Sinus bradycardia: ≤ 30 beats per minutes (bpm), ≥ 8s; Sinus arrest: ≥ 5s; atrioventricular (AV) block (2°, 3°): ≤ 30 bpm, ≥ 8s; atrial fibrillation (AF): > 6 min; non-sustained ventricular tachycardia (VT): ≥ 125 bpm, ≥16 beats; sustained VT: > 30 sec). The main inclusion criteria were: (1) a history of at least 1 HF hospitalization, emergency department visit, or urgent office visit necessitating intravenous (IV) diuretic or augmentation of oral diuretic, IV inotropic, or IV vasodilator or other HF parenteral therapy within 15 days prior to device implant; (2) an implanted Medtronic Reveal XT ILR device (< 15 days post-implant); and (3) LVEF < 40%. Main exclusion criteria were: (1) New York Heart Association (NYHA) Class IV (chronic or ambulatory); (2) planned or previous implant of an implantable cardioverter defibrillator (ICD) or pacemaker device; (3) severe chronic obstructive pulmonary disease; (4) permanent AF at time of enrolment; and (5) ST segment elevation at electrocardiogram (ECG). A Reveal XT ILR was used for continuous cardiac monitoring. The ILR was implanted within 15 days the AHF event. All the patients enrolled received a remote monitoring system and were requested to transmit Reveal XT data on a monthly base or in case any symptoms occurred.

Figure 1. Study design.



Statistical Analysis

Continuous data were summarized as mean and standard deviation or median and 25th-75th percentiles in case of skewed distributions. Absolute and relative frequencies were reported for categorical variables. Kaplan-Meier method was used to display the time to first event. The mean cumulative function (MCF) plot for the number of recurrent events was used to display the overtime trend of the events rate. Statistical analyses were performed using SAS 9.3 for Windows (SAS Institute Inc, Cary, NC).

Results

Baseline Characteristics

The patients on average were 73±10 years old, 12 (67%) were male, and 7 (39%) had ischemic cardiomyopathy. According to guidelines, all the patients at the time of enrollment had no immediate indication to receive a permanent implantable cardiac device: 8 (44%) patients had LVEF > 35%, 2patients were in NYHA functional class I, and 9 (50%) patients were not under optimized pharmacological treatment for HF at the time of the AHF event. Most patients (15/18, 83%) were on beta-blocker therapy (11 were on bisoprolol 2.5 mg twice a day and 4 were on carvedilol 12.5 mg twice a day). Further baseline characteristics are reported in Table 1.

Table 1. Baseline characteristics of study population.

Baseline Patients Characteristics[a]		N=18 (%)
Age, y		73±10
Gender	Male	12 (67%)
Ischemic etiology		7 (39%)
History of AF		8 (44%)
$CHADS_2$ score (for AF patients)		3.0+0.7
History of NS-VT		2 (18%)
QRS complex, ms		106±23
LBBB		4 (22%)
NYHA	Functional class I	2 (11%)
	Functional class II	13 (72%)
	Functional class III	3 (17%)
Cardiovascular-Related Diseases	MI + CAD	6 (35%)
	Hypertension	11 (65%)
	Valvular heart disease	6 (35%)
	Previous cardiovascular surgeries	9 (50%)
	Type 2 diabetes	4 (22%)
Echocardiographic Measurements	LVEF (%)	34±6.0
	LVEF ≤ 35%	10 (56%)
	LVESV, mL	108±38
	LVESV ≥ 100 mL	7 (47%)
Drug Therapy at Discharge	Diuretic	17 (94%)
	ACE inhibitor and/or ARB	16 (89%)
	Beta blocker	15 (83%)
	Amiodarone	10 (56%)
	Anticoagulant	14 (78%)

Abbreviations: ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CAD, coronary artery disease; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MI, myocardial infarction; NS-VT, non-sustained ventricular tachycardia; NYHA, New York Heart Association.

[a]Data are expressed as mean ± standard deviation or absolute (relative) frequencies.

Clinical Outcomes

During a median follow-up of 593 days (mean 509+260), major CV events occurred in 13 patients (72%, median time to first combined event 162 days (39-606)); 11 patients had at least 1 cardiac arrhythmic event, 2 had at least 1 clinical event (CV hospitalization or CV death), and 4 had both arrhythmic and clinical events. Figure 2 shows clinical and arrhythmic events incidence and distribution.

Six (33%) patients experienced 10 major clinical events; 5 (50%) of which were HF-related with 1 patient dying due to HF (terminal rhythm: asystole) and 1 patient dying due to an acute CV event (ruptured cerebral aneurysm). Distribution of detected major clinical and arrhythmic events is reported in Table 2.

Table 2. Type and frequency of clinical and arrhythmic events that occurred[a].

Clinical Events		Events (n=10)	Patients with Events (n=6)
CV death[b], n (%)		2 (20%)	2 (33%)
	of which HF-related death, n (%)	1 (10%)	1 (1.7%)
CV hospitalizations, n (%)		10 (100%)	6 (100%)
	of which HF-related hospitalizations, n (%)	5 (50%)	3 (50%)
Arrhythmic Events		Events (n=1326)	Patients with Events (n=11)
	Synus bradycardia, n (%) (≤ 30 bpm, ≥ 8s)	8 (0.6%)	3 (27%)
	Sinus arrest, n (%) (≥ 5s)	2 (0.2%)	2 (18%)
	AV block, n (%) (≤ 30 bpm, ≥ 8s)	--	--
	AF-AT, n (%) (> 6 min)	1297 (97.7%)	8 (73%)
	Non-Sustained VT, n (%) (≥ 125 bpm, ≥16 beats)	13 (1%)	2 (18%)
	Sustained VT, n (%) (> 30 sec)	6 (0.5%)	2 (18%)

Abbreviations: AF, atrial fibrillation; AT, atrial tachycardia; AV, atrioventricular; CV, cardiovascular; HF, heart failure; VT, ventricular tachycardia.

[a]Data are expressed as absolute (relative) frequencies.

[b]The 2 events of death also had previous hospitalizations.

During follow-up, 3 (16%) patients were implanted with a permanent cardiac device according to current guidelines (in 2 patients who developed sustained-VT, a cardiac resynchronization therapy with defibrillator backup device (CRT-D) was implanted; in the 1 patient with sinus arrest and LVEF < 35%, a single chamber ICD was implanted). Eight patients suffered paroxysmal AF that was often asymptomatic (62%); the mean $CHADS_2$ score in these 8 patients was 3.0+0.7, as all had a $CHADS_2$ score ≥2.

As per heart rate (HR), we computed its circadian behavior: the 2 patients who had a nocturnal HR > 70 bpm for > 85% of the night had major clinical events, while this occurred in only 3/16 (19%) of the patients with nocturnal HR < 70 bmp.

Figure 3 shows Kaplan-Meier analysis for clinical and arrhythmic events, both for time to first combined event (Figure 3a) and for cumulative combined events incidence (Figure 3b).

Figure 2. Clinical and arrhythmic events incidence and distribution.

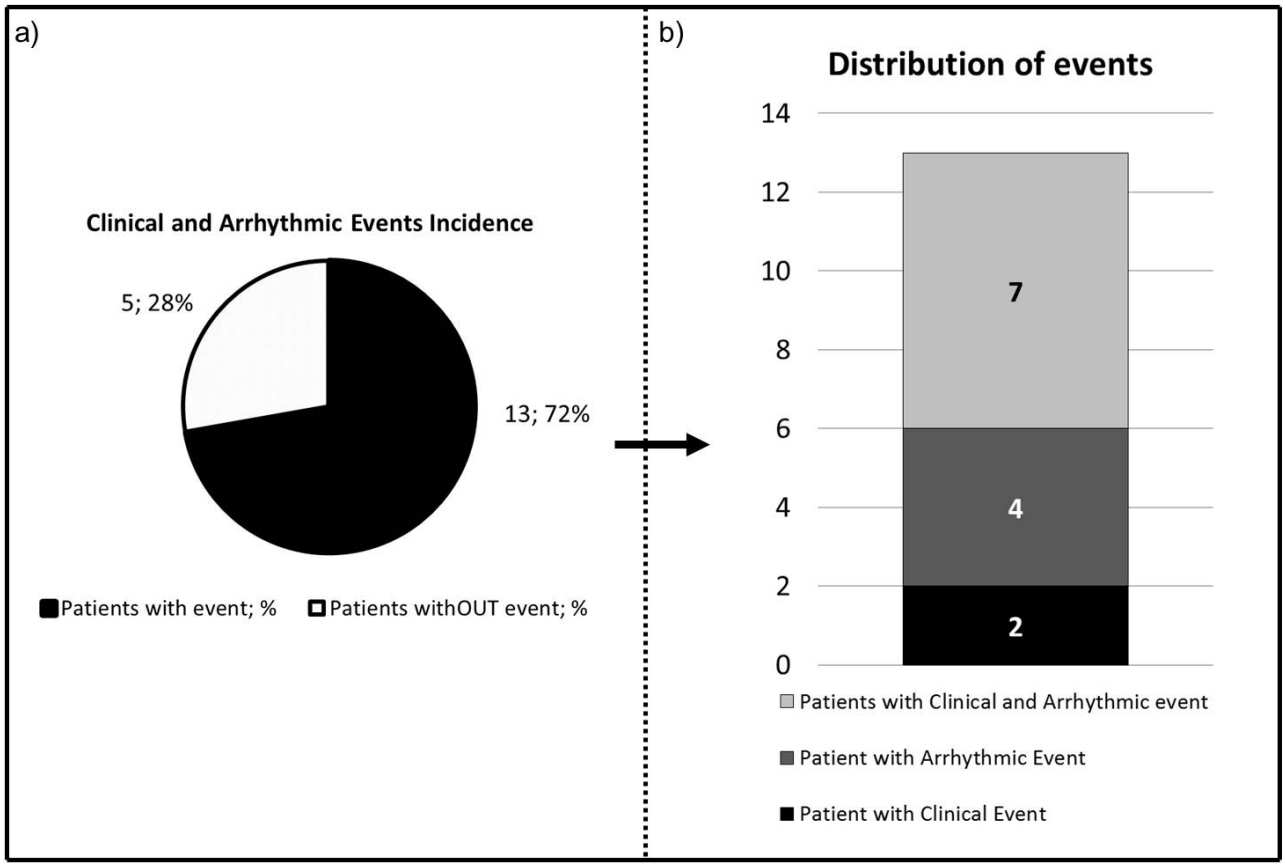
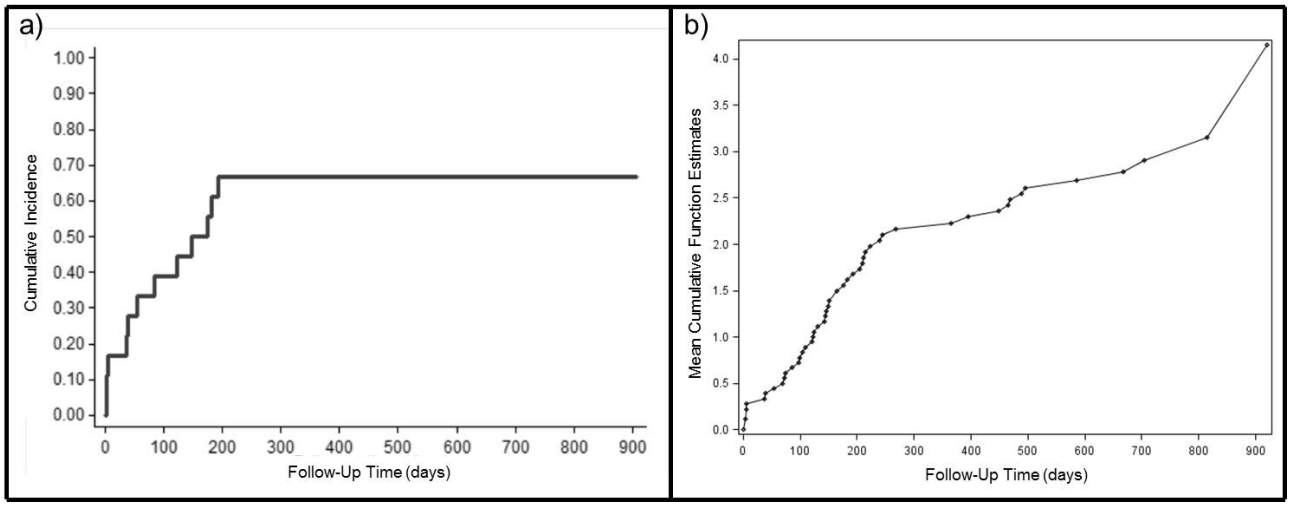


Figure 3. Kaplan-meier analysis for clinical and arrhythmic events.



Discussion

The main finding from this study, which might carry significant clinical implications, is that continuous ECG and HR monitoring by loop recorders might contribute to the early recognition of cardiac rhythm abnormalities contributing to an observed very high incidence of major CV (72%) events. Such high event risk is known to occur in patients with LVEF < 40% who are not eligible for ICD implant within 6 months after an HF hospitalization. The study population, despite its small size, was representative of the clinical reality: elderly patients, prevalently NYHA class II, with a mean $CHADS_2$ score of 3. The high morbidity detected in the study was not unexpected, but the clinical information provided by the CARRYING ON for HF study deserves specific attention. We can conjecture that the appropriate use of remote monitoring as part of a more comprehensive approach to such patients may decrease the observed high re-hospitalization rate after an AHF. The CARRYING-ON HF study was designed to record events but did not prescribe any specific intervention. It is, however, reasonable to believe that the early detection of rhythm and conduction disturbances by ILR will allow clinicians to react appropriately in a more timely manner, avoiding quick progression of the disease and worst outcomes.

In fact, half of the study population had an AHF during the study period. These patients were being treated with a suboptimal HF medical strategy and the continuous monitoring led to subsequent optimal medical titration for HF, arrhythmia management, and stroke prevention. This should be understood in view of the CRYSTAL AF study [9] indicating that stroke may be the first clinical manifestation of AF. The analysis of the time to first combined event (Figure 3) and of the cumulative combined events provides further important information. The first is that a 6-month-long monitoring period is not sufficient to detect a first significant event in all the patients who are bound to have them. Secondly, beyond 6 months a small proportion of combined events occurred possibly because of the fatal event on one side and the optimization of patient management induced by the monitoring device on the other. In this context it is noteworthy that 16/18 (89%) patients had an optimal nocturnal HR (less < 70 bpm). Thus, it may not be incidental that the only 2 patients with an overnight inappropriate HR had clinical events while this occurred in only 3/16 (19%) patients with controlled nocturnal HR. This observation is indeed coherent with the predictive value of HR and its circadian variation [10-11]. Furthermore the ILR detected episodes of sustained VT that met the criteria for 2 CRT-D implants. In a third case, a detection of a life-threatening event occurred: nocturnal long pauses (> 8 sec) were discovered. In this patient, the concomitant presence of LVEF < 35% and the AV conduction disturbance led to a single chamber ICD implant. These 3 cases were diagnosed by the ILR and allowed the timely intervention that prevented a potential life-threatening event.

Limitations

The main limitation of this pilot study is the small number of patients enrolled. Our study, planned as a feasibility and methodology study, was not powered to determine the overall prevalence of CV events after an AHF episode nor to test the effectiveness of ILR in reducing CV events in this population. The primary aim was descriptive as a preliminary fundamental information to design a larger comparative study.

Conclusions

The CARRYING ON for HF study provided meaningful information on the many (72%) patients hospitalized for an acute HF episode who are not eligible, according to current guidelines, to receive an implantable cardiac device and who later develop CV and arrhythmic events during the follow-up.

The present finding provides some background for future prospective studies aimed at the assessment of the risk stratification of continuous cardiac monitoring in HF patients who are not deemed eligible for immediate implantation of a permanent cardiac device.

Acknowledgments

We would like to thank Sabrina De Cicco and Melissa Gioia for their support in data collection. We also thank Alessio Marseglia and Marco Vimercati for the management of data. This work was supported by Medtronic Italia.

Conflicts of Interest

Alessandra Gentili and Silvia Bisetti are Medtronic employees. There are no other conflicts of interest.

References

1. Fonarow GC, ADHERE Scientific Advisory Committee. The Acute Decompensated Heart Failure National Registry (ADHERE): opportunities to improve care of patients hospitalized with acute decompensated heart failure. Rev Cardiovasc Med 2003;4 Suppl 7:S21-S30. [Medline: 14668697]
2. McMurray John J V, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Lip Gregory Y H, Task Force for the DiagnosisTreatment of AcuteChronic Heart Failure 2012 of the European Society of Cardiology, Ben Lamin Hisham A, ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012 Aug;14(8):803-869. [doi: 10.1093/eurjhf/hfs105] [Medline: 22828712]
3. Di LA, Scherillo M, Maggioni AP, Acquarone N, Ambrosio GB, Annicchiarico M, et al. Current presentation and management of heart failure in cardiology and internal medicine hospital units: a tale of two worlds--the TEMISTOCLE study. Am Heart J 2003 Oct;146(4):E12. [doi: 10.1016/S0002-8703(03)00315-6] [Medline: 14564335]
4. Oliva F, Mortara A, Cacciatore G, Chinaglia A, Di LA, Gorini M, et al. Acute heart failure patient profiles, management and in-hospital outcome: results of the Italian Registry on Heart Failure Outcome. Eur J Heart Fail 2012 Nov;14(11):1208-1217. [doi: 10.1093/eurjhf/hfs117] [Medline: 22833614]
5. Tavazzi L, Senni M, Metra M, Gorini M, Cacciatore G, Chinaglia A, IN-HF (Italian Network on Heart Failure) Outcome Investigators. Multicenter prospective observational study on acute and chronic heart failure: one-year follow-up results of IN-HF (Italian Network on Heart Failure) outcome registry. Circ Heart Fail 2013 May;6(3):473-481 [FREE Full text] [doi: 10.1161/CIRCHEARTFAILURE.112.000161] [Medline: 23476054]
6. O'Connor CM, Stough WG, Gallup DS, Hasselblad V, Gheorghiade M. Demographics, clinical characteristics, and outcomes of patients hospitalized for decompensated heart failure: observations from the IMPACT-HF registry. J Card Fail 2005 Apr;11(3):200-205. [Medline: 15812748]

7. Cleland J G F, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, van Gilst W H, Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The EuroHeart Failure survey programme--a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. Eur Heart J 2003 Mar;24(5):442-463 [FREE Full text] [Medline: 12633546]
8. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol 2007 Aug 21;50(8):768-777 [FREE Full text] [doi: 10.1016/j.jacc.2007.04.064] [Medline: 17707182]
9. Sanna T, Diener H, Passman RS, Di LV, Bernstein RA, Morillo CA, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med 2014 Jun 26;370(26):2478-2486. [doi: 10.1056/NEJMoa1313600] [Medline: 24963567]
10. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet 2010 Sep 11;376(9744):875-885. [doi: 10.1016/S0140-6736(10)61198-1] [Medline: 20801500]
11. Adamson PB, Smith AL, Abraham WT, Kleckner KJ, Stadler RW, Shih A, InSync III Model 8042Attain OTW Lead Model 4193 Clinical Trial Investigators. Continuous autonomic assessment in patients with symptomatic heart failure: prognostic value of heart rate variability measured by an implanted cardiac resynchronization device. Circulation 2004 Oct 19;110(16):2389-2394 [FREE Full text] [doi: 10.1161/01.CIR.0000139841.42454.78] [Medline: 15313946]

Abbreviations

ACE: angiotensin-converting enzyme
AF: atrial fibrillation
AHF: acute heart failure
ARB: angiotensin receptor blocker
AV: atrioventricular
bpm: beats per minutes
CAD: coronary artery disease
CARRYING ON for HF: The CARdiac RhYthm monitorING after acute decompensatiON for Heart Failure
CRT-D: cardiac resynchronization therapy with defibrillator back-up device
CV: cardiovascular
ECG: electrocardiogram
HF: heart failure
HR: heart rate
ICD: implantable cardioverter defibrillator
ILR: implantable loop recorder
IV: intravenous
LBBB: left bundle branch block
LVEF: left ventricular ejection fraction
LVESV: left ventricular end-systolic volume
MI: myocardial infarction
NS-VT: non-sustained ventricular tachycardia
NYHA: New York Heart Association
VT: ventricular tachycardia

Edited by G Eysenbach; submitted 26.02.15; peer-reviewed by F Leyva; comments to author 23.10.15; revised version received 18.11.15; accepted 28.01.16; published 26.04.16.

Please cite as:
Vanoli E, Mortara A, Diotallevi P, Gallone G, Mariconti B, Gronda E, Gentili A, Bisetti S, Botto GL
Cardiac Rhythm Monitoring After Acute Decompensation for Heart Failure: Results from the CARRYING ON for HF Pilot Study
JMIR Res Protoc 2016;5(2):e62
URL: http://www.researchprotocols.org/2016/2/e62/
doi:10.2196/resprot.4380
PMID:27118481

Short Paper

Online Focus Group Discussion is a Valid and Feasible Mode When Investigating Sensitive Topics Among Young Persons With a Cancer Experience

Lena Wettergren[1], RN, PhD; Lars E Eriksson[2,3,4], RN, MSc, PhD; Jenny Nilsson[1], RN, MSc (Nursing); Anna Jervaeus[1], RN, MSc, PhD; Claudia Lampic[1], Lic Psych, PhD

[1]Division of Nursing, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Huddinge, Sweden

[2]Medical Management Center (MMC), Department of Learning, Informatics, Management and Ethics (LIME), Karolinska Institutet, Stockholm, Sweden

[3]Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden

[4]School of Health Sciences, City University London, London, United Kingdom

Corresponding Author:
Lena Wettergren, RN, PhD
Division of Nursing
Department of Neurobiology, Care Sciences and Society
Karolinska Institutet
23 300
Huddinge, SE-141 83
Sweden
Phone: 46 524 836 50
Fax: 46 524 888 50
Email: lena.wettergren@ki.se

Related Article:

This is a corrected version. See correction statement: http://www.researchprotocols.org/2016/2/e92/

Abstract

Background: Clinical research often lacks participants of young age. Adding to the small amount of scientific studies that focus on the population entering adulthood, there are also difficulties to recruit them. To overcome this, there is a need to develop and scientifically evaluate modes for data collection that are suitable for adolescents and young adults. With this in mind we performed 39 online focus group discussions among young survivors of childhood cancer to explore thoughts and experiences around dating, being intimate with someone, and having children.

Objective: The aim of the study was to evaluate online focus group discussions as a mode for data collection on sensitive issues among young persons with a cancer experience.

Methods: One hundred thirty-three young persons (16-25 years) previously diagnosed with cancer, participated in 39 synchronous online focus group discussions (response rate 134/369, 36%). The mode of administration was evaluated by analyzing participant characteristics and interactions during discussions, as well as group members' evaluations of the discussions.

Results: Persons diagnosed with central nervous tumors (n=30, 27%) participated to a lower extent than those with other cancer types (n=103, 39%; χ 2= 4.89, *P*=.03). The participants described various health impairments that correspond to what would be expected among cancer survivors including neuropsychiatric conditions and writing disabilities. Even though participants were interested in others' experiences, sexual issues needed more probing by the moderators than did fertility-related issues. Group evaluations revealed that participants appreciated communicating on the suggested topics and thought that it was easier to discuss sex when it was possible to be anonymous toward other group members.

Conclusions: Online focus group discussions, with anonymous participation, are suggested to be a feasible and valid mode for collecting sensitive data among young persons with a cancer experience.

(JMIR Res Protoc 2016;5(2):e86) doi:10.2196/resprot.5616

KEYWORDS

adolescent; data collection; focus groups; Internet; neoplasms; young adult

Introduction

Focus group discussions is an established mode for collecting data that have the possibility to, in some ways, move beyond individual interviews by simultaneously taking different perspectives and opinions into account when letting participants interact during a moderated discussion [1,2]. Such discussions may also be performed online [3], which can increase response rates in groups comfortable using computers (eg, young populations) [4].

Based on the abovementioned, we performed online focus group discussions with young childhood cancer survivors to explore their thoughts about fertility and sexuality. The aims were to investigate what adolescent and young adult survivors of childhood cancer think about the risk of being infertile and how they reason about having biological children [5]. Additionally, we aimed to explore this group's views about sex and sexual experiences and their possible needs for care and support from health care professionals regarding sexual life [6]. The transcripts from the group discussions were analysed inductively with content analysis [7]. The risk of infertility was viewed to negatively impact on well-being and intimate relationships [5]. The findings regarding sexuality showed that many participants had not reflected over the possibility that their cancer experience could impact on sexual life [6]. Still, thoughts and worries were expressed, such as feeling insecure and not keeping up with your peers. Physical complaints included vaginal dryness, difficulties getting and keeping erections, and reaching orgasm.

While online focus group discussions may facilitate discussion of sensitive issues [4], advantages and disadvantages of this mode of data collection in vulnerable populations (eg, patients) are largely unknown [8]. The aim of the present study was therefore to evaluate online focus group discussions as a mode for data collection on sensitive issues among young persons with a cancer experience.

Methods

The main study's procedure and aims have briefly been presented in the introduction. This paper will evaluate the mode of administration (ie, online focus group discussions).

Participants

Four hundred young persons, 16-24 years old, and 5 years or more beyond a childhood cancer diagnosis, were identified through the Swedish Childhood Cancer Registry. Diagnoses were selected based on their potential negative impact on fertility: Hodgkin´s lymphoma, Ewing/Ewing-like sarcoma, osteosarcoma, rhabdomyosarcoma, neuroblastoma, and tumors of the central nervous system (CNS). The register's total population of persons with solid tumors in the age range of focus, except tumors of the CNS, was approached (N=280). As the number of persons treated for tumors of the CNS was large, a random sample was selected (n=120 from the total sample). Thirty-one persons were excluded due to self or parent-reported cognitive disabilities (n=7), other disabilities (n=1), not being possible to reach at a Swedish address (n=19), deceased (n=1), or other reasons, such as undergoing cancer treatment (n=3). Among the remaining 369 eligible participants, 36% (134/369) accepted participation. One discussion included only one participant and was not included in the analysis why the results are based on 133 participants.

Procedure

Ethical approval was obtained from the Regional Ethical Review Board in Stockholm. Potential participants received a letter with information about the study; voluntariness and confidentiality were stressed. Written informed consent was obtained from all participants.

Data Collection

Focus group discussions were performed through an existing chat platform developed together with an Internet consultancy company [9]. Thirty-nine discussions were conducted with two to five participants in each group. Group discussions were performed synchronously and lasted for approximately 90 minutes (range, 65-130). Each group was typically led by two moderators with backgrounds in cancer care, pediatric care, midwifery, and/or psychology. Those who had signed up for a focus group discussion received login details by text message or phone before start of the discussion. The platform allowed the informants access from a computer at any location, using an alias. In this way, participants could be anonymous toward each other while not in relation to the moderators. It was, however, not uncommon that participants chose her/his real name as alias. An effort was made to mix sexes and to have similar ages in the groups. Directly after participation, each participant was invited to anonymously report their experiences from participating in the study in a separate chat forum by answering five items with fixed-response alternatives and four questions with an open response format.

Analysis

The advantages and disadvantages with the mode of data collection was studied in three ways. We analyzed characteristics of those who participated, interactions during discussions, and the participants' evaluation of the focus group discussions.

Results

Who Participated?

The median age of participants was 21 ranging from 16 to 25 (interquartile range 4); self-reported relationship status and sexual experience as disclosed during group discussions are presented in Table 1. All but 4 of 39 conducted groups had mixed sexes. The response rate was higher among those diagnosed with solid tumors than among those diagnosed with CNS-tumors (n=103, 39% vs. n=30, 27%; χ^2= 4.89, *P*=.03). Apart from sexual problems and fertility-related concerns, participants mentioned various health impairments such as being amputated, fatigued, depressed, and having cognitive difficulties.

However, as health was not the focus of this study, we do not know if the mentioned health problems were related to sexuality or fertility.

Table 1. Characteristics of participants.

Self-reported situation	Total	Females	Males
	n=133 (%)	n=67 (%)	n=66 (%)
Relationship status			
Partner relationship	48 (36)	28 (42)	20 (30)
Dating/flirting	5 (5)	3 (5)	3 (5)
Single	62 (47)	28 (42)	34 (52)
Not reported	17 (13)	8 (12)	9 (14)
Sexual experience			
Have sexual experience	103 (77)	58 (87)	45 (68)
No sexual experience	16 (12)	3 (5)	13 (20)
Not reported	14 (11)	6 (9)	8 (12)

All of those who signed up to participate in a group also showed up and almost all of them who started in a group discussion stayed through the whole discussion. Some participants spontaneously declared that they had writing disabilities, which also was obvious in their spelling and grammar. A few, on their own initiative, disclosed that they had a neuropsychiatric disorder such as Asperger's and still, they reported the chat format as feasible. Participants who used an alias, possible to identify as a gendered name, never explicitly expressed having a relationship with someone of the same sex but the opposite was common (ie, heterosexual relationships). Moderators used gender-neutral expressions (eg, partner) when discussing partner relationships.

Were Sensitive Issues Discussed and How Did Participants Interact With Each Other?

Sexual issues needed more probing by the moderators than did fertility-related issues. However, when sex was brought up on the agenda, the issue was discussed. Communication between participants in the group discussions was overall respectful and supportive. Participants encouraged each other to take steps in their lives if they considered something problematic (eg, to meet someone or try a different approach). Different views were often expressed but there were seldom clear disagreements [6]. Participants were curious and asked each other about age, diagnosis, and sometimes where in the country they had received their treatment. Some of them identified themselves and agreed to continue chatting afterward on Facebook.

Participants' Evaluation of the Online Discussions

Directly after participation, group members were invited to anonymously report their experiences in a Web-based survey which 50% (67/134) chose to do. Almost all participants who answered the evaluation experienced their participation as overall positive, and a majority reported that it was easier to discuss when you were anonymous, and that the moderators stimulated the chat (Table 2). Participants' responses to the open questions revealed positive experiences of chatting with others with similar experiences and expressed that the online format made it possible to be anonymous which facilitated sharing of sensitive information. Suggestions for improvement included more developed discussion topics, a higher speed in the discussions, not having discussions with too few participants (ie, 2), and having longer or repeated discussions (Textbox 1).

Table 2. Participants' evaluation of the chat discussions (n=67).

	Highly agree	Somewhat agree	Do not agree
	n (%)	n (%)	n (%)
Overall positive experience	60 (91)	6 (9)	0
Possibility to express yourself[a]	58 (87)	7 (10)	0
The web hindered the discussion[a]	5 (8)	7 (10)	54 (81)
Anonymity made it easy to discuss[a]	38 (57)	10 (15)	17 (26)
Did moderators stimulate the chat?[a]	48 (72)	16 (24)	1 (<1)

[a]Due to missing answers percentages do not reach 100% for all questions

Textbox 1. Examples of participants' answers on the free text items in the evaluation form.

What information would have been difficult to communicate face-to-face?

- *Issues around sex and things like that maybe*
- *Maybe you do not dare to say what you want in a group if you aren't anonymous*
- *To talk about sex and relations is easier behind a screen*

What was good?

- *To hear what others feel and think. The anonymity made it possible to be honest and you could be at home without spending too much time*
- *The anonymity and the internet chat idea was very good, it made it possible to write things you wouldn't dare to share otherwise*

What was bad?

- *I thought the discussion leaders were a little unclear with some questions. I also thought the issues were a bit 'fluffy' and that only 2 persons really discussed*
- *A little slow at times*
- *The time was a bit short*

Do you have any suggestions for improvement?

- *A little more tempo*
- *Have longer time or repeated chat forums*
- *More participants in the chat*

Discussion

Advantages with the Mode

Online focus group discussions, performed with the possibility for participants to be anonymous toward each other, was shown to be a feasible mode for collecting sensitive data among young persons treated for cancer during childhood. Both persons with and without health problems participated in the group discussions. The lower response rate seen for participants diagnosed with CNS tumors may indicate that this mode of data collection is less suitable for certain groups. Still, persons with self-reported cognitive impairments signed up and participated in group discussions and this did not generate problems.

The study partly used a random sampling procedure not typical for these kinds of studies. Without a purposeful sampling technique you risk including persons that may have difficulties to communicate that can result in a less interactive dialogue. However, we did not experience this, which may reflect the fact that we had experienced moderators, preferably two per group, who carefully followed all group members through every discussion. Nevertheless, we recommend the number of participants in online focus group discussions, if conducted synchronously, to be at least three but not to exceed five.

Relation to Previous Findings

The present study confirms previous findings showing that an online format meets the need of convenience commonly addressed by young cancer survivors [4] and may be advantageous for sensitive topics [10] in contexts with high access to computers and Internet [11]. Furthermore, in the present study, the possibility to use an alias to be able to be anonymous while chatting about sensitive issues was highlighted as positive by many participants.

Discussing sexual experiences in groups with mixed sexes was found to be feasible and appreciated in a Swedish context and, to our knowledge, not previously performed among cancer survivors. The approximate numbers of female and male participants who, during a group discussion, reported that they had sexual experiences with a partner are in line with figures for the general population of similar ages [12].

Conclusion

Based on our findings, online focus group discussions are recommended for collecting data on sensitive topics among young people with various health deficiencies. This may be of great value when reaching out to populations who might be difficult to engage in face-to-face focus groups.

Acknowledgments

The study was supported by the Swedish Childhood Cancer Foundation, the Cancer Research Foundations of Radiumhemmet and the Doctoral School in Health Care Sciences at the Karolinska Institutet in Sweden.

Conflicts of Interest

None declared.

References

1. Krippendorff KH. Content Analysis: An Introduction to its Methodology. Thousand Oaks: Sage; 2004.
2. Willis K, Green J, Daly J, Williamson L, Bandyopadhyay M. Perils and possibilities: achieving best evidence from focus groups in public health research. Aust N Z J Public Health 2009;33:131-136. [doi: 10.1111/j.1753-6405.2009.00358.x] [Medline: 19413855]
3. Tates K, Zwaanswijk M, Otten R, van DS, Hoogerbrugge PM, Kamps WA, et al. Online focus groups as a tool to collect data in hard-to-include populations: examples from paediatric oncology. BMC Med Res Methodol 2009;9:15 [FREE Full text] [doi: 10.1186/1471-2288-9-15] [Medline: 19257883]
4. Rabin C, Simpson N, Morrow K, Pinto B. Intervention format and delivery preferences among young adult cancer survivors. Int J Behav Med 2013;20:304-310. [doi: 10.1007/s12529-012-9227-4] [Medline: 22328444]
5. Nilsson J, Jervaeus A, Lampic C, Eriksson LE, Widmark C, Armuand GM, et al. 'Will I be able to have a baby?' Results from online focus group discussions with childhood cancer survivors in Sweden. Hum Reprod 2014;29:2704-2711 [FREE Full text] [doi: 10.1093/humrep/deu280] [Medline: 25344069]
6. Jervaeus A, Nilsson J, Eriksson LE, Lampic C, Widmark C, Wettergren L. Exploring childhood cancer survivors' views about sex and sexual experiences -findings from online focus group discussions. Eur J Oncol Nurs 2016;20:165-172 [FREE Full text] [doi: 10.1016/j.ejon.2015.07.009] [Medline: 26251362]
7. Elo S, Kyngäs H. The qualitative content analysis process. J Adv Nurs 2008;62:107-115. [doi: 10.1111/j.1365-2648.2007.04569.x] [Medline: 18352969]
8. Alshaikh F, Ramzan F, Rawaf S, Majeed A. Social network sites as a mode to collect health data: a systematic review. J Med Internet Res 2014;16:e171 [FREE Full text] [doi: 10.2196/jmir.3050] [Medline: 25048247]
9. Blomberg K, Tishelman C, Ternestedt B, Törnberg S, Levál A, Widmark C. How can young women be encouraged to attend cervical cancer screening? Suggestions from face-to-face and internet focus group discussions with 30-year-old women in Stockholm, Sweden. Acta Oncol 2011;50:112-120. [doi: 10.3109/0284186X.2010.528790] [Medline: 21091087]
10. Elmir R, Schmied V, Jackson D, Wilkes L. Interviewing people about potentially sensitive topics. Nurse Res 2011;19:12-16. [doi: 10.7748/nr2011.10.19.1.12.c8766] [Medline: 22128582]
11. Statistics Sweden. Use of Computers and the Internet by Private Persons in 2013. 2014. URL: http://www.scb.se/Statistik/_Publikationer/LE0108_2013A01_BR_IT01BR1401.pdf [accessed 2016-03-30] [WebCite Cache ID 6gO2fAfLz]
12. Danielsson M, Berglund T, Forsberg M, Larsson M, Rogala C, Tydén T. Sexual and reproductive health: health in Sweden: the National Public Health Report 2012. Chapter 9. Scand J Public Health 2012;40(9 Suppl):176-196. [doi: 10.1177/1403494812459600] [Medline: 23238407]

Abbreviations

CNS: central nervous system

Edited by G Eysenbach; submitted 13.02.16; peer-reviewed by WYS Chou, T Irizarry; comments to author 15.03.16; revised version received 30.03.16; accepted 30.03.16; published 09.05.16.

Please cite as:
Wettergren L, Eriksson LE, Nilsson J, Jervaeus A, Lampic C
Online Focus Group Discussion is a Valid and Feasible Mode When Investigating Sensitive Topics Among Young Persons With a Cancer Experience
JMIR Res Protoc 2016;5(2):e86
URL: http://www.researchprotocols.org/2016/2/e86/
doi:10.2196/resprot.5616
PMID:27161146

Original Paper

Prevalence of Depression in Medical Students at the Lebanese University and Exploring its Correlation With Facebook Relevance: A Questionnaire Study

Wadih J Naja[1*], MD; Alaa H Kansoun[2*]; Ramzi S Haddad[1], MD

[1]Department of Psychiatry, Faculty of Medical Sciences, Lebanese University, Beirut, Lebanon

[2]Faculty of Medical Sciences, Lebanese University, Beirut, Lebanon

[*]these authors contributed equally

Corresponding Author:
Alaa H Kansoun
Faculty of Medical Sciences
Lebanese University
Lebanon, Beirut, Hadath, Lebanese University Dorms
Beirut,
Lebanon
Phone: 961 3619661
Fax: 961 1215714
Email: a.kanso@hotmail.com

Abstract

Background: The prevalence of major depression is particularly high in medical students, affecting around one-third of this population. Moreover, online social media, in particular Facebook, is becoming an intrinsic part in the life of a growing proportion of individuals worldwide.

Objective: Our primary objective is to identify the prevalence of depression in medical students at the Lebanese University Faculty of Medicine, a unique state university in Lebanon, its correlation with the utilization of the interactive features of Facebook, and the way students may resort to these features.

Methods: Students of the Lebanese University Faculty of Medicine were assessed for (1) depression and (2) Facebook activity. To screen for major depression, we used the Patient Health Questionnaire-9 (PHQ-9) scale. To test for Facebook activity, we developed the Facebook Resorting Questionnaire (FbRQ), which measures the degree to which students resort to Facebook.

Results: A total of 365 out of 480 students (76.0%) participated in the survey. A total of 25 students were excluded, hence 340 students were included in the final analysis. Current depression was reported in 117 students out of 340 (34.4%) and *t* tests showed female predominance. Moreover, PHQ-9 score multiple regression analysis showed that feeling depressed is explained 63.5% of the time by specific independent variables studied from the PHQ-9 and the FbRQ. Depression varied significantly among the different academic years ($P<.001$) and it peaked in the third-year students. One-way analysis of variance (ANOVA) showed that depression and resorting to Facebook had a positive and significant relationship ($P=.003$) and the different FbRQ categories had significant differences in resorting-to-Facebook power. The like, add friend, and check-in features students used when resorting to Facebook were significantly associated with depression.

Conclusions: This study showed that depression was highly prevalent among students of the Faculty of Medicine at the Lebanese University. Moreover, Facebook may be a promising, helpful, psychological tool for optimizing the management of depression. Our study brought to bear further questions that now prompt further observation and scrutiny to know more about the high rates of depression in this student population, more so in the part of the world studied, and to the growing role of social media.

(JMIR Res Protoc 2016;5(2):e96) doi:10.2196/resprot.4551

KEYWORDS

depression; Facebook; PHQ-9; FbRQ; Lebanese University Faculty of Medicine

Introduction

On Depression

Depression was shown to have high prevalence rates among university students [1,2]. These rates were even higher when it came to medical students, where depression affected one-third [3] to one-half of this population [4]. Coping strategies, such as social support, were recommended for medical students to improve their quality of life [5]. Moreover, it was shown that social support per se may even be a potent protective factor for depression [6].

On Facebook

On average, there are about 864 million daily active users on Facebook, the most visited online social network (OSN) in the world [7]. Kross et al showed that Facebook negatively affected a person's well-being in two ways: affective well-being (ie, how he/she feels moment to moment) and cognitive well-being [8]. In addition, individuals who have used Facebook accounts longer and users who have a greater number of nonpersonal Facebook friends believe that others' lives are better and are even more pleasant than their own [9]; this and other Facebook-mediated comparisons were associated with greater depression [10]. Furthermore, Forest et al reported that people with low self-esteem will not take advantage of the easy means of disclosure on Facebook, despite their beliefs in such a possibility [11]. In addition, it was reported that the increased usage of Facebook photo applications is correlated with body image disturbance and weight dissatisfaction [12].

As a part of *infodemiology* [13], which is a new method to study health determinants and information on the Internet, Facebook is one possible screening method to study health-related issues. For instance, a previous study based on verbatim text analysis showed that displayers of depressive symptoms are more likely than nondisplayers to have a positive Patient Health Questionnaire-9 (PHQ-9) measure [14].

Furthermore, announcing suicide on Facebook could provide enough time for an intervention [15]. Also, Facebook may be a good means for individuals to disclose their depression, hence enabling others to constantly be updated [16]. Seemingly depressed participants in Social Network Service (SNS) had the opportunity to communicate with peers that they selected. Such behavior may have been promoted by anonymity, hence avoiding face-to-face contact [17].

Finally, depressed people had a declined usage of Facebook features such as *location tagging*, *add friend*, and the *like* feature [18]. However, we were concerned more with the increased usage of Facebook as a possible tool that students could resort to in fighting depression. From this perspective, a subjective report of how each feature is resorted to might be more significant than counting the usage of each. Hence, when it comes to depressed Facebook users, we questioned whether resorting to Facebook may be a means to relieve depressive symptoms.

Objectives

Our primary objective was to study the prevalence of major depression in medical students attending the only state university in Lebanon and its correlation with these students resorting to Facebook.

Methods

Participants

Participants were medical students from the second up to the fifth year who attended the Faculty of Medicine at the Lebanese University. Sixth- and seventh-year students could not be included since they were in clinical rotations in several hospitals. Taking into consideration that all students at the Faculty of Medicine had taken an advanced English course and since lectures are delivered in English, we distributed the questionnaires in English. The survey extended from February 6-25, 2014. We visited each class twice on two consecutive days in order to guarantee maximum attendance.

Questionnaires

Patient Health Questionnaire-9

The PHQ-9 is a reliable and valid criteria-based diagnostic tool for depressive disorders and is used to measure the severity of depression [19]. Indeed, this scale has a high specificity (94%) and a relatively low sensitivity (73%) [19]. Up to the date of our field work, the PHQ-9 was not validated in the Lebanese population.

Facebook Resorting Questionnaire

Previous reports focused on one of two things in screening Facebook features related to depression: (1) declined Facebook activity [18] or (2) disclosures on Facebook that showed depression [14-16]. We assembled a new questionnaire—the Facebook Resorting Questionnaire (FbRQ)—that aimed to study the tendency of users to resort to Facebook features and the objectives of their usage. The FbRQ assesses the reasons users eventually resort to Facebook features during a current depressive state. Our questionnaire was not designed to measure time spent on Facebook or how many times each feature is used.

The FbRQ was comprised of seven questions targeting the different features of Facebook and the purpose underlying their utilization:

1. Question about the *like* feature: “Do you like topics on Facebook that you couldn’t own, meet, visit...in your real life?” What mattered was whether this feature allowed the user to stay up to date with the subject of interest.

2. Question about the *location-tagging* feature: “Do you have the habit of tagging your current location wherever you go?” This tag feature used by Facebook friends could provide the user with the possibility to navigate new locations and to check them.

3. Question about the *disclosure* feature: “Do you feel that Facebook is a way to express your feelings or whatever you want to declare in your real life and you do better in expressing on Facebook than on a real scale?” The disclosure feature might

provide the user with a basis for social support and electronic feedback that could become a source for generating new ideas.

4. Question about the *add friend* feature: "When you want to meet someone, do you feel that Facebook, by the feature *add friend* and further chatting, makes you more comfortable than a verbal meeting?" This question and answer provided an understanding about the clinical importance of depression and whether the user found it easier to add and meet friends on Facebook compared to real life.

5. Question about the *photo* feature: "Do you think that Facebook, by posting photos, saves your best life moments and helps you evoke your positive memories?" Posting photos is another feature that users tend to use. Sticking to our objectives, we aimed to detect whether this feature helped the user recall positive memories that the user would then ruminate about.

6. Question about the aim behind using Facebook: "Is Facebook a way to show the best out of your life?"

7. Question about the aim behind using Facebook: "Does Facebook render your voice audible and your existence noticeable?" Questions 6 and 7 aimed to help us understand the motives behind the use of Facebook.

The FbRQ was chiefly designed to cover all the above-mentioned points of every Facebook feature and aim of usage. Multimedia Appendix 1 is a snapshot that shows the FbRQ. Each question was given 1 point if answered positively, for a total of 7 points. We decided to divide users resorting to Facebook into three categories: low (0-1 points), moderate (2-3 points), or high (4-7 points). We also collected some sociodemographic data concerning the following: gender, academic year, psychiatric history, and whether users were smokers or nonsmokers, among other criteria.

Survey Leaflet

The survey was totally anonymous. The ethics committee at our university required that we provide clear information to the participants prior to their written consent (see Multimedia Appendices 2 and).

Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics for Windows version 16.0 (IBM Corp). Correlation analysis between depression and resorting to Facebook, along with sociodemographics, was performed using the chi-square test for which we calculated the *P* value and Cramer's V value, which is the appropriate measure of association. We performed *t* tests to show the predisposition to depression concerning gender. Furthermore, one-way analysis of variance (ANOVA) was conducted to determine the significance of the relationship between resorting to Facebook and depression, the variability of depression among the different academic years, as well as determining a significant difference between each FbRQ category. Moreover, multiple regression analysis was conducted to examine the relationship between different variables in the study for which we calculated the R^2value, which reflects the degree of correlation, and the *F* statistic, which tells us if the model is a good fit. Statistical significance for hypothesis testing was set at 5% ($P<.05$).

Results

Overview

A total of 365 of 480 students (76.0%) took the survey; the remaining students were absent on the days of our survey. A total of 25 students out of 365 (6.8%) were excluded from the study because some did not complete the three questionnaires; 9 of these students refused to participate. Hence, we included a total of 340 students in the study. The sociodemographic characteristics of the sample are summarized in Table 1.

Table 1. Sociodemographic characteristics of the sample (n=340).

Characteristics	n (%)
Participants who took the survey (n=480)	365 (76.0)
Participants with depression	117 (34.4)
Males	145 (42.6)
Females	195 (57.4)
Participants with functional impairment	256 (75.3)
Participants living in dorms	196 (57.6)
Married	3 (0.9)
Smokers	35 (10.3)
Participants with psychiatric history	62 (18.2)

On the PHQ-9 scale, for a cut-off of 10, the prevalence rate of depression was 34.4% (117/340). Severity was distributed as follows: out of 117 students, 5 (4.3%) had severe depression, 32 (27.4%) had moderate depression, and 80 (68.4%) had mild depression. Suicidal thoughts in depressed students—represented by Question 9 on the PHQ-9 scale—were attributed to 27.4% (32/117) of students. Table 2 shows the multiple regression analysis conducted between Question 2 of the PHQ-9 as a dependent variable and Questions 1, 3, 4, 6, 8, 9, and 10 of the PHQ-9 and Question 2 of the FbRQ as independent variables. The R^2value reached 63.5%, the *F* statistic showed that the model was a good fit, and this regression was a good model

(*P*<.001). As plotted in Figure 1 and as seen in Table 3 , after a one-way ANOVA, depression scores averaged 8.7, 9.0, 7.5, and 6.2, and depression reached 41.5%, 46.9%, 31.6%, and 21.4% in the second through the fifth year, respectively. The calculated value of *F* was 6.1 (*P*<.001). Comparing the different academic year classes, the statistical significance was owed only to the relationship between year 5 with respect to second- and third-year students (*P*<.05).

Table 2. Multiple regression analysis and the significance of the independent variables in affecting the dependent variable.

Model	Unstandardized coefficients		Standardized coefficients	*t*	*P*
	B	SD	Beta		
(Constant)	.051	.081	N/A[a]	0.630	.52
FbRQ[b]Question 2	.314	.149	.091	2.109	*.03* [c]
PHQ-9[d]Question 1	.192	.043	.210	4.456	*<.001*
PHQ-9 Question 3	.062	.038	.077	1.616	.10
PHQ-9 Question 4	.155	.044	.168	3.532	*<.001*
PHQ-9 Question 6	.184	.046	.197	3.988	*<.001*
PHQ-9 Question 8	.073	.051	.066	1.440	.10
PHQ-9 Question 9	.108	.059	.083	1.845	.06
PHQ-9 Question 10	.281	.062	.209	4.518	*<.001*

[a]N/A: not applicable.

[b]FbRQ: Facebook Resorting Questionnaire.

[c]Significant values are shown in italics (*P*<.05).

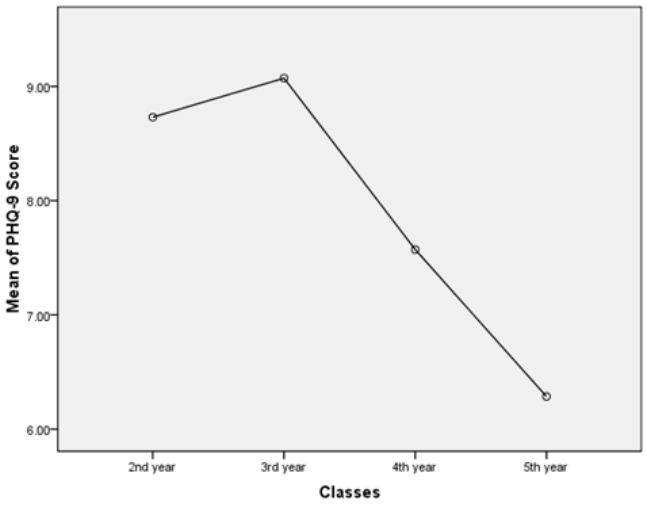
[d]PHQ-9: Patient Health Questionnaire-9.

Table 3. Variation of depression means with respect to the different classes, and model analyses (n=340).

Classes or models	Number of students, n (%)	Depression mean	SD	SE	95% CI
Class					
Second year	89 (26.2)	8.7303	4.1609	0.4411	7.8538-9.6068
Third year	83 (34.4)	9.0723	4.8459	0.5319	8.0142-10.1304
Fourth year	98 (28.8)	7.5714	4.6061	0.4653	6.6480-8.4949
Fifth year	70 (20.6)	6.2857	4.2054	0.5026	5.2830-7.2885
Total	340 (100)	7.9765	4.5745	0.2481	7.4885-8.4645
Model					
Fixed effects	N/A[a]	N/A	4.4746	0.2427	7.4991-8.4538
Random effects	N/A	N/A	N/A	0.6042	6.0538-9.8992

[a]N/A: not applicable.

Figure 1. Mean depression score by class year. PHQ-9: Patient Health Questionnaire-9.



Patient Health Questionnaire-9 and Sociodemographic Parameters

Among sociodemographics, the chi-square test showed a significant relationship between depression and gender only (*P*=.007), as shown in Table 4. In addition, Cramer's V value was significant (*P*=.007) and equaled .189. To determine which gender was more predisposed to depression, a *t* test was performed and showed that females had higher rates of depression than males with a factor of 1.8, as shown in Table 5.

Table 4. Depression categories distributed by gender (n=340).

Participants	Depression category[a], n (%)				Total, n (%)	Pearson chi-square *P* value
	<10	10-14	15-19	≥20		
Gender						
Male	109 (32.1)	28 (8.2)	7 (2.1)	1 (0.3)	145 (42.6)	.007[b]
Female	114 (33.5)	52 (15.3)	25 (7.4)	4 (1.2)	195 (57.4)	N/A[c]
Total	223 (65.6)	80 (23.5)	32 (9.4)	5 (4.5)	340 (100)	N/A

[a]Level of depression divided into the following categories, with scores in parentheses: *no depression* (<10), *mild* (10-14), *moderate* (15-19), and *severe* (≥20).

[b]Significant values are shown in italics (*P*<.05).

[c]N/A: not applicable.

Table 5. Difference in depression between males and females, and *t* tests (n=340).

Participants	n (%)	Depression mean	SD	SE
Gender				
Male	145 (42.6)	6.9310	4.2617	0.3539
Female	195 (57.4)	8.7538	4.6541	0.3333

Patient Health Questionnaire-9 and Facebook Resorting Questionnaire

Table 6 is a result of the one-way ANOVA showing that, out of 340 students, resorting to Facebook was high in 61 students (17.9%), moderate in 149 students (43.8%), and low in 130 students (38.2%). It was shown that there is a positive and significant relationship between the depression mean and the categories related to resorting to Facebook, whereby the depression mean was 6.9 in the low FbRQ group, 8.4 in the moderate group, and 9.0 in the high group. The *F* value was 5.843 (*P*=.003). Comparing the different FbRQ groups, the relationship was significant between the low and moderate groups (*P*=.03), and between the low and high groups (*P*=.01); however, it was not significant between the moderate and high groups.

Table 6. Variation of resorting to Facebook with respect to depression mean (n=340).

Groups or models		n (%)	Depression mean	SD	SE	95% CI
FbRQ [a] groups						
	Low	130 (38.2)	6.9615	4.3122	0.3782	6.2132-7.7098
	Moderate	149 (43.8)	8.4027	4.5291	0.3710	7.6695-9.1359
	High	61 (17.9)	9.0984	4.8673	0.6232	7.8518-10.3449
	Total	340 (100)	7.9765	4.5745	0.2481	7.4885-8.4645
Model						
	Fixed effects	N/A[b]	N/A	4.5105	0.2446	7.4953-8.4576
	Random effects	N/A	N/A	N/A	0.6332	5.2523-10.7007

[a]FbRQ: Facebook Resorting Questionnaire.

[b]N/A: not applicable.

There was no statistically significant relationship between the sociodemographic parameters studied and the FbRQ results as determined by the chi-square test. However, a regression analysis was performed locking the PHQ-9 score as a dependent variable and all the Facebook features as the independent ones.

The R^2equaled 25.3%, the model was a good fit, and the regression was a good model (*P*<.001). Table 7 shows the different ratios and the significance of each independent variable.

Table 7. Different ratios and significance of each independent variable.

Model	Unstandardized coefficients		Standardized coefficients	*t*	*P*
	B	SD	Beta		
(Constant)	.893	.065	N/A[a]	13.83	*<.001* [b]
FbRQ[c]Question 1	.153	.072	.093	2.13	*.03*
FbRQ Question 2	.617	.148	.181	4.17	*<.001*
FbRQ Question 3	-.102	.100	-.046	-1.02	.30
FbRQ Question 4	.191	.086	.095	2.23	*.02*
FbRQ Question 5	-.085	.076	-.051	-1.11	.26
PHQ-9[d]Question 6	.150	.093	.073	1.61	.10
PHQ-9 Question 7	.131	.087	.071	1.50	.13

[a]N/A: not applicable.

[b]Significant values are shown in italics (*P*<.05).

[c]FbRQ: Facebook Resorting Questionnaire.

[d]PHQ-9: Patient Health Questionnaire-9.

Discussion

On Depression

The current prevalence of depression in our sample (34.4%) is slightly higher than what is reported in the literature, which is around 30% [1,2]. Studies on Question 9 of the PHQ-9 showed the suicidal ideation in the studied sample to be lower than in previous reports (23%) [20]. Nevertheless, it is always considered high since a significant proportion of people reporting suicidal ideation accounted for half of fatal or nonfatal suicide attempts [20]. Multiple regression analyses showed the question of depressive mood (Question 2), locked as the dependent variable, to correlate highly with other PHQ-9 items; hence, reports of feeling down or depressed by the students was explained 63.5% of the time by all the independent variables studied. Among these variables, the problems of interest in doing things, fatigue, regarding one's self as a failure, and functionality were positively and significantly correlated and, thus, each 1% increase in these problems will increase feelings of depression by a factor of 0.19%, 0.15%, 0.1%, and 0.28%, respectively. On the other hand, a 1% increase in resorting to the *check-in* Facebook feature was associated with a 0.31% increase in feeling depressed, as shown in Table 2. Moreover, depression varied significantly among the different academic year classes and it peaked in the third year, which can be explained by the female predominance, then decreased gradually to a minimum PHQ-9 average of 6.2 in the fifth year. Female predominance was observed with a factor of 1.8, which is consistent with other reports [6,14,21]. From Cramer's V value of .189, we can conclude that this significant relationship was

low to moderate. Finally, our results regarding family history as a predisposing factor is not consistent with the literature [6].

On Resorting to Facebook

Overview

About one-third of students with Facebook accounts are active on Facebook [14,16]. Moreover, depressed users are expected to exhibit a decreased usage of Facebook [18]; however, in our sample a depressed user had an increased need to resort to Facebook. The one-way ANOVA came to show that as the mean of depression increases, resorting to Facebook increases as well (*P*=.003). Hence, depressed medical students at the Faculty of Medicine are more likely than the nondepressed students to resort to Facebook, which leads to the hypothesis that Facebook may be a coping mechanism for depression. Moreover, this analysis provides credibility for the FbRQ by showing that the difference in resorting to Facebook is significant between each and every FbRQ category, except when it comes to comparing the moderate and high categories. Unlike prior studies [14] where resorting to Facebook was higher among females, there was no predilection to resorting to Facebook among genders.

What is common to the features surveyed by the FbRQ scale is that resorting to Facebook provides some pattern of social life without necessarily improving deficient communication skills. Users' subjective reports on the FbRQ show that Facebook may provide users who have a tendency to experience depression a chance to stay in contact with topics of interest, new places, and horizons; to ruminate on positive memories; express ideas; meet friends; and show the best out of their lives. According to the multiple regression analysis, resorting to the *like*, *add friend*, and *check-in* features was associated with depression; for each 1% increase in their usage, the PHQ-9 scores increased by 0.1, 0.6, and 0.1%, respectively. Hence, Facebook could have a positive psychosocial impact by allowing users to resort to these features.

Facebook in Relation to Psychotherapy

Interpersonal therapy aims to (1) improve communication skills and (2) increase self-esteem [22]. Facebook improved depression in university students [23] by expressing the opinions of a depressed person that are usually suppressed on a daily basis; this was demonstrated by Questions 6 and 7 on the FbRQ, in addition to the *add friend* feature, chatting, and the *like* feature.

On the other hand, Facebook was shown to clearly improve self-esteem [24]. Indeed, Internet use improved self-esteem as well as social support, while decreasing the percentage of depression and loneliness [25]. This seems to be linked to the *add friend* feature and the aim of the usage of Facebook as per the responses to the FbRQ.

Facebook, as a humanistic therapy, provides a social environment where individuals may compare old and new habits or attitudes with friends. At the same time, individuals may find out that similar problems may also be encountered by others, hence providing some kind of relief [26]. In conclusion, psychotherapies are providing hope, empathy, and care; hence, individuals who are supported by close friends and caring people are less likely to need or seek therapy [26].

Facebook Social Support

Notably, social support is a key protective factor against depression [6]. Computer-mediated interaction has been shown to improve a user's confidence over the course of a conversation and strengthens judgments while negotiating. Most importantly, it helps a person get rid of uncertain behaviors [27]. On the other hand, lonely people find it hard to introduce themselves to, or take the first step in meeting, new people [4]. Facebook may be an option to overcome those difficulties by allowing an individual to choose the contact of his/her preference.

Study Limitations

As a cross-sectional study, our results were confined to comparing, and not eliciting, a cause-and-effect relationship between depression improvement and resorting to Facebook. The standardized PHQ-9 questionnaire had not been validated in the Lebanese population during our survey. On the other hand, the FbRQ is a novel tool that we developed due to the lack of an equivalent standardized questionnaire; its point of weakness lies in not using a continuous variable scale.

Conclusions

Depression was shown to be highly prevalent among medical students of the Lebanese University. Moreover, depressed Facebook users were more likely than nondepressed users to resort to Facebook; the subjective report by the FbRQ allows us to hypothesize that Facebook may be a means to alleviate depressive symptoms. Specifically, among all the Facebook features, *like*, *check-in*, and *add friend* may be of therapeutic significance. These results should stimulate health care providers to question the high depression rate in this student population and to acknowledge the possible role of Facebook in a multidisciplinary treatment strategy to relieve depression.

Acknowledgments

This study was funded by the authors and had no other sponsors. Our acknowledgements go to Mr Raed Bou Chebel for his generous assistance in statistical analysis. We also acknowledge the Dean of the Faculty of Medicine, Pr Boutros Yared, who made the survey feasible. We are very grateful to Dr Nadine Yared for her assistance in planning the survey. Finally, we thank Dr Nevine Matar for proofreading our paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Snapshot of the Facebook Resorting Questionnaire (FbRQ).

[PDF File (Adobe PDF File), 289KB - resprot_v5i2e96_app1.pdf]

Multimedia Appendix 2

Survey cover showing the contents.

[PDF File (Adobe PDF File), 163KB - resprot_v5i2e96_app2.pdf]

Multimedia Appendix 3

Survey introduction.

[PDF File (Adobe PDF File), 300KB - resprot_v5i2e96_app3.pdf]

References

1. Ibrahim AK, Kelly SJ, Adams CE, Glazebrook C. A systematic review of studies of depression prevalence in university students. J Psychiatr Res 2013 Mar;47(3):391-400. [doi: 10.1016/j.jpsychires.2012.11.015] [Medline: 23260171]
2. Sarokhani D, Delpisheh A, Veisani Y, Sarokhani M, Manesh R, Sayehmiri K. Prevalence of depression among university students: A systematic review and meta-analysis study. Depress Res Treat 2013;2013:373857 [FREE Full text] [doi: 10.1155/2013/373857] [Medline: 24187615]
3. Hirata FC, Lima MC, de Bruin VM, Nóbrega PR, Wenceslau GP, de Bruin PF. Depression in medical school: The influence of morningness-eveningness. Chronobiol Int 2007;24(5):939-946. [doi: 10.1080/07420520701657730] [Medline: 17994347]
4. Gupta S, Basak P. Depression and type D personality among undergraduate medical students. Indian J Psychiatry 2013 Jul;55(3):287-289 [FREE Full text] [doi: 10.4103/0019-5545.117151] [Medline: 24082252]
5. Sreeramareddy CT, Shankar PR, Binu VS, Mukhopadhyay C, Ray B, Menezes RG. Psychological morbidity, sources of stress and coping strategies among undergraduate medical students of Nepal. BMC Med Educ 2007;7:26 [FREE Full text] [doi: 10.1186/1472-6920-7-26] [Medline: 17678553]
6. Garber J. Depression in children and adolescents: Linking risk research and prevention. Am J Prev Med 2006 Dec;31(6 Suppl 1):S104-S125. [doi: 10.1016/j.amepre.2006.07.007] [Medline: 17175406]
7. Facebook Newsroom. 2015. Company info URL: http://newsroom.fb.com/company-info/ [WebCite Cache ID 6VemrxCzU]
8. Kross E, Verduyn P, Demiralp E, Park J, Lee DS, Lin N, et al. Facebook use predicts declines in subjective well-being in young adults. PLoS One 2013;8(8):e69841 [FREE Full text] [doi: 10.1371/journal.pone.0069841] [Medline: 23967061]
9. Chou HG, Edge N. "They are happier and having better lives than I am": The impact of using Facebook on perceptions of others' lives. Cyberpsychol Behav Soc Netw 2012 Feb;15(2):117-121. [doi: 10.1089/cyber.2011.0324] [Medline: 22165917]
10. Steers MN, Wickham RE, Acitelli LK. Seeing everyone else's highlight reels: How Facebook usage is linked to depressive symptoms. J Soc Clin Psychol 2014 Oct;33(8):701-731. [doi: 10.1521/jscp.2014.33.8.701]
11. Forest AL, Wood JV. When social networking is not working: Individuals with low self-esteem recognize but do not reap the benefits of self-disclosure on Facebook. Psychol Sci 2012 Mar;23(3):295-302. [doi: 10.1177/0956797611429709] [Medline: 22318997]
12. Meier EP, Gray J. Facebook photo activity associated with body image disturbance in adolescent girls. Cyberpsychol Behav Soc Netw 2014 Apr;17(4):199-206. [doi: 10.1089/cyber.2013.0305] [Medline: 24237288]
13. Eysenbach G. Infodemiology and infoveillance: Framework for an emerging set of public health informatics methods to analyze search, communication and publication behavior on the Internet. J Med Internet Res 2009;11(1):e11 [FREE Full text] [doi: 10.2196/jmir.1157] [Medline: 19329408]
14. Moreno MA, Christakis DA, Egan KG, Jelenchick LA, Cox E, Young H, et al. A pilot evaluation of associations between displayed depression references on Facebook and self-reported depression using a clinical scale. J Behav Health Serv Res 2012 Jul;39(3):295-304 [FREE Full text] [doi: 10.1007/s11414-011-9258-7] [Medline: 21863354]
15. Ruder TD, Hatch GM, Ampanozi G, Thali MJ, Fischer N. Suicide announcement on Facebook. Crisis 2011;32(5):280-282. [doi: 10.1027/0227-5910/a000086] [Medline: 21940257]
16. Moreno MA, Jelenchick LA, Egan KG, Cox E, Young H, Gannon KE, et al. Feeling bad on Facebook: Depression disclosures by college students on a social networking site. Depress Anxiety 2011 Jun;28(6):447-455 [FREE Full text] [doi: 10.1002/da.20805] [Medline: 21400639]
17. Takahashi Y, Uchida C, Miyaki K, Sakai M, Shimbo T, Nakayama T. Potential benefits and harms of a peer support social network service on the Internet for people with depressive tendencies: Qualitative content analysis and social network analysis. J Med Internet Res 2009;11(3):e29 [FREE Full text] [doi: 10.2196/jmir.1142] [Medline: 19632979]
18. Park S, Lee SW, Kwak J, Cha M, Jeong B. Activities on Facebook reveal the depressive state of users. J Med Internet Res 2013;15(10):e217 [FREE Full text] [doi: 10.2196/jmir.2718] [Medline: 24084314]

19. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: Validity of a brief depression severity measure. J Gen Intern Med 2001 Sep;16(9):606-613 [FREE Full text] [Medline: 11556941]
20. Simon GE, Rutter CM, Peterson D, Oliver M, Whiteside U, Operskalski B, et al. Does response on the PHQ-9 Depression Questionnaire predict subsequent suicide attempt or suicide death? Psychiatr Serv 2013 Dec 1;64(12):1195-1202 [FREE Full text] [doi: 10.1176/appi.ps.201200587] [Medline: 24036589]
21. Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, editors. Psychiatric disorders. In: Harrison's Principles of Internal Medicine. 18th edition. New York, NY: McGraw-Hill; 2012:3522-3545.
22. Simon H. University of Maryland Medical Center. 2013. Depression URL: http://umm.edu/health/medical/reports/articles/depression [accessed 2016-05-14] [WebCite Cache ID 6hVq3N8be]
23. Wright KB, Rosenberg J, Egbert N, Ploeger NA, Bernard DR, King S. Communication competence, social support, and depression among college students: A model of Facebook and face-to-face support network influence. J Health Commun 2013;18(1):41-57. [doi: 10.1080/10810730.2012.688250] [Medline: 23030518]
24. Gonzales AL, Hancock JT. Mirror, mirror on my Facebook wall: Effects of exposure to Facebook on self-esteem. Cyberpsychol Behav Soc Netw 2011;14(1-2):79-83. [doi: 10.1089/cyber.2009.0411] [Medline: 21329447]
25. Shaw LH, Gant LM. In defense of the Internet: The relationship between Internet communication and depression, loneliness, self-esteem, and perceived social support. Cyberpsychol Behav 2002 Apr;5(2):157-171. [doi: 10.1089/109493102753770552] [Medline: 12025883]
26. Myers DG. Psychology. New York, NY: Worth Publishers; 1986.
27. Tidwell LC, Walther JB. Computer-mediated communication effects on disclosure, impressions, and interpersonal evaluations: Getting to know one another a bit at a time. Human Comm Res 2002 Jul;28(3):317-348. [doi: 10.1111/j.1468-2958.2002.tb00811.x]

Abbreviations

ANOVA: analysis of variance
FbRQ: Facebook Resorting Questionnaire
N/A: not applicable
OSN: online social network
PHQ-9: Patient Health Questionnaire-9
SNS: Social Network Service

Edited by G Eysenbach; submitted 17.04.15; peer-reviewed by B Jeong, Q Cheng; comments to author 15.12.15; revised version received 29.12.15; accepted 21.03.16; published 31.05.16.

Please cite as:
Naja WJ, Kansoun AH, Haddad RS
Prevalence of Depression in Medical Students at the Lebanese University and Exploring its Correlation With Facebook Relevance: A Questionnaire Study
JMIR Res Protoc 2016;5(2):e96
URL: http://www.researchprotocols.org/2016/2/e96/
doi:10.2196/resprot.4551
PMID:27246394

Original Paper

Acceptance, Usability and Health Applications of Virtual Worlds by Older Adults: A Feasibility Study

Nicole Cook[1], PhD, MPA; Sandra L Winkler[2], PhD, OTR/L

[1]Master of Public Health program, College of Osteopathic Medicine, Nova Southeastern University, Fort Lauderdale, FL, United States

[2]James A. Haley Veterans Hospital, Tampa, FL, United States

Corresponding Author:
Nicole Cook, PhD, MPA
Master of Public Health program
College of Osteopathic Medicine
Nova Southeastern University
3200 South University Drive
Fort Lauderdale, FL, 33314
United States
Phone: 1 9542621505
Fax: 1 9542621505
Email: nc570@nova.edu

Abstract

Background: Virtual worlds allow users to communicate and interact across various environments, scenarios, and platforms. Virtual worlds present opportunities in health care to reduce the burden of illness and disability by supporting education, rehabilitation, self-management, and social networking. The application of virtual worlds to older adults who bear the burden and cost of health conditions associated with age has not been evaluated.

Objective: The aim of this study is to explore the usability, ease of use, and enjoyment of a virtual world by older adults, the types of virtual world activities that older adults may engage in, and the perceptions of older adults regarding the application of virtual worlds in health care.

Methods: This quasi-experimental pre-post design research was guided by the Technology Acceptance Model (TAM). Participants were recruited from a Lifelong Learning Institute (LLI) program at Nova Southeastern University. Participants attended four training sessions over a 5-week period in the Second Life (SL) virtual world. Subjects were surveyed before and after the training on perceived ease of use, attitudes towards technology, behavioral intention to use the system, facilitating conditions, effort expectancy, and self-efficacy.

Results: Older adults (N=19) completed the informed consent and attended the first training session, and 11 participants (58%, 11/19) completed the full training and the post survey. Completers (82%, 9/11) were more likely than non-completers (37%, 3/8) to consider themselves technologically savvy (P=.048), and to express confidence in being able to use the virtual world (100%, 11/11 vs 37%, 3/8; P=.002). All completers (100%, 11/11) perceived that SL has application in health behaviors and disease and reducing social isolation among people who are homebound. Of the completers, 10 (91%, 10/11) responded that they enjoyed learning how to use SL. Completers suggested that future trainings include more assistants and smaller groups.

Conclusions: This pilot study suggests that virtual worlds can be both a feasible and an applicable method to promote health among some seniors. Future research on virtual worlds with older populations should consider using state-of-the art technology including large monitors, providing a minimum of one trainer for every two to three participants, and distributing a comprehensive training manual at the start of the training to support organization and recall.

(JMIR Res Protoc 2016;5(2):e81) doi:10.2196/resprot.5423

KEYWORDS

Second Life; virtual worlds; older adults; seniors; health care; training

Introduction

As the population ages, the burden and cost of health conditions associated with age, including chronic disease and dementing illnesses is growing [1]. Strategies that promote self-management of chronic disease, cognitive function, and social connectedness contribute to improved health outcomes and quality of life [2-4]. Among other methods, computer-based interventions including computer-based gaming, interactive multimedia systems, exergaming, and virtual worlds are emerging as innovative methods to promote health among older adults [5-8].

Virtual worlds are three-dimensional computer-simulated environments that users navigate via Avatars to communicate and interact across various environments, scenarios, and platforms. In the past decade, virtual worlds have emerged as important tools for socialization, engagement, networking, and entertainment, virtually changing how people interact, communicate, and collaborate [9]. Internet-based virtual worlds offer opportunities in health care to reduce the burden of illnesses and disability through promoting rehabilitation [10-12], self-management of disease [13-18], healthy lifestyle behaviors [19-21], and social networking [11,22]. However, most research and evaluations on the application of virtual worlds in health are conducted among younger, computer literate populations, though the application to older adults has been identified [23].

Older adults comprise an important population for virtual computer and Web-based health interventions, including virtual worlds [24]. Today, 59% of adults 65 years of age use the Internet [24]. Usage increases with higher education, higher income, and lower age. Among seniors who reported using the Internet, more than two thirds of them go online every day. Similarly, among seniors who use social networking sites, 81% reported using them daily or near-daily.

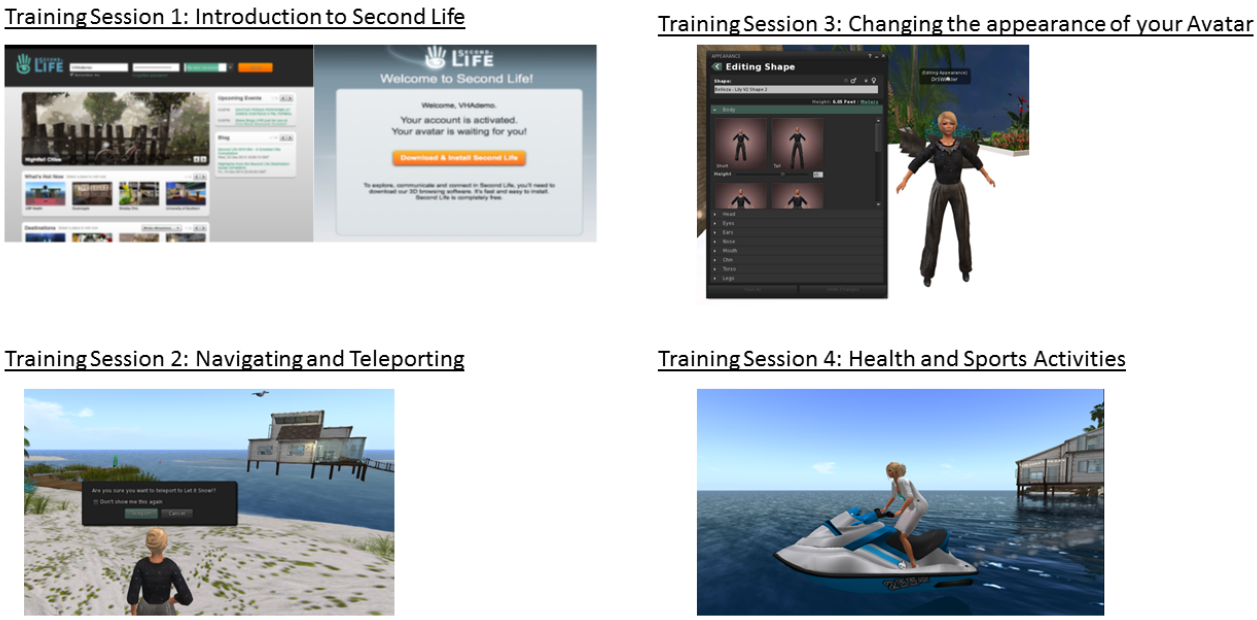
Use of virtual worlds among seniors is low, but is expected to increase [25,26]. Currently there is a lack of evidence regarding the acceptance, adoption, and health applications of virtual worlds among older adults. Here, a pilot study was conducted to inform on the feasibility and potential health care applications of using a virtual world environment with older adults. The specific research aims of this study are as follows: (1) to understand the usability, ease of use, and enjoyment of a virtual world environment by older adults, (2) probe engagement and types of virtual world activities by older adults, and (3) identify older adults' perceptions regarding the application of virtual worlds in health care.

Methods

Study Design

A quasi-experimental pre-post design was used. After providing written consent subjects completed a pre-test, which included questions regarding demographics, computer and digital device usage, and potential advantages of virtual worlds (Multimedia Appendix 1). Subjects then attended four training sessions over a 5-week period using the Second Life (SL) virtual world in the computer lab at Nova Southeastern University. SL is the largest virtual world. Conceptualized by Philip Rosedale who founded Linden Lab, SL offers a persistent, open, unlimited, and highly customizable space. The content of SL is created by its users who rent virtual land (islands). The training was conducted by a faculty member. Another faculty member and one student were available to provide direct support to participants at each training session. The training topics covered were (1) introduction to SL, "friending" and messaging (week 1); (2) navigating and teleporting in SL (week 2); (3) changing the appearance of your Avatars (week 3); and (4) health and sports activities (week 4). Screen shots demonstrating examples of activities performed in SL during training are shown in Figure 1. Subjects completed a 19 question post-test assessing their experience with the virtual world, the potential advantages of virtual worlds, and the specific health applications of virtual worlds. The post-test is provided in Multimedia Appendix 2. Subjects who completed all four training sessions received a US $60 gift card to a local supermarket chain.

Figure 1. Screen shots demonstrating examples of activities performed in Second Life during training sessions.



Participants and Setting

Participants were recruited from the Lifelong Learning Institute (LLI) at Nova Southeastern University's College of Osteopathic Medicine. As an educational extension program the LLI attracts many active and educated older adults from the nearby community.

Study investigators made recruiting announcements during LLI events and were available during LLI educational program breaks to discuss the training program with interested members. Though recruitment was slow at first, an interested LLI board member agreed to make several announcements to his peers, appealing to those interested in technology resulting in higher interest. Inclusion criteria for the study included having an email address and availability to attend the training programs. There were no exclusion criteria.

Conceptual Framework

The research was guided by the Technology Acceptance Model (TAM) [27]. The TAM is an extension of the Theory of Reasoned Action (TRA) which predicts a person's behavioral intention based on attitudes and subjective norms [28]. TAM extends TRA by predicting acceptance of information technologies and assumes that two major variables of interest drive an individual's acceptance of technology: perceived usefulness and perceived ease of use [29]. TAM has been used successfully to test a variety of computer technologies in dividers settings and user groups, including in health care [30-35]. TAM evolved over several iterations into the Unified Theory of Acceptance and Use of Technology (UTAUT) [36]. To our knowledge, this is the first application of TAM and the extended UTAUT towards understanding acceptance and adoption of virtual worlds among older adults.

Outcome Measures

The pre- and post-survey instruments were developed by the investigators based on validated items used in the development and testing of the TAM and UTAUT [27,36]. The tool measured perceived ease of use, attitudes towards technology, behavioral intention to use the system, facilitating conditions, effort expectancy, and self-efficacy. The pre-survey included questions on demographic characteristics, current computer and device usage, technological savviness, confidence in using the virtual world, and perceived usefulness of virtual worlds. The post-survey tool included the same set of questions regarding perceived usefulness as in the baseline survey and assessed activities performed in SL as a result of the training. The post-survey tool also included five open-ended questions to inform on specific lessons that could be learned through this pilot and applied to future research on virtual worlds and seniors.

Data Collection

Study data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at Nova Southeastern University [37]. REDCap is a secure, Web-based application designed to support data capture for research studies providing (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for importing data from external sources.

Statistical Analyses

We performed bivariate analysis of baseline completer and non-completer demographic characteristics using *t* test for independent samples for age and the Pearson chi-square statistic for categorical data. Paired-sample *t* tests were used to compare

changes in self-reported usefulness on a scale from 1 (strongly agree) to 5 (strongly disagree) among completers and to estimate power for future studies. An alpha of .05 was used for each test without correction for multiple comparisons. Descriptive statistics were used to describe activities completed and perceptions regarding the application of virtual worlds to health. All analyses were conducted in SPSS (V23).

Results

Study Participants

There were 19 older adults who completed the informed consent and baseline survey and 10 older adults who completed the 4-week training program. One participant missed the last class, however, the material was reviewed with the participant at the end of the prior training. This participant's post-test was included with the completers, for an overall number of 11 completers, and a completer to non-completer rate of 58% (11/19).

The demographic and baseline characteristics of completers and non-completers are summarized in Table 1. The mean age of participants was 71.2 among both completers and non-completers. Completers (82%, 8/11) were statistically more likely than non-completers (37%, 3/8) to consider themselves technologically savvy (*P*=.048) and to express confidence in being able to use the virtual world (100%, 11/11 vs 37%, 3/8, *P*=.002). There was an absolute difference in mean hours on the computer of 3.65, but this difference was not significant. Though not significant, completers were more likely to agree or strongly agree with the perceived benefits of a virtual world in terms of usefulness in managing health (36%, 4/11 vs 25%, 2/8), usefulness for social interaction (45%, 5/11 vs 37%, 3/8), usefulness to themselves (36%, 4/11 vs 25%, 2/8), and usefulness in terms of improving quality of life (27%, 3/11 vs 25%, 2/8).

Activities Performed in Second Life

Activities performed in SL by completers are listed in Table 2. While faculty and graduate students verified that all completers performed all of the activities assessed at each class, several participants in the post-survey said that they were not able to "friend each other", find new places to visit, go shopping in SL or change their Avatar's appearance in SL.

Table 1. Baseline demographic and characteristics of non-completers and completers of a virtual world training program (N=19).

Characteristic	Non-completers (n=8)	Completers (n=11)	*P* value
Age[a], mean	71.2	71.2	.99
Hours on computer per week[a], mean	8.75	12.4	.31
Male, %	50	36	.55
College graduate, %	75	91	.55
"I consider myself to be technologically savvy", agree/strongly agree (%)	37	82	.048
"I am confident I will be able to use the virtual world", yes (%)	37	100	.002
"A virtual world could be useful in managing my health", agree/strongly agree (%)	25	36	.60
"A virtual world could be useful for social interaction", agree/strongly agree, %	37	45	.73
"A virtual world could be useful to me", agree/strongly agree (%)	25	36	.60
"Using a virtual world could improve the quality of my life", agree/strongly agree (%)	25	27	.91

[a]One completer did not provide age or mean hours on computer per week.

Table 2. Activities in Second Life performed by completers during the training program (N=11).

Activity	n, (%)
"Friending each other"	6 (54)
Finding new places to visit	9 (82)
Teleporting	11 (100)
Shopping	8 (73)
Changing your Avatar's appearance	9 (82)
Sports activities (eg, jet skiing, parasailing, fishing, etc)	11 (100)

Usefulness of Second Life

The change in perceived usefulness of SL was analyzed in terms of managing health, social interaction, overall usefulness, and improvement in quality of life among completers (Table 3). Though only the usefulness of SL for social interaction approached significance (*P*=.046) there was improvement across three of the four questions from baseline to follow-up.

Application of Second Life to Health and Ease of Use

The application of SL to health and the ease of use of SL among completers was assessed (Table 4). All subjects (100%, 11/11) responded that SL is applicable to health behaviors and disease and that SL can be applied to reduce social isolation among people who are homebound. Of the participants, 10 (91%, 10/11) responded that they enjoyed learning how to use SL. In addition, 8 (73%, 8/11) and 9 (82%, 9/11) responded that it was easy for them to learn to create their Avatar and that it was easy for them to navigate their Avatar in SL, respectively.

Table 3. Changes in mean score of usefulness of Second Life among completers improved from baseline to follow-up (N=11).

Usefulness	Baseline completers score[a], mean	Follow-up completers score[a], mean	*P* value
"A virtual world could be useful in managing my health"	2.82	2.27	.051
"A virtual world could be useful for social interaction"	2.55	1.91	.046
"A virtual world could be useful to me"	2.60	2.40	.55
"Using a virtual world could improve the quality of my life"	2.80	3.10	.47

[a]Mean score based on a 1 (strongly agree) to 5 (strongly disagree) scale.

Table 4. Participants' perception regarding ease of use and applications of Second Life to health (N=11).

Application	n (%)
Application of Second Life to health behaviors and disease	11 (100)
Application of Second Life to self-management and chronic conditions	6 (54)
Application of Second Life to support brain health among people with dementing illnesses	7 (64)
Application of Second Life to support behavior and lifestyle change (eg, physical activity)	6 (54)
Application of Second Life to reduce social isolation among people who are homebound	11 (100)
I enjoyed learning how to use Second Life?	10 (91)
It was easy for me to learn to create an Avatar in Second Life?	8 (73)
It was easy for me to learn to navigate my Avatar in Second Life?	9 (82)

Qualitative Feedback on Second Life

Participants also responded to open-ended questions regarding what they liked about SL, what they least liked about SL, their motivation to participate in the training, and potential improvements both in terms of the SL application and the training program. In summary, respondents liked the graphics, the variety of virtual experiences (eg, virtual travel) and engaging in fantasies and other sports activities that they would not normally engage in real life (eg, flying, power sailing). Several respondents also said they enjoyed designing their own Avatars and creating environments that are "outside the norm". In terms of what they liked least, several respondents said they found SL frustrating (difficulty maneuvering the Avatar and/or not knowing where to go when they arrive at a site), that the on-screen help is limited and hard to understand, and that there is a long learning curve. One respondent also noted that the computer lab environment where the training took place was overloaded and crashed. With regards to motivation to participate, all participants responded that they wanted to help with interesting research and/or to learn something new. Feedback with regards to improving the usability of SL for the senior population and improving the training are provided in Table 5. The responses to both questions are combined as there was significant overlap.

Table 5. Respondent feedback on improving the usability of Second Life for the senior population and improving the training program for seniors in SL (N=11).

Feedback	n (%)
Provide more assistants during training; provide individualized or small-group training	5 (45)
Teach exercises slower in a step-by-step manner	4 (36)
Provide a comprehensive, more organized training program and manual; simplify directions	3 (27)
Enlarge the print on the screen	2 (18)
Make it less challenging to navigate in Second Life	1 (9)
Provide the training on an Apple platform	1 (9)

Discussion

Principal Findings

Findings from this pilot study to investigate the feasibility and potential health care applications of using a virtual world environment with older adults suggest that perceived usefulness of virtual worlds in terms of health, managing health, overall usefulness, and improving quality of life increased following the training program. Seniors who considered themselves technologically savvy and are confident in their ability to learn the virtual world technology were more likely to complete the training compared to those who had less confidence and self-reported themselves as not technologically savvy. Seniors who completed the training were successful at creating Avatars, learning to "friend each other", instant messaging, teleporting, and engaging in activities in SL. All completers reported that SL has application in health and managing disease, as well as to reduce social isolation among people who are homebound.

Limitations

A limitation of the study was the high number of drop-outs. During the first class participants (N=19) were instructed to set up their SL account. However, the trainers did not know that there was a limit on the number of new accounts that could be set up per Internet Protocol (IP) address. As a result, many participants had difficulty creating accounts. Trainers resolved this issue by connecting to personal hotspots on cell phones, but the interruption contributed to frustration that may have resulted in drop-outs. Participants were also frustrated that they had to wait, often for several minutes, for assistance. In retrospect, because subjects learned how to use an Avatar at different rates and had varying levels of attention, several smaller groups should have been formed with at least one trainer to two to three participants. Persons providing assistance to participants needed to have mastered basic Avatar and SL skills, which was not always the case in this study. While most completers reported they enjoyed learning SL (100%, 11/11), that they found it easy to create an Avatar (73%, 8/11), and navigate in SL (82%, 9/11), there were other important lessons learned through this pilot. Participants experienced frustration with using and navigating in SL. Some of the frustration can be attributed to the computer lab conditions. The computer lab was equipped with laptops, which met the recommended requirements for screen resolution and graphics, but only had 14 inch screens. In addition, some activities in SL were slow at certain points in the training, likely due to Internet congestion caused by a large number of computers working simultaneously with intense graphic displays. A few of the computers even crashed.

In addition to increasing the number of trainers available to support setting up accounts and using high-end technology with large monitors, suggested improvements for future trainings include providing more support during each of the trainings and providing a comprehensive training manual. There were several challenges to maintaining a tempo acceptable for all participants. First, some participants failed to remember their username and password in subsequent trainings and then not having access to their email accounts to access the email from SL to reset their credentials. Second, subjects were at different stages of readiness to use an Avatar in a virtual world, making it difficult to learn new skills as a group. More SL technologically savvy students wanted to press ahead with learning new skills while others in the class were still learning previously-taught tasks. Future projects may want to consider grouping participants by tempo. In addition, while handouts were provided to students at the beginning of each training, there was no overall comprehensive training manual. In retrospect, such a manual would have helped with organizing the material and facilitating recall of previously taught activities. Plus, many participants wanted to practice on their home computers for which the manual would have been conducive.

Effect Size

One of the purposes of a pilot study is to calculate an effect size for more robust, larger-scale studies. To this end, in a post-hoc analysis, we calculated the magnitude of the effect of the change in participant reported usefulness (composite of four questions) of SL pre- and post-training. Using a power of 80% and an alpha of .05, we calculated that 90 participants should be enrolled in future studies to achieve a medium effect size (30%). Precaution should be taken when applying our effect size to future studies as we modified TAM questions to fit our population and virtual world technology. It is also important to note that older adults who participated in this pilot had a college degree and that estimated results may vary if the study is replicated with a less-educated population.

Conclusions

The purpose of this pilot study was to test the feasibility and applicability of virtual worlds to older adults. This pilot suggests that virtual worlds can be both a feasible and applicable method to promote health among some seniors. Future research on virtual worlds with older populations should consider using state-of-the art technology including large monitors, providing a minimum of one trainer for every two to three participants, and distributing a comprehensive training manual at the start of the training to support organization and recall.

Acknowledgments

Funding for this research was provided by a grant from Nova Southeastern University, Health Professions Division.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Pre-test questionnaire to assess acceptance, usability, and health applications of virtual worlds among older adults.

[PDF File (Adobe PDF File), 16KB - resprot_v5i2e81_app1.pdf]

Multimedia Appendix 2

Post-test assessing the experience with the virtual world, potential advantages of virtual worlds, and specific health applications of virtual worlds among completers.

[PDF File (Adobe PDF File), 16KB - resprot_v5i2e81_app2.pdf]

References

1. Centers for Disease Control Prevention, US Dept of Health and Human Services. The State of AgingHealth in America 2013. 2013. URL: http://www.cdc.gov/features/agingandhealth/state_of_aging_and_health_in_america_2013.pdf [accessed 2016-02-01] [WebCite Cache ID 6eyM6zTAF]
2. Cochran J, Conn VS. Meta-analysis of quality of life outcomes following diabetes self-management training. Diabetes Educ 2008;34(5):815-823 [FREE Full text] [doi: 10.1177/0145721708323640] [Medline: 18832286]
3. Woods B, Thorgrimsen L, Spector A, Royan L, Orrell M. Improved quality of life and cognitive stimulation therapy in dementia. Aging Ment Health 2006 May;10(3):219-226. [doi: 10.1080/13607860500431652] [Medline: 16777649]
4. Tomaka J, Thompson S, Palacios R. The relation of social isolation, loneliness, and social support to disease outcomes among the elderly. J Aging Health 2006 Jun;18(3):359-384. [doi: 10.1177/0898264305280993] [Medline: 16648391]
5. Brox E, Luque L, Evertsen G, Hernandez J. Exergames for Elderly. : Social exergames to persuade seniors to increase physical activity. Proceedings of the 2011 5th International Conference on Pervasive Computing Technologies for Healthcare (PervasiveHealth); 2011 Presented at: 5th International Conference on Pervasive Computing Technologies for Healthcare (Pervasive Health); 2011 May 23-26; Dublin, Ireland p. 23-26 URL: http://www.helmholtz-muenchen.de/fileadmin/JOIN/PDF/PID1790829-Exergames.pdf [WebCite Cache ID 6gxoS44VD]
6. Hall AK, Chavarria E, Maneeratana V, Chaney BH, Bernhardt JM. Health benefits of digital videogames for older adults: a systematic review of the literature. Games Health J 2012 Dec;1(6):402-410. [doi: 10.1089/g4h.2012.0046] [Medline: 26192056]
7. Zhang F, Kaufman D. Physical and cognitive impacts of digital games on older adults: a meta-analytic review. J Appl Gerontol 2015 Jan 13. [doi: 10.1177/0733464814566678] [Medline: 25586268]
8. Toril P, Reales JM, Ballesteros S. Video game training enhances cognition of older adults: a meta-analytic study. Psychol Aging 2014 Sep;29(3):706-716. [doi: 10.1037/a0037507] [Medline: 25244488]
9. Mennecke B, McNeill D, Roche E, Bray D, Townsend A, Lester J. Communicaions of the Association for Information Systems. 2008. Second life and other virtual worlds: a roadmap for research URL: http://www.bus.iastate.edu/mennecke/CAIS-Vol22-Article20.pdf [accessed 2016-01-05] [WebCite Cache ID 6eJmscq7a]
10. Brewer LC, Kaihoi B, Zarling KK, Squires RW, Thomas R, Kopecky S. The use of virtual world-based cardiac rehabilitation to encourage healthy lifestyle choices among cardiac patients: intervention development and pilot study protocol. JMIR Res Protoc 2015;4(2):e39 [FREE Full text] [doi: 10.2196/resprot.4285] [Medline: 25857331]
11. Stewart S, Hansen TS, Carey TA. Opportunities for people with disabilities in the virtual world of Second Life. Rehabil Nurs 2010;35(6):254-259. [Medline: 21140720]
12. Beard L, Wilson K, Morra D, Keelan J. A survey of health-related activities on second life. J Med Internet Res 2009;11(2):e17 [FREE Full text] [doi: 10.2196/jmir.1192] [Medline: 19632971]
13. Johnson C, Feinglos M, Pereira K, Hassell N, Blascovich J, Nicollerat J, et al. Feasibility and preliminary effects of a virtual environment for adults with type 2 diabetes: pilot study. JMIR Res Protoc 2014;3(2):e23 [FREE Full text] [doi: 10.2196/resprot.3045] [Medline: 24713420]
14. Ruggiero L, Moadsiri A, Quinn LT, Riley BB, Danielson KK, Monahan C, et al. Diabetes island: preliminary impact of a virtual world self-care educational intervention for african americans with type 2 diabetes. JMIR Serious Games 2014;2(2) [FREE Full text] [doi: 10.2196/games.3260] [Medline: 25584346]
15. Rosal MC, Heyden R, Mejilla R, Capelson R, Chalmers KA, Rizzo DM, et al. A virtual world versus face-to-face intervention format to promote diabetes self-management among african american women: a pilot randomized clinical trial. JMIR Res Protoc 2014;3(4):e54 [FREE Full text] [doi: 10.2196/resprot.3412] [Medline: 25344620]
16. Johnson C, Feenan K, Setliff G, Pereira K, Hassell N, Beresford HF, et al. Building a virtual environment for diabetes self-management education and support. Int J Virtual Communities Soc Netw 2013;5(3) [FREE Full text] [Medline: 25699133]
17. Vorderstrasse A, Shaw RJ, Blascovich J, Johnson CM. A theoretical framework for a virtual diabetes self-management community intervention. West J Nurs Res 2014 Oct;36(9):1222-1237 [FREE Full text] [doi: 10.1177/0193945913518993] [Medline: 24451083]

18. Vorderstrasse AA, Melkus GD, Pan W, Lewinski AA, Johnson CM. Diabetes learning in virtual environments: testing the efficacy of self-management training and support in virtual environments (randomized controlled trial protocol). Nurs Res 2015;64(6):485-493. [doi: 10.1097/NNR.0000000000000128] [Medline: 26505161]
19. Kirschner J. Congenital muscular dystrophies. Handb Clin Neurol 2013;113:1377-1385. [doi: 10.1016/B978-0-444-59565-2.00008-3] [Medline: 23622361]
20. Heller B, Wheat JS, Mawson S, Wright P. Second lives for the third age: using virtual worlds to encourage exercise participation in older people. In: The Engineering of Sport 7. Paris: Springer; 2008:191-198.
21. Sullivan DK, Goetz JR, Gibson CA, Mayo MS, Washburn RA, Lee Y, et al. A virtual reality intervention (Second Life) to improve weight maintenance: rationale and design for an 18-month randomized trial. Contemp Clin Trials 2016 Jan;46:77-84. [doi: 10.1016/j.cct.2015.11.019] [Medline: 26616535]
22. Ghanbarzadeh R, Ghapanchi AH, Blumenstein M, Talaei-Khoei A. A decade of research on the use of three-dimensional virtual worlds in health care: a systematic literature review. J Med Internet Res 2014;16(2):e47 [FREE Full text] [doi: 10.2196/jmir.3097] [Medline: 24550130]
23. Molloy F. Grandma Gamers - Virutal Worlds Offer Aged Care Solutions. 2014. URL: http://ehealthspace.org/news/grandma-gamers-virtual-worlds-offer-aged-care-solutions [WebCite Cache ID 6eJoXJlLW]
24. Smith A. Older Adults and Technology Use. 2014. URL: http://www.pewinternet.org/2014/04/03/older-adults-and-technology-use/ [WebCite Cache ID 6eJopuV3c]
25. Siriaraya P, Ang CS. Characteristics and usage patterns of older people in a 3D online multi-user virtual environment. Comput Hum Beh 2012 Sep;28(5):1873-1882. [doi: 10.1016/j.chb.2012.05.005]
26. Siriaraya P, Ang C, Bobrowicz A. Exploring the potential of virtual worlds in engaging older people and supporting healthy aging. Behav Inform Technol 2012;33(3):13. [doi: 10.1080/0144929X.2012.691552]
27. Davis FD. Perceived usefulness, perceived ease of use, and user acceptance of information technology. MIS Quarterly 1989 Sep;13(3):319-340 [FREE Full text] [doi: 10.2307/249008]
28. Fishbein M, Ajzen I. Belief, Attitude, Intention, and Behavior: An Introduction to Theory and Research. Reading, MA: Addison-Wesley Pub Co; 1975.
29. Hofer B. Technology Acceptance As a Trigger for Successful Virtual Project Management: A Study of Business Use of Virtual Worlds. Technology Acceptance As a Trigger for Successful Virtual Project Management: A Study of Business Use of Virtual Worlds; 2009. URL: http://mci.academia.edu/BernhardHofer [accessed 2016-01-05] [WebCite Cache ID 6eJqwTTTA]
30. Kowitlawakul Y. The technology acceptance model: predicting nurses' intention to use telemedicine technology (eICU). Comput Inform Nurs 2011 Jul;29(7):411-418. [doi: 10.1097/NCN.0b013e3181f9dd4a] [Medline: 20975536]
31. Jen W. The adoption of mobile weight management services in a virtual community: the perspective of college students. Telemed J E Health 2010 May;16(4):490-497. [doi: 10.1089/tmj.2009.0126] [Medline: 20507202]
32. Abdekhoda M, Ahmadi M, Dehnad A, Hosseini AF. Information technology acceptance in health information management. Methods Inf Med 2014;53(1):14-20. [doi: 10.3414/ME13-01-0079] [Medline: 24248003]
33. Kuo K, Liu C, Ma C. An investigation of the effect of nurses' technology readiness on the acceptance of mobile electronic medical record systems. BMC Med Inform Decis Mak 2013;13:88 [FREE Full text] [doi: 10.1186/1472-6947-13-88] [Medline: 23938040]
34. Kim J, Park H. Development of a health information technology acceptance model using consumers' health behavior intention. J Med Internet Res 2012;14(5):e133 [FREE Full text] [doi: 10.2196/jmir.2143] [Medline: 23026508]
35. Holden RJ, Karsh B. The technology acceptance model: its past and its future in health care. J Biomed Inform 2010 Feb;43(1):159-172 [FREE Full text] [doi: 10.1016/j.jbi.2009.07.002] [Medline: 19615467]
36. Venkatesh V, Morris MG, Davis GB, Davis FD. User accetpance of information tehcnology: toward a univied view. MIS Quarterly 2003;27(3):425-478 [FREE Full text]
37. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009 Apr;42(2):377-381 [FREE Full text] [doi: 10.1016/j.jbi.2008.08.010] [Medline: 18929686]

Abbreviations

LLI: Lifelong Learning Institute
REDCap: Research Electronic Data Capture
SL: Second Life
TAM: Technology Acceptance Model
TRA: Theory of Reasoned Action
UTAUT: Unified Theory of Acceptance and Use of Technology

Edited by G Eysenbach; submitted 10.12.15; peer-reviewed by J Brixey, A Andrade; comments to author 30.12.15; revised version received 06.01.16; accepted 04.02.16; published 02.06.16.

Please cite as:
Cook N, Winkler SL
Acceptance, Usability and Health Applications of Virtual Worlds by Older Adults: A Feasibility Study
JMIR Res Protoc 2016;5(2):e81
URL: http://www.researchprotocols.org/2016/2/e81/
doi:10.2196/resprot.5423
PMID:27256457

Original Paper

Web Health Monitoring Survey: A New Approach to Enhance the Effectiveness of Telemedicine Systems

Maria Francesca Romano[1*], MSc; Maria Vittoria Sardella[1*], MSc; Fabrizio Alboni[1*], MSc

Institute of Economics, Scuola Superiore Sant'Anna, Pisa, Italy

[*]all authors contributed equally

Corresponding Author:
Maria Francesca Romano, MSc
Institute of Economics
Scuola Superiore Sant'Anna
piazza Martiri della Libertà 33
Pisa, 56127
Italy
Phone: 39 50883388
Fax: 39 50883344
Email: mariafrancesca.romano@sssup.it

Abstract

Background: Aging of the European population and interest in a healthy population in western countries have contributed to an increase in the number of health surveys, where the role of survey design, data collection, and data analysis methodology is clear and recognized by the whole scientific community. Survey methodology has had to couple with the challenges deriving from data collection through information and communications technology (ICT). Telemedicine systems have not used patients as a source of information, often limiting them to collecting only biometric data. A more effective telemonitoring system would be able to collect objective and subjective data (biometric parameters and symptoms reported by the patients themselves), and to control the quality of subjective data collected: this goal be achieved only by using and merging competencies from both survey methodology and health research.

Objective: The objective of our study was to propose new metrics to control the quality of data, along with the well-known indicators of survey methodology. Web questionnaires administered daily to a group of patients for an extended length of time are a Web health monitoring survey (WHMS) in a telemedicine system.

Methods: We calculated indicators based on paradata collected during a WHMS study involving 12 patients, who signed in to the website daily for 2 months.

Results: The patients' involvement was very high: the patients' response rate ranged between 1.00 and 0.82, with an outlier of 0.65. Item nonresponse rate was very low, ranging between 0.0% and 7.4%. We propose adherence to the chosen time to connect to the website as a measure of involvement and cooperation by the patients: the difference from the median time ranged between 11 and 24 minutes, demonstrating very good cooperation and involvement from all patients. To measure habituation to the questionnaire, we also compared nonresponse rates to the items between the first and the second month of the study, and found no significant difference. We computed the time to complete the questionnaire both as a measure of possible burden for patient, and to detect the risk of automatic responses. Neither of these hypothesis was confirmed, and differences in time to completion seemed to depend on health conditions. Focus groups with patients confirmed their appreciation for this "new" active role in a telemonitoring system.

Conclusions: The main and innovative aspect of our proposal is the use of a Web questionnaire to virtually recreate a checkup visit, integrating subjective (patient's information) with objective data (biometric information). Our results, although preliminary and if need of further study, appear promising in proposing more effective telemedicine systems. Survey methodology could have an effective role in this growing field of research and applications.

(JMIR Res Protoc 2016;5(2):e101) doi:10.2196/resprot.5187

KEYWORDS

Web questionnaire; Web health monitoring survey; telemedicine; virtual checkup; survey quality; quality indicators; paradata

Introduction

Survey methodology and medical research are becoming more connected: statisticians have always cooperated with clinicians in the analysis of collected data, and in recent years new research questions have arisen, along with new research fields (eg, health technology assessment and health economics). The aging European population and the interest in a healthy population in western countries have contributed to the increase in the number of health surveys, such as the English Longitudinal Study of Ageing (ELSA, since 2002) [1], the Survey of Health, Ageing and Retirement in Europe (SHARE, individuals from 20 European countries aged ≥50 years) [2], and the Health and Retirement Study (HRS) since 1992 in United States [3], to cite only the most well-known and relevant for the number of countries involved or for the systematic nature of the survey.

In all these surveys, as well as in more traditional clinical trials, the role of methodology in survey design, data collection, and data analysis is clear and recognized by the whole scientific community. The role of statisticians in clinical trials is now complemented by survey methodology: patients are often surveyed at the beginning and at the end of the trial to assess their well-being or other characteristics connected to the topic under investigation. Furthermore, patients are often requested to give feedback on their satisfaction with health structures, and, last but not least, health data management and analysis are now mandatory in health services assessment. Therefore, the contact points between medical and statistical research are numerous. Due to the complexity of research topics, the requested skills and knowledge are multidisciplinary and interdisciplinary: the role of researchers has been changing, and researchers now need to interconnect with each other, in order to achieve their research goals.

In the same years, survey methodology has had to couple with the challenges deriving from data collection through information and communications technology, the movement from landline telephones to mobiles and smartphones, and the increasing spread of Wi-Fi connections: modes and techniques to collect responses from people is always changing [4-8]. Guidelines and standards to follow are constantly being updated in order to be able to cover ever-changing and dynamic situations and data gathering modes [9,10], and new metrics derived from macro- and microparadata are being proposed and tested [11-16]. At the same time, the evolution of information and communications technology is giving a strong push to telemonitoring, telemedicine, and home rehabilitation systems [17-21]: new systems are being tested, and are quickly evolving from static to wireless devices, and from obtrusive to less-obtrusive equipment, also making it possible to follow patients and collect their information on their activities and reactions potentially everywhere and continuously.

In our opinion, there are new and common challenges for medicine and survey methodology. Which data are useful to be collected and analyzed? How? And when? What is the data's value for the well-being of the patient, which is the ultimate aim of a telemonitoring system? What about the quality and usefulness of the data collected?

In the vast scientific literature on telemedicine systems, we have found only a few reports of systems that use data and information coming directly from patients [22-27], although several systems, as for example Philips' eCareCompanion and eCareCoordinator [28], are now moving on to collecting this information through tablets or smartphones [29,30]. Surely researchers are exploring the implications of how and when these subjective data are collected, their utility for effective monitoring, and, more relevant from our point of view, whether there is a quality control process for this subjective information and how it works, but results have not reached the publication stage.

Our vision is that an effective telemonitoring system would be able to 1) collect objective and subjective data at the same time (biometric parameters and symptoms reported by the patients themselves), 2) control the quality of data collected, and 3) analyze data both at the individual and at an aggregated level.

This ambitious goal can be achieved only by using (and merging) all the technologies and skills available from both survey methodology and health research. In this paper we focus on the contribution of subjective data, that is, data reported by the patients themselves, about themselves, in way that simulates a standard medical examination: this, in our opinion, constitutes the real innovation in the scheme above.

From Acquisition of Vital Signs to an Integrated Telemedicine System

It is quite obvious that remote monitoring and telemedicine systems apply only to patients with chronic conditions. For them, a remote monitoring system is extremely useful, as it is designed to store data collected directly at the patient's home, with the goal of detecting as soon as possible any worsening of the patient's health status.

Patient-doctor communication seems to be neglected in home monitoring, and yet it is always present in medical checkups (and in their telephone communications). Data and information are always the objects of the patient-doctor communication in each (first or follow-up) medical visit, and yet it seems that telemedicine systems do not include this relevant source of information. Generally, patient-doctor communication is face-to-face. In the first contact with the patient, the physician starts with a clinical interview: this allows the physician to know how the patient feels and the symptoms that he or she reports, and it precedes the objective physical examination. Thereafter, the patient undergoes further examinations (electrocardiography, echocardiography, chest x-ray, etc, and laboratory tests according to the physician's request). Only after all the data and information have been collected and read is the physician able to confirm the diagnosis and prescribe suitable therapy.

We underline that—as physicians themselves state—listening to the patient's account of his or her symptoms and feelings is key to acquiring all of the information about the patient's health status. To have only biometric or laboratory data is not sufficient for making a correct diagnosis and consequent decisions, for taking actions, and for giving prescriptions. For patients with a chronic disease, there are recognized guidelines (standardized by each disease) that have to be followed in a medical checkup:

guidelines recommend not only which laboratory and other tests to take, but also that the symptoms reported by the patients themselves be recorded. Last but not least, patients with chronic diseases are increasingly able to recognize and communicate correct and useful information about their conditions. From these considerations, it follows that a remote monitoring system must have the aim of daily collecting vital signs and biometric data, as well as subjective data, from the patient.

Information and communications technology tools and survey methodology allow for collection of these types of data according to the ideal standards: the questions (asked by a physician) and the responses (given by the patient) can be easily recognized as simulating a questionnaire, whose content and frequency of administration are determined by physicians.

The Role of Survey Methodology in Health Monitoring

The medical checkup can be transformed into a computer-assisted Web interview, and the Web-collected data can be used to generate a longitudinal survey. Subjective data can be analyzed together with objective data in order to have an assessment of the patient's health status or to detect potential risks.

In chronic diseases, the checkup visit can be more easily transformed into a structured questionnaire, because the clinical interview focuses mainly on presenting symptoms and their variations since the last visit. It is possible to acquire and store on a daily basis (or with a different periodicity; in any case, more frequently than the face-to-face checkup visits) all responses and information given by the patient. More important, it is possible to analyze both clinical and patient variables (measured at the same time) along appropriate longitudinal statistical models.

The aging of the population in western countries calls for the unavoidable and necessary use of a system to automatically assess the health status of patients with chronic conditions, supporting and complementing face-to-face clinic activities, with the aim of focusing the efforts of medical staff on the most serious cases. In order to reliably automate prediction of the state of health of a chronically ill patient, it is also necessary to ensure that data collection is at the highest possible level of reliability and that the data are validated according to metrics established and accepted by the scientific community.

To sum up, in a telemedicine system, questionnaires can be administered (almost) daily for a group of patients for an extended length of time. Are the questionnaires collected in a telemedicine system similar to a longitudinal survey? If we consider that a survey "is a systematic method for gathering information from (a sample of) entities for the purposes of constructing quantitative descriptors of the attributes of the larger population of which the entities are members" [5], then the answer is indeed positive, and we name it a Web health monitoring survey (WHMS).

Quality Measures of a WHMS

If "the quality of a survey is best judged not by its size, scope, or prominence, but by how much attention is given to [preventing, measuring, and] dealing with the many important problems that can arise" [31], then it is relevant to compare the American Association of Public Opinion Research's (AAPOR) criteria to "produce a quality survey" with the particular situation of a WHMS (Table 1) [31].

Table 1. Comparison between the American Association of Public Opinion Research's (AAPOR) criteria [31] for a general survey and the features of a Web health monitoring survey (WHMS).

	AAPOR survey criteria	Features of a WHMS
Points better addressed by a WHMS	Have specific goals.	Have specific goals.
	Consider alternatives.	Consider alternatives.
	Take great care in matching question wording to the concepts being measured and the population studied.	Easier than in other fields of research. More attention to question wording in different languages or contexts.
	Maximize cooperation or response rates within the limits of ethical treatment of human subjects.	Patients are strictly involved and their active role in the monitoring system can stimulate a high participation rate, a high response rate, and a low item nonresponse rate. The patient AND the patient's relatives or caregivers can have more positive feelings in participating in the survey.
Points easily respected by a WHMS	Select samples that well represent the population to be studied	The sample is not probabilistic, rather it resembles an opt-in one.
	Use designs that balance costs with errors.	Use designs that balance costs with errors.
	Pretest questionnaires and procedures.	Pretest questionnaires and procedures.
	Train interviewers carefully on interviewing techniques and the subject matter of the survey.	Train and supervise patients (and doctors).
	Use appropriate statistical analytic and reporting techniques.	Use appropriate statistical analytic and reporting techniques.
	Develop and fulfill pledges of confidentiality given to respondents.	Develop and fulfill pledges of confidentiality given to respondents.
	Disclose all methods of the survey to allow for evaluation and replication.	Disclose all methods of the survey to allow for evaluation and replication.
Point to be studied for a WHMS	Check quality at each stage.	New indicators and metrics are required.

Methods

The main contribution that survey methodologists can make to WHMS is related to the quality of the survey at each stage.

As a first contribution, we offer some indicators, calculated on data collected during the trial of an integrated telemedicine system (*Assistenza domiciliare allo SCOmpenso cardiaco attraverso Le Tecniche Avanzate di comunicazione digitale*, or ASCOLTA, the Italian word for listen) [32] conducted in 2011 in Pisa, Italy, involving 12 patients with a diagnosis of heart failure. We collected both biometric and subjective data for a period of 2 months for 11 patients and for <1 month for 1 patient, who was the only one hospitalized for noncardiac problems and was thus not included in the study. Patients had to connect daily to a website, at the time most convenient for the patients themselves. A Web questionnaire—dynamically constructed with a different number of questions (and answers) according to the patient's clinical condition—collected the patients' health data, including additional physical data (weight and arterial pressures) measured and reported by the patients themselves. At the end of the questionnaire, the system asked the patient to wear wireless electrocardiograph, pulse oximetry oxygen saturation, and respiratory rate recorders for 5 minutes. The patients were free to ask for a new connection at their discretion.

We have previously described and discussed the positive contribution of subjective data to detecting potential risks [32]: variables obtained during a virtual visit substantially contributed to assessment of clinical status (69% of correct classifications), similar to the traditional biometric variables (70%), as assessed by a random forest classification algorithm. The combined use of both variables led to a more correct classification of the patient's health status (84%).

The questionnaire (see Multimedia Appendix 1 for the English translation) was designed under cardiologists' supervision, tested, and transformed into a Web questionnaire. The wording of questions and answers and their sequence were in accordance with European Society of Cardiology guidelines [33] for heart failure patients and with the cardiologists' clinical experience.

We also collected paradata during the study period, along with instrumental and subjective data.

During the 2-month trial, we collected a total of 478 records from 11 patients, 243 for the first month and 235 for the second month.

As described before, a WHMS is a longitudinal survey that is quite different from a panel survey in terms of duration and contents; therefore, we needed more specific indicators than the well-known and consolidated indicators available in the literature [12,34,35].

We therefore propose the use of indicators that measure the response and attrition rates at the patient level. The item nonresponse rate is calculated as a proxy of the patient's cooperation. To measure whether there was any habituation to a daily questionnaire, we compared the time span to complete the questionnaire between the two halves of the entire study

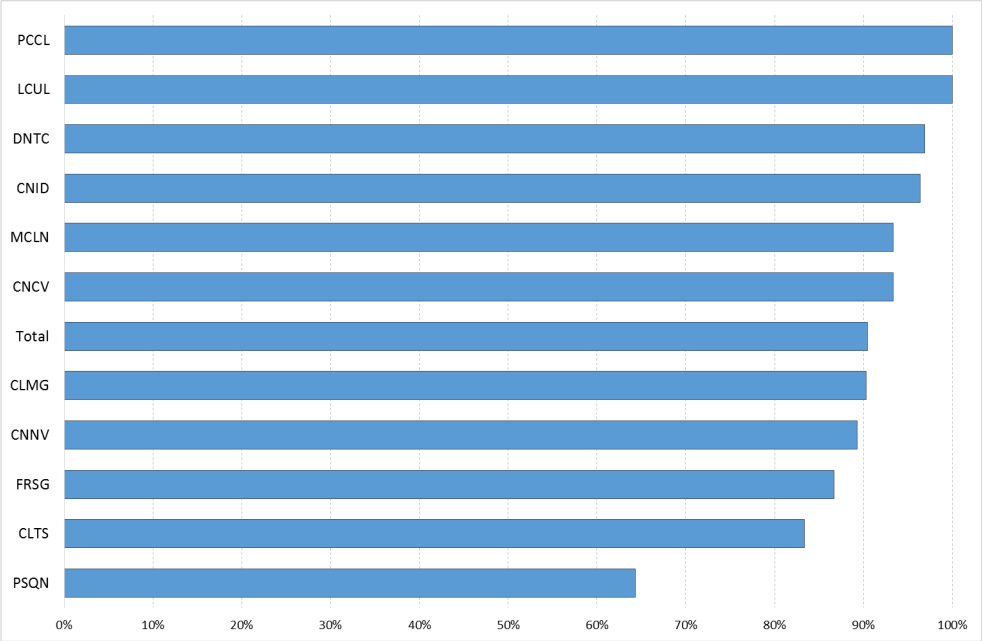
period. Finally, we measured the consistency of the time chosen to complete the questionnaire as a proxy of the patient's compliance and satisfaction. Focus groups with patients were organized and conducted both at the beginning and at the end of the trial.

Results

Patient Adherence and Response Rate

As expected, patients were very cooperative due to an effective strategy to encourage patient involvement. The number of missing questionnaires was very low. Figure 1 illustrates the response rate by each patient.

Figure 1. Response rate, by patient, during the 2-month ASCOLTA study.



Item Nonresponse

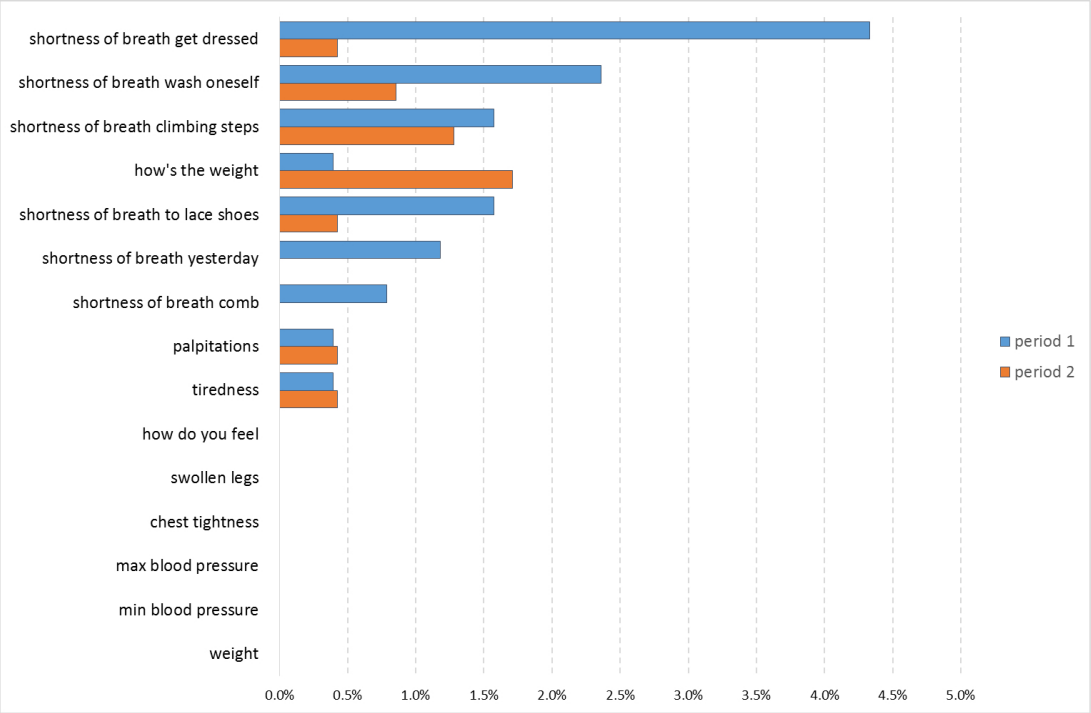
We measured the rate of nonresponse to each item, obtaining good results (Table 2). The 3 biometric variables that the patients were asked to report in the questionnaire all had a nonresponse rate of 0%, which we interpret as denoting a cooperative attitude among all of the patients: during the final focus group the patients expressed positive reactions for their active role.

Table 2. Rate of nonresponse to questionnaire items (N=514).

Items	Nonresponses	
	n	%
Overall feeling	2	0.39
Weight relative to previous day	31	6.03
Swollen legs	5	0.97
Shortness of breath yesterday	4	0.78
Shortness of breath when combing	28	5.45
Shortness of breath when washing	34	6.61
Shortness of breath when getting dressed	38	7.39
Shortness of breath when tying shoes	31	6.03
Shortness of breath when climbing steps	33	6.42
Palpitations	2	0.39
Chest tightness	2	0.39
Tiredness	2	0.39
Maximum blood pressure	0	0
Minimum blood pressure	0	0
Weight	0	0

To measure habituation to the questionnaire, we compared the item nonresponses between the first and the second month. We found no significant differences (Figure 2).

Figure 2. Comparison of nonresponses to questionnaire items by period of the study (period 1: first month; period 2: second month) and by question.



Time to Complete the Questionnaire

From paradata collected, we calculated the time spent to complete the questionnaires both for the daily and the discretionary questionnaires (Table 3). The time required seemed to depend on the patients' health conditions; in general, time required was very short and acceptable, and at our advice was not perceived as a burden by the patient.

Table 3. Time spent to complete the daily and discretionary questionnaires, by patient.

Patient	Daily		Discretionary		Total	
	n	Mean time (min.s)	n	Mean time (min.s)	n	Mean time (min.s)
CLMG	73	1.07	1	8.00	74	1.12
CLTS	55	1.08	0	0	55	1.08
CNCV	20	1.36	1	4.00	21	1.43
CNID	85	1.46	1	1.00	86	1.45
CNNV	24	1.03	1	1.00	25	1.02
DNTC	22	3.49	3	2.20	25	3.38
FRSG	27	1.27	1	1.00	28	1.26
LCUL	46	1.46	0	0	46	1.46
MCLN	57	1.09	1	1.00	58	1.09
PCCL	50	1.34	5	1.24	55	1.33
PSQN	19	1.16	2	1.30	21	1.17
Total	478	1.31	16	2.04	494	1.32

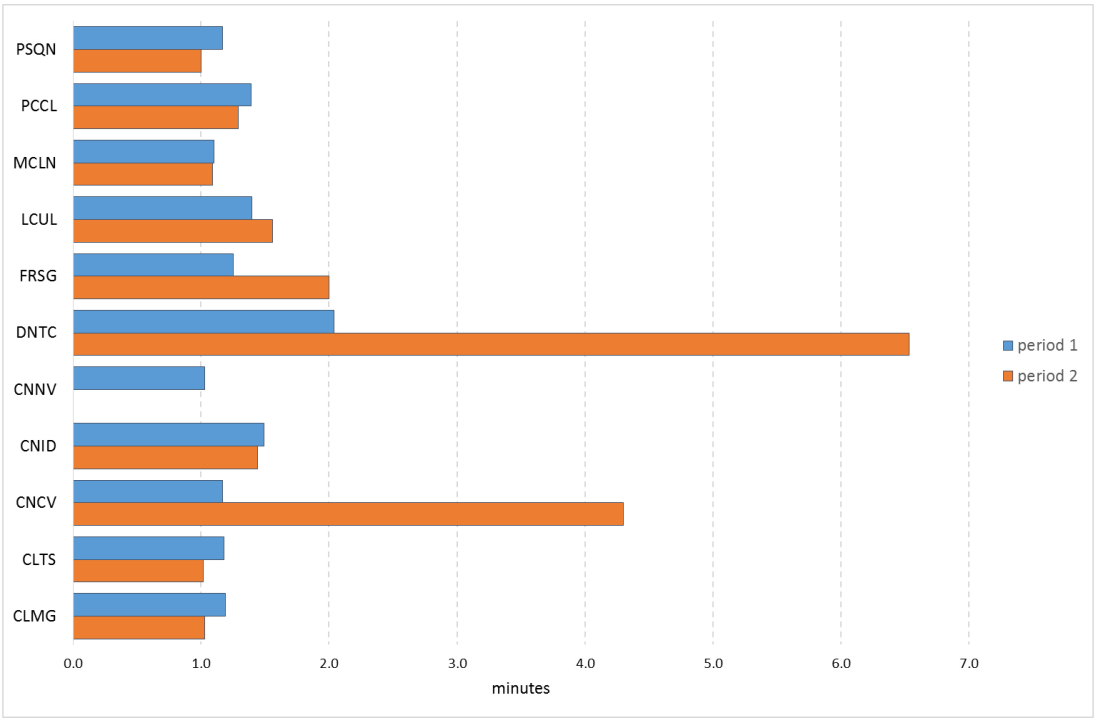
We also tested for difference in completion time between the first and second period (Figure 3 and Table 4). Although the difference was statistically significant for 3 patients, the overall difference was not.

Table 4. Time (min.s) spent to complete the daily questionnaires: comparison between first and second period of the study, by patient.

Patient	Period		*t* test	*P* value	*df*
	First half	Second half			
CLMG	1.09	1.05	0.71	.48	71
CLTS	1.16	1.02	2.10	.04[a]	53
CNCV	1.00	2.20	–2.47	.02[a]	18
CNID	1.37	1.56	–0.51	.61	83
CNNV	1.05	1.00	0.92	.37	22
DNTC	2.04	6.53	–1.71	.10	20
FRSG	1.47	1.05	1.18	.25	25
LCUL	1.37	2.10	–1.10	.28	44
MCLN	1.08	1.14	–0.49	.63	55
PCCL	1.30	1.41	–0.49	.63	48
PSQN	1.30	1.05	2.13	.05[a]	17
Total	1.25	1.37	–1.06	.29	476

[a]Significant difference ($P \leq .05$).

Figure 3. Time spent to complete the questionnaires, by patient and by period of the study (period 1: first month; period 2: second month).



Patients' Chosen Time of Day to Complete the Questionnaire

To accommodate the patient's lifestyle, each one could choose the hour of the day when they would complete the questionnaire, with an interval of ±1 hour (Table 5).

During the final focus group, the patients expressed their appreciation for this support, and therefore their behavior is a proxy of a cooperative attitude.

Table 5. Time of day chosen to complete the questionnaire, by patient.

Patient	Total no. of daily questionnaires completed	Median time at start of questionnaire (h.min.s)	Mean time at start of questionnaire (h.min.s)	Mean difference from median	Mean difference from mean
CLMG	73	8.05.00	8.13.39	18.27	17.54
CLTS	55	14.42.00	14.42.11	16.13	15.46
CNCV	20	15.23.00	15.33.14	13.53	15.51
CNID	85	17.48.30	17.45.53	14.28	14.42
CNNV	24	19.24.30	19.14.28	24.33	26.3
DNTC	22	9.45.00	9.55.55	22.55	25.3
FRSG	27	9.29.30	9.25.56	18.13	18.11
LCUL	46	8.20.00	8.26.29	22.26	22.12
MCLN	57	9.20.00	9.30.47	17.02	19.25
PCCL	50	7.56.30	8.36.28	11.51	31.42
PSQN	19	20.07.00	19.58.11	20.09	19.32

The mean difference was about 20 minutes, both from the median and from the mean.

Discussion

It is worth noting that our WHMS is part of a telemedicine system, making its goal different from that of other health surveys such as a Web-based daily questionnaire for health [26]. Telemedicine data are collected and must be analyzed at the patient level, because the main goal is to assess the health status of the single patient. On the contrary, in epidemiological studies the focus is on measuring health parameters for the entire population.

Moreover, a WHMS is designed for patients with chronic conditions, and therefore they may already be greatly involved in the survey or their cooperative attitude can be reinforced: no incentive is needed, because the implicit incentive for each patient is to get better attention from the medical staff and to contribute actively to the management of their chronic disease. As a consequence, all indicators based on response rate (although—or perhaps because—they have values never obtained in a general survey) seem less relevant to measure the quality of the WMHS. Nonetheless, their trend over time for longer study is worth computing and controlling.

WHMS is a longitudinal survey with very strict periodicity, even daily, which could be a burden for the respondent [36], resulting in a possible high attrition rate. The attrition rate at the patient level is therefore relevant in monitoring the quality of data collection. Our results demonstrate that this risk is very low, taking into account that only a few minutes are required to complete the questionnaire.

Even with a diligent patient, there is the risk that patients' responses will become automatic. The results we obtained led us to reject the hypothesis of the presence of automatic responses; therefore, the patient's responses are deemed to be reliable.

Signing in to the daily questionnaire and the patients' choice of when during the day to sign in seem a good measure of their cooperation.

Focus groups with patients confirmed the efficacy of the questionnaire and the positive reactions of patients to the new mode of collecting this information. Patients appreciated their new active role in the ASCOLTA system.

Study Limitations

We acknowledge that our study has some critical limitations, such as the small number of patients studied and the short duration of the longitudinal survey. Furthermore, the study involved only patients with heart failure. Other paradata can be collected, such as those needed to measure response latency or time-to-click [16,37].

In more general terms, the digital skills of potential respondents to a WHMS is a challenge: a sample of patients with chronic conditions would be older, and the greater digital divide in this group could be a barrier to their participation in such a survey [38-40].

Many aspects of a WHMS deserve to be developed, by applying the same approach to other kinds of chronic pathologies (eg, chronic obstructive pulmonary disease, diabetes, and hypertension) [41,42]. Moreover, the expansion of wireless technologies on platforms such as smartphones and tablets will enable the collection of biometric data to extend even to people who are not yet ill (eg, people at risk) or to healthy people who participate in amateur sports. In addition, although this is an open field, the reactions of medical staff to the virtual visit are worth investigating, as patient satisfaction is further explored [43-47].

Information and communications technology solutions can be applied to facilitate and enable patient-doctor communication [48-53]. Many virtual medical visit applications are being developed [54-56] and the increasing number of websites testifies to patients' willingness to play a more active role in their own health management [57,58].

The main and innovative aspect of our proposal is the use of a Web questionnaire to virtually recreate a checkup visit, integrating subjective (patient information) with objective data (biometric information) in a unique database that can be analyzed with appropriate statistical methods. We suggest here some indicators to control the process of data collection, along with criteria already established by survey methodology, but we are conscious that other specific metrics need to be studied.

Our results, although preliminary, appear promising and, in our opinion, could be of significance to the ongoing debate about the most appropriate type of telemonitoring and remote care of patients. Further studies, in a larger population, could be useful to ultimately confirm our preliminary results and to provide a more efficient cost-benefit ratio, according to health technology assessment.

Survey methodology could have an effective role in this growing field of research and applications.

In agreement with the Couper's statement that "We constantly need to hone our skills, update our knowledge, and expose ourselves to new developments in other disciplines and fields of research and application." [59], we think that monitoring of health data is a challenge for survey methodologists. Skills and competencies of survey methodologists and statisticians must guide data collection and data analysis in health monitoring surveys.

Acknowledgments

ASCOLTA Project was funded by the Regione Toscana (BANDO UNICO R&S, anno 2008 POR CREO Attività 1.6 Linea A) to a pool of firms (CAEN SpA - leader, Evidence Srl, EMAC Srl, Develer Srl, Sinergest Srl, Laboratori ARCHA Srl). Sant'Anna School of Advanced Studies (Institute of Economics, Institute of Life Sciences, and Institute of Communication, Information, and Perception Technologies) and the Department Cardiac Thoracic and Vascular Department (University of Pisa) gave scientific support. The project was presented in April 2009, approved in April 2010, and concluded in March 2012.

The study protocol was approved by the Ethical Committee of the Hospital of Pisa (Study No. 3461/2011, presented November 29, 2011, approved February 9, 2012).

Conflicts of Interest

None declared.

Multimedia Appendix 1

Questionnaires used (English translation).

[PDF File (Adobe PDF File), 21KB - resprot_v5i2e101_app1.pdf]

References

1. ELSA English Longitudinal Study of Ageing: Insight Into a Maturing Population. London, UK: The Institute for Fiscal Studies; 2011. URL: http://www.elsa-project.ac.uk/ [accessed 2015-09-16] [WebCite Cache ID 6baPyVpwv]
2. Survey of Health Ageing Retirement. Munich, Germany: SHARE-ERIC; 2013. URL: http://www.share-project.org/ [accessed 2015-09-16] [WebCite Cache ID 6baQ8bPKh]
3. Health and Retirement Study. Ann Arbor, MI: Institute for Social Research, University of Michigan; 2015. URL: http://hrsonline.isr.umich.edu/; [accessed 2015-09-16] [WebCite Cache ID 6baQMLZqF]
4. Conrad FG, Schober MF, editors. Envisioning the Survey Interview of the Future. Hoboken, NJ: Wiley-Interscience; 2008.
5. Groves R, Fowler FJ, Couper M, Lepkowski J, Singer E, Tourangeau R. Survey Methodology. New York, NY: Wiley; 2009.
6. Couper MP. The future of modes of data collection. Public Opinion Q 2011 Dec 15;75(5):889-908. [doi: 10.1093/poq/nfr046]
7. Callegaro M, Baker R, Bethlehem J, Goritz A, Krosnick J, Lavrakas P, editors. Online Panel Research: A Data Quality Perspective. Chichester, UK: Wiley; 2014:A.
8. Callegaro M, Lozar MK, Vehovar V, editors. Web Survey Methodology. Los Angeles, CA: Sage; 2015.
9. Link MW, Murphy J, Schober MF, Buskirk TD, Hunter Childs J, Langer Tesfaye C. Mobile technologies for conducting, augmenting and potentially replacing surveys: executive summary of the AAPOR Task Force on Emerging Technologies in Public Opinion Research. Public Opinion Q 2014 Nov 25;78(4):779-787. [doi: 10.1093/poq/nfu054]
10. AAPOR. Standard Definitions: Final Dispositions of Case Codes and Outcome Rates for Surveys 8th edition. URL: http://www.aapor.org/AAPORKentico/Communications/AAPOR-Journals/Standard-Definitions.aspx [accessed 2015-09-30] [WebCite Cache ID 6bvatGOYY]
11. Heerwegh D. Explaining response latencies and changing answers using client-side paradata from a Web survey. Soc Sci Comput Rev 2003 Aug 01;21(3):360-373. [doi: 10.1177/0894439303253985]
12. Callegaro M, DiSogra C. Computing response metrics for online panels. Public Opinion Q 2009 Jan 29;72(5):1008-1032. [doi: 10.1093/poq/nfn065]

13. Kreuter F, editor. Improving Surveys With Paradata: Analytic Uses of Process Information. Hoboken, NJ: Wiley & Sons; 2013.
14. Schouten B, Shlomo N, Skinner C. Indicators for monitoring and improving representativeness of responses. J Off Statistics. 2011. (2) p. 231-253 URL: http://www.jos.nu/Articles/abstract.asp?article=272231 [WebCite Cache ID 6heShR8lj]
15. Sirkis R, Jans M. Using statistical process control to understand variation in computer assisted personal interviewing data. 2011 Presented at: Joint Statistical Meetings; July 30-August 4, 2011; Miami Beach, FL p. 477-489 URL: http://www.amstat.org/sections/srms/proceedings/ [WebCite Cache ID 6heSlaIdj]
16. Couper MP, Kreuter F. Using paradata to explore item level response times in surveys. J Royal Stat Soc Ser A (Stat Soc) 2013;176:271-286. [doi: 10.1111/j.1467-985X.2012.01041.x]
17. Nangalia V, Prytherch DR, Smith GB. Health technology assessment review: remote monitoring of vital signs--current status and future challenges. Crit Care 2010;14(5):233 [FREE Full text] [doi: 10.1186/cc9208] [Medline: 20875149]
18. Anker D, Koehler F, Abraham WT. Telemedicine and remote management of patients with heart failure. Lancet 2011 Aug 20;378(9792):731-739. [doi: 10.1016/S0140-6736(11)61229-4] [Medline: 21856487]
19. Chaudhry SI, Mattera JA, Curtis JP, Spertus JA, Herrin J, Lin Z, et al. Telemonitoring in patients with heart failure. N Engl J Med 2010;363(24):2301-2309. [doi: 10.1056/NEJMoa1010029]
20. Desai AS. Home monitoring heart failure care does not improve patient outcomes: looking beyond telephone-based disease management. Circulation 2012 Feb 14;125(6):828-836 [FREE Full text] [doi: 10.1161/CIRCULATIONAHA.111.031179] [Medline: 22331920]
21. Bashshur RL, Shannon GW, Smith BR, Alverson DC, Antoniotti N, Barsan WG, et al. The empirical foundations of telemedicine interventions for chronic disease management. Telemed J E Health 2014 Sep;20(9):769-800 [FREE Full text] [doi: 10.1089/tmj.2014.9981] [Medline: 24968105]
22. Little M, Wicks P, Vaughan T, Pentland A. Quantifying short-term dynamics of Parkinson's disease using self-reported symptom data from an Internet social network. J Med Internet Res 2013;15(1):e20 [FREE Full text] [doi: 10.2196/jmir.2112] [Medline: 23343503]
23. Bellos C, Papadopoulos A, Rosso R, Fotiadis D. Identification of COPD patients' health status using an intelligent system in the CHRONIOUS wearable platform. IEEE J Biomed Health Inform 2014 May;18(3):731-738. [doi: 10.1109/JBHI.2013.2293172] [Medline: 24808219]
24. Bellos C, Papadopoulos A, Rosso R, Fotiadis D. CHRONIOUS: clinical validation of the CHRONIOUS wearable system in patients with chronic disease. 2013 Presented at: 35th Annual International Conference of the IEEE EMBS; July 3-7, 2013; Osaka, Japan p. 7084-7087.
25. Steele GC, Khan AI, Kuluski K, McKillop I, Sharpe S, Bierman AS, et al. Improving patient experience and primary care quality for patients with complex chronic disease using the electronic patient-reported outcomes tool: adopting qualitative methods into a user-centered design approach. JMIR Res Protoc 2016 Feb;5(1):e28 [FREE Full text] [doi: 10.2196/resprot.5204] [Medline: 26892952]
26. Sugiura H, Ohkusa Y, Akahane M, Sano T, Okabe N, Imamura T. Development of a web-based survey for monitoring daily health and its application in an epidemiological survey. J Med Internet Res 2011;13(3):e66 [FREE Full text] [doi: 10.2196/jmir.1872] [Medline: 21946004]
27. Dorsch MP, Farris KB, Bleske BE, Koelling TM. A web application for self-monitoring improves symptoms in chronic systolic heart failure. Telemed J E Health 2015 Apr;21(4):267-270. [doi: 10.1089/tmj.2014.0095] [Medline: 25654615]
28. Open A World of Cloud-Based Collaborative Care. Amsterdam, Netherlands: Koninklijke Philips N.V; 2015. URL: http://www.usa.philips.com/healthcare-innovation/about-health-suite/applications-health-suite [accessed 2015-09-16] [WebCite Cache ID 6baQj6qVt]
29. Lygidakis C, Wallace P, Tersar C, Marcatto F, Ferrante D, Della VR, et al. Download your doctor: implementation of a digitally mediated personal physician presence to enhance patient engagement with a health-promoting Internet application. JMIR Res Protoc 2016 Mar;5(1):e36 [FREE Full text] [doi: 10.2196/resprot.5232] [Medline: 26944482]
30. McLean G, Murray E, Band R, Saunderson K, Hanlon P, Little P, et al. Digital interventions to promote self-management in adults with hypertension: protocol for systematic review and meta-analysis. JMIR Res Protoc 2015 Nov;4(4):e133 [FREE Full text] [doi: 10.2196/resprot.4648] [Medline: 26589728]
31. American Association for Public Opinion Research. Best Practices for Research. Oakbrook Terrace, IL: AAPOR; 2016. URL: http://www.aapor.org/Standards-Ethics/Best-Practices.aspx [accessed 2016-05-18] [WebCite Cache ID 6hb0FpeaO]
32. Romano MF, Sardella MV, Alboni F, L'Abbate A, Mariotti R, Di Bello V. The informative contribution of the “virtual medical visit” in a new heart failure telemedicine integrated system. Telemed J E Health 2014 Jun;20(6):508-521. [doi: 10.1089/tmj.2013.0225] [Medline: 24712556]
33. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012 Jul;33(14):1787-1847 [FREE Full text] [doi: 10.1093/eurheartj/ehs104] [Medline: 22611136]

34. Eysenbach G. Improving the quality of Web surveys: the Checklist for Reporting Results of Internet E-Surveys (CHERRIES). J Med Internet Res 2004 Sep 29;6(3):e34 [FREE Full text] [doi: 10.2196/jmir.6.3.e34] [Medline: 15471760]
35. Eysenbach G. The law of attrition. J Med Internet Res 2005;7(1):e11 [FREE Full text] [doi: 10.2196/jmir.7.1.e11] [Medline: 15829473]
36. Axinn WG, Jennings EA, Couper MP. Response of sensitive behaviors to frequent measurement. Soc Sci Res 2015 Jan;49:1-15 [FREE Full text] [doi: 10.1016/j.ssresearch.2014.07.002] [Medline: 25432599]
37. Callegaro M. Using paradata to improve the quality of web surveys: some examples and applications. London, UK: Royal Statistical Society; 2014 Presented at: Conference on Paradata From surveys research to practice; 2014; London, UK URL: http://www.southampton.ac.uk/s3ri/news/events/2014/06/26_paradata_from_survey_research_to_practice.page [WebCite Cache ID 6hkG1poio]
38. Gracia E, Herrero J. Internet use and self-rated health among older people: a national survey. J Med Internet Res 2009 Dec;11(4):e49 [FREE Full text] [doi: 10.2196/jmir.1311] [Medline: 19955041]
39. Romano MF, Sardella MV, Alboni F, Russo L, Mariotti R, Nicastro I, et al. Is the digital divide an obstacle to e-health? An analysis of the situation in Europe and in Italy. Telemed J E Health 2015 Jan;21(1):24-35. [doi: 10.1089/tmj.2014.0010] [Medline: 25495564]
40. Jones J, Cassie S, Thompson M, Atherton I, Leslie SJ. Delivering healthcare information via the internet: cardiac patients' access, usage, perceptions of usefulness, and web site content preferences. Telemed J E Health 2014;20(3):223-228. [doi: 10.1089/tmj.2013.0182] [Medline: 24404814]
41. Wang J, Wang Y, Wei C, Yao NA, Yuan A, Shan Y, et al. Smartphone interventions for long-term health management of chronic diseases: an integrative review. Telemed J E Health 2014 Jun;20(6):570-583. [doi: 10.1089/tmj.2013.0243] [Medline: 24787747]
42. Bellos C, Papadopoulos A, Rosso R, Fotiadis D. CHRONIOUS: A wearable platform for monitoringmanagement of patients with chronic disease. 2011 Presented at: 33rd Annual International Conference of the IEEE EMBS; August 30-September 3, 2011; Boston, MA p. 864-867.
43. Bostock Y, Hanley J, McGown D, Pinnock H, Padfield P, McKinstry B. The acceptability to patients and professionals of remote blood pressure monitoring using mobile phones. Primary Health Care 2009 Jul 28;10(4):299-308. [doi: 10.1017/S1463423609990107]
44. Cafazzo JA, Leonard K, Easty AC, Rossos PG, Chan CT. Patient perceptions of remote monitoring for nocturnal home hemodialysis. Hemodial Int 2010 Oct;14(4):471-477. [doi: 10.1111/j.1542-4758.2010.00473.x] [Medline: 20955280]
45. Matlock D. Big Brother is watching you: what do patients think about ICD home monitoring? Circulation 2010;122(4):319-321. [doi: 10.1161/CIRCULATIONAHA.110.966515]
46. Or CKL, Karsh B, Severtson DJ, Burke LJ, Brown RL, Brennan PF. Factors affecting home care patients' acceptance of a web-based interactive self-management technology. J Am Med Inform Assoc 2011 Jan;18(1):51-59 [FREE Full text] [doi: 10.1136/jamia.2010.007336] [Medline: 21131605]
47. McBride DL, Levasseur SA, Li D. Development and validation of a web-based survey on the use of personal communication devices by hospital registered nurses: pilot study. JMIR Res Protoc 2013;2(2):e50 [FREE Full text] [doi: 10.2196/resprot.2774] [Medline: 24280660]
48. Alkhaldi G, Hamilton FL, Lau R, Webster R, Michie S, Murray E. The effectiveness of technology-based strategies to promote engagement with digital interventions: a systematic review protocol. JMIR Res Protoc 2015;4(2):e47 [FREE Full text] [doi: 10.2196/resprot.3990] [Medline: 25921274]
49. Antonelli D, Bellomo D, Bruno G, Villa A. Evaluating collaboration effectiveness of patient-to-doctor interaction in a healthcare territorial network. In: Camarinha-Matos LM, Xu L, Afsarmanesh H, editors. Collaborative Networks in the Internet of Services. Berlin, Germany: Springer; 2012:128-136.
50. Boulos MNK, Wheeler S, Tavares C, Jones R. How smartphones are changing the face of mobile and participatory healthcare: an overview, with example from eCAALYX. Biomed Eng Online 2011;10:24 [FREE Full text] [doi: 10.1186/1475-925X-10-24] [Medline: 21466669]
51. Lindberg B, Nilsson C, Zotterman D, Söderberg S, Skär L. Using information and communication technology in home care for communication between patients, family members, and healthcare professionals: a systematic review. Int J Telemed Appl 2013;2013:461829 [FREE Full text] [doi: 10.1155/2013/461829] [Medline: 23690763]
52. Bert F, Giacometti M, Gualano MR, Siliquini R. Smartphones and health promotion: a review of the evidence. J Med Syst 2014 Jan;38(1):9995. [doi: 10.1007/s10916-013-9995-7] [Medline: 24346929]
53. Mattsson S, Olsson EMG, Alfonsson S, Johansson B, Carlsson M. Measuring use of health-related support on the Internet: development of the Health Online Support Questionnaire (HOSQ). J Med Internet Res 2015 Nov;17(11):e266 [FREE Full text] [doi: 10.2196/jmir.4425] [Medline: 26589638]
54. Mahler SA, Burke GL, Duncan PW, Case LD, Herrington DM, Riley RF, et al. HEART pathway accelerated diagnostic protocol implementation: prospective pre-post interrupted time series design and methods. JMIR Res Protoc 2016 Jan;5(1):e10 [FREE Full text] [doi: 10.2196/resprot.4802] [Medline: 26800789]

55. Eissens van der Laan MR, van Offenbeek MAG, Broekhuis H, Slaets JPJ. A person-centred segmentation study in elderly care: towards efficient demand-driven care. Soc Sci Med 2014 Jul;113:68-76. [doi: 10.1016/j.socscimed.2014.05.012] [Medline: 24852657]
56. Dixon RF, Rao L. Asynchronous virtual visits for the follow-up of chronic conditions. Telemed J E Health 2014 Jul;20(7):669-672. [doi: 10.1089/tmj.2013.0211] [Medline: 24784174]
57. Society for Participatory Medicine. e-patients.net. 2015. URL: http://e-patients.net/ [accessed 2015-09-28] [WebCite Cache ID 6bsqC48iO]
58. PatientsLikeMe. 2015. URL: https://www.patientslikeme.com/ [accessed 2016-05-18] [WebCite Cache ID 6bsqSGnlx]
59. Couper M. Is the sky falling? New technology, changing media, and the future of surveys. Survey Res Methods 2013;7(3):145-156. [doi: 10.18148/srm/2013.v7i3.5751]

Abbreviations

AAPOR: American Association of Public Opinion Research
ASCOLTA: Assistenza domiciliare allo SCOmpenso cardiaco attraverso Le Tecniche Avanzate di comunicazione digitale
ELSA: English Longitudinal Study of Ageing
HRS: Health and Retirement Study
SHARE: Survey of Health, Ageing and Retirement in Europe
WHMS: Web health monitoring survey

Edited by G Eysenbach; submitted 05.10.15; peer-reviewed by E Afari-kumah, P Giacomelli, W Glinkowski; comments to author 29.03.16; revised version received 25.04.16; accepted 13.05.16; published 06.06.16.

Please cite as:
Romano MF, Sardella MV, Alboni F
Web Health Monitoring Survey: A New Approach to Enhance the Effectiveness of Telemedicine Systems
JMIR Res Protoc 2016;5(2):e101
URL: http://www.researchprotocols.org/2016/2/e101/
doi:10.2196/resprot.5187
PMID:27268949

Original Paper

Consumers' Patient Portal Preferences and Health Literacy: A Survey Using Crowdsourcing

Mary Zide[1], MLIS, PhD; Kaitlyn Caswell[1]; Ellen Peterson[2]; Denise R Aberle[3], MD; Alex AT Bui[3], PhD; Corey W Arnold[3], PhD

[1]Department of Bioengineering, University of California, Los Angeles, Los Angeles, CA, United States

[2]Department of Biology, Florida Agricultural and Mechanical University, Tallahassee, FL, United States

[3]Medical Imaging Informatics, Department of Radiological Sciences, University of California, Los Angeles, Los Angeles, CA, United States

Corresponding Author:
Mary Zide, MLIS, PhD
Department of Bioengineering
University of California, Los Angeles
924 Westwood Blvd
Suite 420
Los Angeles, CA, 90024
United States
Phone: 1 5102075012
Fax: 1 3107943544
Email: mmcnamara@ucla.edu

Abstract

Background: eHealth apps have the potential to meet the information needs of patient populations and improve health literacy rates. However, little work has been done to document perceived usability of portals and health literacy of specific topics.

Objective: Our aim was to establish a baseline of lung cancer health literacy and perceived portal usability.

Methods: A survey based on previously validated instruments was used to assess a baseline of patient portal usability and health literacy within the domain of lung cancer. The survey was distributed via Amazon's Mechanical Turk to 500 participants.

Results: Our results show differences in preferences and literacy by demographic cohorts, with a trend of chronically ill patients having a more positive reception of patient portals and a higher health literacy rate of lung cancer knowledge ($P<.05$).

Conclusions: This article provides a baseline of usability needs and health literacy that suggests that chronically ill patients have a greater preference for patient portals and higher level of health literacy within the domain of lung cancer.

(JMIR Res Protoc 2016;5(2):e104) doi:10.2196/resprot.5122

KEYWORDS

consumer health information; health literacy; eHealth; patient portal

Introduction

Life expectancy has nearly doubled in the last century [1], due in part to preventive care, screening protocols, and the conversion of previously lethal diseases into manageable, chronic conditions through medical advances. Recently, lung cancer screening with computed tomography (CT) has been shown to significantly reduce lung cancer mortality and has resulted in paradigm shifts such that screening is now a covered medical procedure by both third party payers and Medicare [2], providing the opportunity for more patients to be screened. However, lung cancer is still the single greatest cause of cancer-related death. Accurate and timely patient education is considered to be one of the critical elements underlying improvements in public health, to better inform patients of the underlying causes of their conditions, the measures they can take to mitigate risk, and the basis, and balance of benefits to risks, of certain interventions.

However, low levels of health literacy are seen as a hurdle to accessing health information [3]. The US Department of Health and Human Services defines health literacy as patients' ability to acquire, read, and understand health information in order to make health decisions appropriate to their situation [4]. The National Center for Education Statistics maintains that health literacy is crucial for all adults to understand and improve their health, as they encounter health information in a variety of

digital and hardcopy formats (eg, websites, blogs, federated search engines, magazine articles, pamphlets, prescription directions) [5].

Further study of patients' health literacy in the subject of lung cancer is necessary to inform the design of patient education tools. Lung cancer screening protocols have recently been revised due to the findings in [2], demonstrating the efficacy of annual CT scans for high-risk individuals. Given the major policy change in lung cancer screening, it is expected that moderate patient education will be required to better understand the etiologies of lung cancer and basis for screening. eHealth apps are a potentially potent medium for the task of providing educational materials.

The term eHealth can be broadly described as the use of information technology in health care, examples of which include patient portals, personal fitness apps that run on mobile phones or personal computers, and digital consumer health educational guidelines. eHealth tools are increasingly available; however, availability does not ensure greater health literacy or increased use of these tools. The term usability refers to the ease of use and learnability of a tool, the measure of which can serve as one gauge of the effectiveness of a tool in helping the user reach their objectives [6]. Usability is necessary to ensure use of and application of the information within eHealth technologies [7,8]. Contributing to perceived usability is perceived feasibility. Feasibility, which can be defined as the effectiveness of an intervention, can be further divided into eight areas of focus, including acceptability, for example, how users react to an intervention, and demand, for example, an estimated need of a tool [8].

While no design will be able to anticipate all information needs, the content of a patient portal has the potential to influence perceived usability and satisfaction, as well as improve health literacy and outcomes [9,10]. Generally, a patient portal is a secure website that provides individuals with access to their personal medical information [11]. Although there has not been lengthy discussion on the content of portals in particular, the content of personal health records (PHRs) has received more attention. Basic consensus has been reached on certain data points that should be included: problem lists, procedures, lab tests, diagnoses, and notes [7,12-15]. These data points would likely prove beneficial in a portal as well. Portals also have a range of functions not available in PHRs, such as the ability to email a physician, renew a prescription, view clinical reports, and make appointments. However, patient information needs may differ by diagnosis, and in order to improve health literacy and outcomes, some diagnoses may require more specific additional information, educational content, and functions [7,16]. For instance, cancer patients have been shown to want access to targeted information about their particular diagnosis (benign vs cancerous), treatments (chemotherapy, radiation, surgery), and prognosis (quality of life, 5-year survival) [17]. However, the specific needs of cancer patients by diagnosis are not well known. Identifying these needs, as well as their literacy levels on specific subjects, would prove helpful in the design of tools meant to serve specific populations, such as lung cancer. Before this can be done, it is necessary to establish a baseline of a general population's information needs.

Additionally, as lung cancer is the leading cause of cancer death and the majority of lung cancer cases are due to tobacco smoke, it is important that the general population be informed regarding lung cancer and the means through which risk can be mitigated (smoking cessation) [18]. While campaigns to inform the general population of this health issue have been wide spread, it is important to document how effective these campaigns have been in providing health consumers with knowledge, especially when considering recent reforms to screening protocol. Assessment of lung cancer literacy can help to inform portal module design aimed at improving literacy rates.

As an initial starting point, we were interested in two areas of study: (1) understanding the perceived usability and, in turn, feasibility of information content of patient portals of a convenience cohort taken from the general public, and (2) the demand for lung cancer specific health literacy of a convenience cohort taken from the general public. Our goal was to establish a baseline to understand how perspectives and literacy vary by basic patient (consumer) demographics.

Methods

To assess baseline health information needs and preferences, as well as lung cancer knowledge, a survey was developed based on previously validated surveys [19,20], which were designed for the purposes of documenting patients' health portal preferences and lung cancer knowledge. While the questions in our survey are taken from these validated tools, not all questions from the original surveys were used. Instead, in an effort to keep our survey concise and focused, we chose those questions that most closely focused on our concerned topics, perceived usability and feasibility of patient portals, and lung cancer knowledge. We chose to rely on prior validated surveys, as developing and validating a survey would require considerable additional research beyond our current scope. Our instrument consisted of three modules (see Multimedia Appendix 1). The first module captured information needs and preferences regarding patient portals posed as statements that were rated by participants on a 7-point Likert scale ranging from 1 (completely disagree) to 7 (completely agree). The second module consisted of factual statements about lung cancer and computed tomography with multiple choice answers, of which only one answer was correct. The third module contained demographic questions, based primarily on the US census [21]. Two free-text questions allowed participants to describe concerns and the effects of using a portal. This study was certified exempt by an internal review board committee at University of California, Los Angeles (UCLA).

Recruitment

The survey was distributed via the website MTurk, a crowdsourcing Internet site devoted to human intelligence tasks [22] that has been used in prior medical informatics studies [23-26] and in the evaluation of consumer health tools [27,28]. The MTurk site was used as it has been demonstrated by those studies as a reliable method to survey a convenience sample and because it provided access to individuals across the country, as opposed to one geographical area. The survey was made available only to those MTurk participants within the United

States. The survey was posted on the MTurk website for 3 weeks in May 2015. Participants were invited to complete the survey with the guarantee of compensation of US $1 per completed survey; each participant completed only one survey. The first 500 individuals to fully complete the survey were chosen as a convenience sample for purposes of analysis. We sought 250 participants age 41 and older, and 250 participants age 40 and younger. To do this, the survey was distributed twice, once as a survey available to those who were age 40 and younger, and once as a survey to those who were age 41 and older. Participants were asked to affirm their age cohort.

Statistical Analysis

Power and Statistical Tests

A power analysis indicated that in order to demonstrate a 0.95 power with alpha=.025, we would require 324 participants. Survey results were analyzed using SPSS version 20 software. Statistically significant results are those with a *P* value ≤.05. Independent *t*-tests and one-way analyses of variance (ANOVAs) were used in univariate analyses to determine differences in information needs and preferences based on mean values of demographic variables. Chi-square was used in univariate analysis to identify differences in health literacy based on mean demographic variables. To determine if combinations of demographic variables can predict dependent variables, stepwise logistic regression was done using all significant variables from univariate analysis, with each model using the independent variable(s) that had significant univariate results for a particular question ($P \leq .05$). Logistic regression was used in order to make the data as parsimonious as possible, as the number of cases per group were limited. Alongside *P* values, log-odds, and prediction probabilities, Nagelkerke R^2values were also reported. The Nagelkerke R^2statistic is used to demonstrate how useful the independent variables are in predicting the dependent variable [29].

Variables

All variables can be seen in Multimedia Appendix 2. Due to sparse data, the demographic variables sex and race were collapsed into dichotomous variables (seen Multimedia Appendix 1). The variable sex included one response listed as "other." This single response was eliminated from univariate analysis of portal preferences based on sex. For logistic regression, the 7-point Likert scales used to record patient portal responses were also dichotomized as follows: Agree (Scores 5-7) and Disagree (Score 1-4). For regression analysis, a score of 4 on Likert scale responses was included within the Disagree category, as the purpose of our analysis was to compare those who agreed to others. For lung cancer knowledge variables, binary values were coded as "0" for incorrect and "1" for correct.

Results

Only surveys with no missing data elements were analyzed. Participants who returned surveys with missing data were contacted via email and invited to supply the missing data points. There was no consistent pattern to the types of data elements not completed. The surveys of participants who supplied the missing data were included in analysis. In total, out of the 500 surveys issued, 473 complete surveys were collected.

User Demographics

The majority of participants were white (389/473, 82.2%) (see Table 1). Although accounting for fewer respondents, Asian (26/474, 5.4%) and black (25/473, 5.2%) participants were the second largest group and were roughly equivalent. The majority of participants had some college education, with very few (27/473, 5.7%) participants listing high school as their highest level of educational attainment. Roughly half of respondents reported an annual income of US $35,000 or less. Participants tended to spend over 11 hours a week online (349/473, 73.7%), but most had used a portal 10 times or less (216/473, 45.6%) or had never used a patient portal (174/473, 36.7%). This rate of portal use suggests that responses to the survey are both a measure of needs for those with experience using a portal, and expectations for those who have not used a portal before.

Table 1. Demographic results.

Demographics		n	%
Age in years			
	18-20	14	3
	21-30	131	27.7
	31-40	95	20.1
	41-50	139	29.4
	51-60	73	15.4
	61-70	19	4
	71-80	1	0.2
	Prefer not to answer	1	0.2
Race			
	White	389	82.2
	Asian	26	5.4
	American Indian	2	0.4
	Pacific Islander	2	0.4
	Black	25	5.2
	Another race	7	1.4
	Unknown or prefer not to answer	3	0.6
	Two or more races	19	4
Education			
	High school	27	5.7
	Some college	164	34.6
	Associate degree	63	13.3
	Bachelor’s degree	176	37.2
	Graduate degree	43	9
Income, USD			
	$0-35,000	237	50.1
	$36,000-50,000	95	20
	$51,000-75,000	80	16.9
	$76,000 or more	55	11.6
	Prefer not to answer	6	1.2
Times using a portal			
	Never	174	36.7
	1-10 times	216	45.6
	11-50 times	71	15
	51 times or more	9	1.9
	Prefer not to answer	3	0.6
Time online, hours			
	1-5 hours	35	7.3
	6-10 hours	87	18.3
	11 hours or more	349	73.7
	Prefer not to answer	2	0.4
Sex			

Demographics		n	%
	Male	244	51.5
	Female	228	48.2
	Other	1	0.2

Evaluation Outcomes

Influence of Participant Characteristics on Patient Portal Questions

Patient response frequencies to all survey questions can be seen in Multimedia Appendix 3 , and results to all univariate analyses can be seen in Multimedia Appendix 4. Demographic variables that significantly influenced participant perceptions of patient portal usability and feasibility are shown in Table 2. For all significant results, females rated statements about portal perceptions with higher positive responses. For example, the average Likert response to the question "Portals are not difficult to use" was 4.97 for males and 5.32 for females (*P*=.009). Females tended to have higher, more positive average Likert scores across all questions relating to portal use.

Respondents reporting a chronic illness also tended to have more positive views of portals, with higher average ratings than those without chronic illness. The average response was significantly higher for chronically ill participants for all four questions relating to portals (see Table 2). This trend was also seen across all questions relating to portal preferences.

Differences in responses significantly varied based on the number of times participants had used a patient portal. However, there was no consistent trend seen across answers. Additionally, while not statistically significant, 33% of participants reported concern about "unauthorized access" to their patient portal.

Table 2. Statistically significant results of univariate analysis of patient portal preferences.

Independent variable	Survey question	Eta^2	*P*
Sex [a]			
	Portals are not difficult to use.	0.014	.009
	Using a portal can make me accomplish tasks (eg, review my diagnoses and tests) quickly in managing my personal health information.	0.009	.044
Chronic illness			
	A portal can be useful to manage my personal health information.	0.025	.003
	Using a portal can make me accomplish tasks (eg, review my diagnoses and tests) quickly in managing my personal health information.	0.29	.001
	A personalized portal can suit my needs of managing my personal health information.	0.014	.034
	It should be easy to become skillful at using a portal.	0.027	.001
Portal use			
	A personalized portal can suit my needs of managing my personal health information.	0.036	.002
	Using a portal can make me accomplish tasks (eg, review my diagnoses and tests) quickly in managing my personal health information.	0.035	.002
	A portal can be useful to manage my personal health information.	0.023	.025
	Using a portal with a health encyclopedia can provide me with health care knowledge and education.	0.023	.025
	It should be easy to become skillful at using a portal.	0.030	.007

[a]Independent variable that utilized an independent *t* test; all others used ANOVAs.

Influence of Patient Characteristics on Lung Cancer Screening Knowledge

Questions pertaining to lung cancer and chest CT had multiple choice answers, of which one answer was correct. The chronic illness predictor was most frequently associated with correct responses (see Table 3). Those reporting a chronic illness had a higher rate of correct answers for three of the four significant results. However, those not reporting chronic illness performed better on the two questions with the outcome variable "Someone who has quit smoking…" and "Lung cancer is one of the most common cancers."

Table 3. Statistically significant results of univariate analysis of demographic variables on lung cancer knowledge.

Independent variable	Survey question	*P*
Education		
	In the past, before the CT scan was introduced, the chance of dying due to lung cancer after diagnosis was high.	.005
Income		
	A change of cough pattern is a frequent sign of lung cancer.	.034
	Coughing up blood is a frequent sign of lung cancer.	.030
Smoking habit		
	Lung cancer is one of the most common cancers.	.036
Hours online		
	CT images are made with X-rays.	.016
	To complete a CT scan, subjects must undress their upper body.	.006
	Lung cancer is infectious.	.030
Sex		
	Coughing up blood is a frequent sign of lung cancer.	<.001
Chronic illness		
	CT images are made with X-rays.	.012
	To complete a CT scan, subjects must undress their upper body.	.017
	A change of cough pattern is a frequent sign of lung cancer.	.014
	Lung cancer is infectious.	<.001
Portal use		
	Lung cancer is infectious.	<.001

Other predictors with significant test results included time spent online, income, education, smoking habit, sex, and portal use. Time spent online had the second highest number of significant tests with three results. However, there was no consistent pattern observed within the rates of answers, with those who spent more time sometimes outperforming and sometimes underperforming those who spent less time. For the income predictor, correct answers to the question “Coughing up blood is a frequent sign of lung cancer” increased as income increased, until the level of US $76,000 or more. Those who made US $76,000 or more a year had a lower rate of correct answers than those who made less. For the smoking habit predictor, those who smoked had a slight but significantly lower rate of correct answers (78.4% versus 78.7%) for the question “Lung cancer is one of the most common cancers.” Men had a significantly higher rate of correct answers for the question “Coughing up blood is a frequent sign of lung cancer” than women (75.4% vs 73.7%). As portal use increased, correct answers to the question “Lung cancer is infectious” decreased. There was no pattern observed in response rates for the question “In the past, before the CT scan was introduced…” when stratified by the education predictor, nor for the question “A change of cough pattern is a frequent sign of lung cancer” response rates when stratified by the income predictor.

Logistic Regression

Stepwise logistic regression was performed for demographic variables that had statistically significant relationships as seen in Tables 2 and 3. Statistically significant results for logistic regression are seen in Table 4. Increased portal use was positively associated with agreeing with the statement “It should be easy to become skillful at using a portal,” meaning participants who used a portal more than 10 times were more likely to agree with the statement. However, prediction success was weak with 32.6% of outcomes correctly predicted. The chronic illness predictor was positively associated with having the correct answer for “A change of cough pattern is a frequent sign of lung cancer,” indicating that those with a chronic illness were more likely to choose the correct answer for the question. However, prediction was not improved in comparison to the constant model, remaining at 52.4%.

Table 4. Statistically significant results for logistic regression analysis.

Independent variable	Survey question	Log-odds	*P*	Nagelkerke R^2	Prediction percentage correct, %
Portal use					
	It should be easy to become skillful at using a portal.	0.996	.016	0.024	32.6
Chronic illness					
	A change of cough pattern is a frequent sign of lung cancer.	0.611	.008	0.020	52.4

Discussion

Principal Results and Comparisons With Prior Work

In this study, a convenience cohort of the general public was asked to rate their perceptions of usability and feasibility of patient portals and knowledge of lung cancer, in order to demonstrate the demand for lung cancer knowledge and status of patient portal usability. Overall, we observed that respondents reporting chronic illness tended to have more positive opinions of patient portals and to perform better on lung cancer knowledge questions than those without a chronic condition. Chronically ill patients having a more positive opinion of eHealth is a finding that has also been observed [30,31]. Similarly, a review of literature on portals found that participant interest in patient portals varied by health status [32].

Interestingly, some studies have found that chronically ill patients may have lower health literacy [33,34]. In contrast, a study found that those with a chronic illness reported higher rates of literacy regarding test results [35]. In our work, it may be that the higher performance we observed relates to higher levels of educational attainment, as those respondents reporting chronic illness in our survey more frequently had Associate, Bachelor's, and Master's degrees than those reporting no chronic illness (14.6% vs 12.9%, 39.8% vs 36.8%, and 9.7% vs 8.8% respectively).

Having used a portal was associated with significant difference in opinions of patient portals. However, there was no consistent trend observed, with some statements being rated in higher agreement by those who had used portals more and other statements being rated higher by those who had used them less. It is also worth noting that for those who had never used a portal, these statements are measuring expectations of portals, while with those who have used portals, these statements are measuring experience. These results suggest that opinions about the usability of portals do not demonstrate a clear trend whether being drawn based on expectations or experience.

We also found that women reported more positive ratings of portals. While use does not equal preference, positive ratings may be influenced by the higher use of portals we observed in this survey (19.7% of women had used a portal over ten times, compared to 14.3% of men), which is consistent with higher eHealth resource use observed in women [36-38]. We also documented a statistically significant difference in correct responses for lung cancer knowledge stratified by the amount of time spent online. Others have found similar relationships between Internet use and health literacy [34], but our results showed no consistent trend and are inconclusive.

Although two logistic regression models had significant *P* value results, neither model had strong prediction success. While the low *P* values (<.05) indicate that the findings are unlikely due to chance, the prediction values, as well as the Nagelkerke R^2values, indicate that these models will not perform prediction well. Further research is required to determine predictors that would predict answer cohorts to these questions successfully.

Finally, 33% of participants noted that they were "concerned about unauthorized access," which was the most commonly chosen option (seem Multimedia Appendix 4 , Question 26). In other work, security was a concern for two thirds of health information consumers, although users of PHRs had less observed concern [39]. The overall percentage of participants concerned with security in this study was less than in [39]. However, a similar trend was observed with 32.5% of those who had used a portal more than 10 times were concerned with unauthorized access while 33.1% of those who had used a portal 10 times or less were concerned. Similarly, security has also been a concern [40]. This common theme suggests that eHealth users may associate eHealth tools with a lack of security. This concern has the potential to impact portal use, as it would likely limit satisfaction and perceived usability and, thus, feasibility.

Limitations

There are several limitations to this study that may have influenced our results. Most importantly, we used a convenience sample of the first 500 respondents to a survey posted on MTurk. As such, the results derive from Internet users; those with less Internet experience may well have different views regarding patient portals and lung cancer health literacy than those documented here. Our respondents also had higher levels of education than seen in the US population [41], which may have influenced health literacy. Moreover, although we specifically asked respondents not to look up answers to lung cancer questions, we have no guarantee that responses were not informed by additional online queries.

An additional limitation is the potential bias that may be introduced by the use of a digital survey format. Others have found that patients who have used eHealth technology have more positive opinions of it than those who do not [42], suggesting that experience with technology can cause one to

regard it more favorably. Here, completing a digital survey on eHealth may bias respondents to rate statements about patient portals more highly.

Conclusion

This work documents a baseline for consumer information needs and health literacy within the domain of lung cancer. Our results suggest that women and those with chronic illness had more positive views of patient portals and that chronically ill patients had higher health literacy in lung cancer. Although chronically ill patients are a likely user group for patient portals, non chronically ill patients can also benefit from opportunities to manage and learn about their health as well as mitigate risk via portals. Given this, the results suggest a need for further lung cancer education with opportunities to use patient portals to better educate individuals who do not have a chronic illness about lung cancer. Further study is also needed in order for portals to better address the information needs of patients who are not chronically ill in order to improve perceived usability and feasibility.

This baseline can be used in future comparison studies as well as to inform portal design to improve usability and raise lung cancer health literacy with educational modules. Our future work includes designing a patient portal influenced by these results and then surveying a patient population at UCLA who will have access to the portal, to compare those survey results to this baseline, in order to identify any difference between them.

Acknowledgments

This work is supported by NIH/NCI Grant R01 LM011333, NIH/NCI Grant 5T32 EB01664003, and UCLA HBCU Grant 285247.

Conflicts of Interest

None declared.

Multimedia Appendix 1

[PDF File (Adobe PDF File), 43KB - resprot_v5i2e104_app1.pdf]

Multimedia Appendix 2

[PDF File (Adobe PDF File), 64KB - resprot_v5i2e104_app2.pdf]

Multimedia Appendix 3

[PDF File (Adobe PDF File), 42KB - resprot_v5i2e104_app3.pdf]

Multimedia Appendix 4

[PDF File (Adobe PDF File), 68KB - resprot_v5i2e104_app4.pdf]

References

1. Burton DM. National Institute on Aging.: US Department of Health and Human Services; 2007. Living Long and Well in the 21st Century: Strategic Directions for Research on Aging URL: https://www.nia.nih.gov/about/living-long-well-21st-century-strategic-directions-research-aging/introduction [accessed 2015-09-10] [WebCite Cache ID 6bRWopTKD]
2. National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011 Aug 4;365(5):395-409 [FREE Full text] [doi: 10.1056/NEJMoa1102873] [Medline: 21714641]
3. Zeng QT, Tse T, Crowell J, Divita G, Roth L, Browne AC. Identifying consumer-friendly display (CFD) names for health concepts. In: AMIA Annu Symp Proc. 2005 Presented at: AMIA Annual Symposium; 10/22/2005-10/26/2005; Washington, DC p. 859-863 URL: http://europepmc.org/abstract/MED/16779162 [WebCite Cache ID 6heURCWRJ]
4. US Department of Health and Human Services. National Action Plan to Improve Health Literacy. Washington, DC; 2010. URL: http://health.gov/communication/hlactionplan/pdf/Health_Literacy_Action_Plan.pdf [accessed 2016-05-11] [WebCite Cache ID 6hQxeC5DM]
5. Kutner M, Greenberg E, Jin Y, Paulsen C. Results from the 2003 National Assessment of Adult Literacy. Washington, DC: US Department of Education; 2006. The Health Literacy of America's Adults URL: https://www.healthypeople.gov/2020/tools-resources/evidence-based-resource/health-literacy-america%E2%80%99s-adults-results-2003-national [accessed 2016-05-11] [WebCite Cache ID 6hQxxospW]
6. Rosenbaum S. Usability evaluations versus usability testing: when and why? IEEE Transactions on Professional Communication 1989;32(4):283-288.

7. Rosenbaum S. Usability evaluations versus usability testing: when and why? IEEE Trans Profess Commun 2011;32(4):210-216. [doi: 10.1109/47.44533]
8. Bowen DJ, Kreuter M, Spring B, Cofta-Woerpel L, Linnan L, Weiner D, et al. How we design feasibility studies. Am J Prev Med 2009 May;36(5):452-457 [FREE Full text] [doi: 10.1016/j.amepre.2009.02.002] [Medline: 19362699]
9. Tang PC, Overhage JM, Chan AS, Brown NL, Aghighi B, Entwistle MP, et al. Online disease management of diabetes: engaging and motivating patients online with enhanced resources-diabetes (EMPOWER-D), a randomized controlled trial. J Am Med Inform Assoc 2013 May 1;20(3):526-534 [FREE Full text] [doi: 10.1136/amiajnl-2012-001263] [Medline: 23171659]
10. Krist AH, Woolf SH, Rothemich SF, Johnson RE, Peele JE, Cunningham TD, et al. Interactive preventive health record to enhance delivery of recommended care: a randomized trial. Ann Fam Med 2012;10(4):312-319 [FREE Full text] [doi: 10.1370/afm.1383] [Medline: 22778119]
11. Health Information Technology. 2013. What is a Patient Portal? URL: https://www.healthit.gov/providers-professionals/faqs/what-patient-portal [accessed 2016-05-11] [WebCite Cache ID 6hR0XHgcH]
12. Tobacman JK, Kissinger P, Wells M, Prokuski J, Hoyer M, McPherson P, et al. Implementation of personal health records by case managers in a VAMC general medicine clinic. Patient Educ Couns 2004 Jul;54(1):27-33. [doi: 10.1016/S0738-3991(03)00184-8] [Medline: 15210257]
13. Tang PC, Ash JS, Bates DW, Overhage JM, Sands DZ. Personal health records: definitions, benefits, and strategies for overcoming barriers to adoption. J Am Med Inform Assoc 2006;13(2):121-126 [FREE Full text] [doi: 10.1197/jamia.M2025] [Medline: 16357345]
14. Bridgford A, Davis TME. A comprehensive patient-held record for diabetes. Part one: initial development of the Diabetes Databank. Pract Diab Int 2001 Sep;18(7):241-245. [doi: 10.1002/pdi.236]
15. Raisinghani MS, Young E. Personal health records: key adoption issues and implications for management. Int J Electron Healthc 2008;4(1):67-77. [doi: 10.1504/IJEH.2008.018921] [Medline: 18583296]
16. Hess R, Bryce CL, McTigue K, Fitzgerald K, Zickmund S, Olshansky E, et al. The diabetes patient portal: patient perspectives on structure and delivery. Diabetes Spectrum 2006;19(2):106-109. [doi: 10.2337/diaspect.19.2.106]
17. McNamara M, Arnold C, Sarma K, Aberle DR, Garon E, Bui AAT. Patient Portal Preferences: Perspectives on Imaging Information. J Assoc Inf Sci Technol 2015 Aug 1;66(8):1606-1615 [FREE Full text] [doi: 10.1002/asi.23269] [Medline: 26191535]
18. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014;64(1):9-29 [FREE Full text] [doi: 10.3322/caac.21208] [Medline: 24399786]
19. van den Bergh KAM, Essink-Bot ML, van Klaveren RJ, de Koning HJ. Informed participation in a randomised controlled trial of computed tomography screening for lung cancer. Eur Respir J 2009 Sep;34(3):711-720 [FREE Full text] [doi: 10.1183/09031936.00098908] [Medline: 19282345]
20. Wu H. Chapter 3: Questionnaire Surveys. In: Exploring Healthcare Consumer Acceptance of Personal Health Information Technology. College Park, MD: Department of Information Systems University of Maryland; 2013:348.
21. US Census Data.: US Census Bureau; 2013. URL: http://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?pid=ACS_13_5YR_DP05&src=pt [WebCite Cache ID 6aiDafEqH]
22. Amazon Mechanical Turk. URL: https://requester.mturk.com/ [accessed 2015-08-11] [WebCite Cache ID 6aiE11hse]
23. Gottlieb A, Hoehndorf R, Dumontier M, Altman RB. Ranking adverse drug reactions with crowdsourcing. J Med Internet Res 2015;17(3):e80 [FREE Full text] [doi: 10.2196/jmir.3962] [Medline: 25800813]
24. Kristan J, Suffoletto B. Using online crowdsourcing to understand young adult attitudes toward expert-authored messages aimed at reducing hazardous alcohol consumption and to collect peer-authored messages. Transl Behav Med 2015 Mar;5(1):45-52 [FREE Full text] [doi: 10.1007/s13142-014-0298-4] [Medline: 25729452]
25. Cui L, Carter R, Zhang G. Evaluation of a novel Conjunctive Exploratory Navigation Interface for consumer health information: a crowdsourced comparative study. J Med Internet Res 2014;16(2):e45 [FREE Full text] [doi: 10.2196/jmir.3111] [Medline: 24513593]
26. MacLean DL, Heer J. Identifying medical terms in patient-authored text: a crowdsourcing-based approach. J Am Med Inform Assoc 2013;20(6):1120-1127 [FREE Full text] [doi: 10.1136/amiajnl-2012-001110] [Medline: 23645553]
27. Yu B, Willis M, Sun P, Wang J. Crowdsourcing participatory evaluation of medical pictograms using Amazon Mechanical Turk. J Med Internet Res 2013;15(6):e108 [FREE Full text] [doi: 10.2196/jmir.2513] [Medline: 23732572]
28. Turner AM, Kirchhoff K, Capurro D. Using crowdsourcing technology for testing multilingual public health promotion materials. J Med Internet Res 2012;14(3):e79 [FREE Full text] [doi: 10.2196/jmir.2063] [Medline: 22664384]
29. Bewick V, Cheek L, Ball J. Statistics review 14: Logistic regression. Crit Care 2005 Feb;9(1):112-128 [FREE Full text] [doi: 10.1186/cc3045] [Medline: 15693993]
30. Parker RM, Ratzan SC, Lurie N. Health literacy: a policy challenge for advancing high-quality health care. Health Affairs 2003;22(4):147-153 [FREE Full text] [Medline: 12889762]
31. Neter E, Brainin E. eHealth literacy: extending the digital divide to the realm of health information. Journal of Medical Internet Research 2012;14(1):19 [FREE Full text] [doi: 10.2196/jmir.1619] [Medline: 22357448]

32. Irizarry T, DeVito Dabbs A, Curran CR. Patient Portals and Patient Engagement: A State of the Science Review. J Med Internet Res 2015;17(6):e148 [FREE Full text] [doi: 10.2196/jmir.4255] [Medline: 26104044]
33. Parker RM, Ratzan SC, Lurie N. Health literacy: a policy challenge for advancing high-quality health care. Health Aff (Millwood) 2003;22(4):147-153 [FREE Full text] [Medline: 12889762]
34. Neter E, Brainin E. eHealth literacy: extending the digital divide to the realm of health information. J Med Internet Res 2012;14(1):e19 [FREE Full text] [doi: 10.2196/jmir.1619] [Medline: 22357448]
35. Mák G, Smith FH, Leaver C, Hagens S, Zelmer J. The Effects of Web-Based Patient Access to Laboratory Results in British Columbia: A Patient Survey on Comprehension and Anxiety. J Med Internet Res 2015;17(8):e191 [FREE Full text] [doi: 10.2196/jmir.4350] [Medline: 26242801]
36. Ralston JD, Rutter CM, Carrell D, Hecht J, Rubanowice D, Simon GE. Patient use of secure electronic messaging within a shared medical record: a cross-sectional study. J Gen Intern Med 2009 Mar;24(3):349-355 [FREE Full text] [doi: 10.1007/s11606-008-0899-z] [Medline: 19137379]
37. Beckjord EB, Finney Rutten LJ, Squiers L, Arora NK, Volckmann L, Moser RP, et al. Use of the internet to communicate with health care providers in the United States: estimates from the 2003 and 2005 Health Information National Trends Surveys (HINTS). J Med Internet Res 2007 Jul;9(3):e20 [FREE Full text] [doi: 10.2196/jmir.9.3.e20] [Medline: 17627929]
38. Fox S, Jones S. The social life of health information: Americans' pursuit of health takes place within a widening network of both online and offline sources. Washington, DC: Pew Internet and American Life Project; 2009. URL: http://www.pewinternet.org/files/old-media//Files/Reports/2009/PIP_Health_2009.pdf [accessed 2014-10-01] [WebCite Cache ID 6T08AHdFO]
39. Udem T. Consumers and Health Information Technology. A National Survey. Oakland, CA: California Health Care Foundation; 2010. URL: http://www.chcf.org/publications/2010/04/consumers-and-health-information-technology-a-national-survey [accessed 2015-09-10] [WebCite Cache ID 6bRWcuIz3]
40. Tieu L, Sarkar U, Schillinger D, Ralston JD, Ratanawongsa N, Pasick R, et al. Barriers and Facilitators to Online Portal Use Among Patients and Caregivers in a Safety Net Health Care System: A Qualitative Study. J Med Internet Res 2015;17(12):e275 [FREE Full text] [doi: 10.2196/jmir.4847] [Medline: 26681155]
41. Kena G, Musu-Gillette L, Robinson J, Wang X, Rathbun A, Zhang J, et al. The Condition of Education. Washington, DC: National Center for Education Statistics; 2015. URL: http://nces.ed.gov/pubs2015/2015144.pdf [accessed 2015-09-10] [WebCite Cache ID 6bRY3zODR]
42. Ancker JS, Silver M, Miller MC, Kaushal R. Consumer experience with and attitudes toward health information technology: a nationwide survey. J Am Med Inform Assoc 2013 Jan 1;20(1):152-156 [FREE Full text] [doi: 10.1136/amiajnl-2012-001062] [Medline: 22847306]

Abbreviations

ANOVA: one-way analysis of variance
CT: computed tomography
PHRs: personal health records
UCLA: University of California, Los Angeles

Edited by G Eysenbach; submitted 10.09.15; peer-reviewed by E Boogerd, B Crotty; comments to author 22.11.15; revised version received 05.01.16; accepted 23.03.16; published 08.06.16.

Please cite as:
Zide M, Caswell K, Peterson E, Aberle DR, Bui AAT, Arnold CW
Consumers' Patient Portal Preferences and Health Literacy: A Survey Using Crowdsourcing
JMIR Res Protoc 2016;5(2):e104
URL: http://www.researchprotocols.org/2016/2/e104/
doi:10.2196/resprot.5122
PMID:27278634

Original Paper

Mediators of Atherosclerosis in South Asians Living in America: Use of Web-Based Methods for Follow-Up and Collection of Patient-Reported Outcome Measures

Namratha R Kandula[1], MPH, MD; Ankita Puri-Taneja[2], PhD; David E Victorson[3], PhD; Swapna S Dave[2], MPH, MBBS; Alka M Kanaya[4], MD; Mark D Huffman[5], MPH, MD

[1]Feinberg School of Medicine, Division of General Internal Medicine, Department of Preventive Medicine, Northwestern University, Chicago, IL, United States

[2]Feinberg School of Medicine, Northwestern University, Chicago, IL, United States

[3]Feinberg School of Medicine, Department of Medical Social Sciences, Northwestern University, Chicago, IL, United States

[4]UCSF School of Medicine, University of California at San Francisco, San Francisco, CA, United States

[5]Feinberg School of Medicine, Department of Preventive Medicine, Northwestern University, Chicago, IL, United States

Corresponding Author:
Namratha R Kandula, MPH, MD
Feinberg School of Medicine
Division of General Internal Medicine, Department of Preventive Medicine
Northwestern University
750 N Lake Shore Drive
10th Floor
Chicago, IL, 60611
United States
Phone: 1 3125036470
Fax: 1 3125033350
Email: nkandula@nm.org

Abstract

Background: A key challenge for longitudinal cohort studies is follow-up and retention of study participants. Participant follow-up in longitudinal cohort studies is costly and time-consuming for research staff and participants.

Objective: This study determined the feasibility and costs of using Web-based technologies for follow-up and collection of patient-reported outcomes in the Mediators of Atherosclerosis in South Asians Living in America (MASALA) study.

Methods: The MASALA study is a community-based cohort of 906 South Asians in the United States. Since the baseline in-person visits (2010-2013), a yearly telephone follow-up survey was used to assess participants' health status and incidence of cardiovascular disease. A Web-based version of the follow-up survey was developed using the REDCap (Research Electronic Data Capture) Web app. Participants from the Chicago field center who were due for their annual follow-up and who had a valid email address were sent an email link to a secure online portal where they could complete the survey. Telephone follow-up was used with nonresponders.

Results: A link to the Web survey was emailed to 285 participants (February to October 2014) and the overall completion rate was 47.7% (136/285). One-third of participants who were unresponsive (n=36) to annual telephone follow-up completed the Web survey. Web responders were younger, more likely to be married, and to have higher education and income compared (P<.05) to telephone-only responders. Web survey development involved 240 hours of research staff time. Since launching, the Web-based survey has required 3 hours per week of staff time.

Conclusions: Although electronic follow-up will not be a panacea for cohort operations, it will serve as an adjunctive strategy to telephonic follow-up for maximizing cohort retention with lower costs.

(JMIR Res Protoc 2016;5(2):e95) doi:10.2196/resprot.5448

KEYWORDS

cardiovascular diseases; cohort studies; Internet; South Asian

Introduction

Population-based cardiovascular cohort studies contribute important scientific information about risk factors and pathophysiology of cardiovascular disease by collecting high-quality detailed data linked to longitudinal outcomes. However, longitudinal follow-up of cohorts can be costly, time-consuming, and burdensome to research staff and study participants. The balance of cost, data validity, and feasibility is increasingly important for determining the value of traditional population-based cohorts [1]. To remain relevant in a technologically evolving world, cohort studies should be able to capture data using newer methods, such as Web-based follow-up, without sacrificing participant retention rates [2,3]. This study determined the feasibility and costs of using Web-based technologies to longitudinally follow participants in a cardiovascular cohort study, the Mediators of Atherosclerosis in South Asians Living in the United States (MASALA) study.

Methods

The MASALA study is a community-based longitudinal cohort study designed to understand the risk factors and etiology of cardiovascular disease (CVD) among South Asians living in the United States aged 40 to 84 years who were free of CVD at baseline [4]. Baseline clinical visits were conducted from 2010 to 2013. Once per year, follow-up was conducted using a brief telephone survey to assess changes in participants' health status, hospitalizations, procedures, and self-reported CVD events. In 2013, the Chicago site received pilot funding to implement and test the feasibility of using Web-based technology for participant follow-up and patient-reported outcomes (PRO) measurement and data collection. Starting in 2014, participants from the Chicago site who had provided a valid email address were given the option of completing the annual follow-up using a Web-based survey. This study was approved by the Institutional Review Board at Northwestern University, Chicago, IL, and informed consent was administered to all participants at the study baseline visit.

Choice of Web-Based Platform

Initially, the study team evaluated three Web-based platforms: SurveyGizmo, Assessment Center [5], and REDCap (Research Electronic Data Capture) [6]. SurveyGizmo is a proprietary electronic survey tool that was used for follow-up of cohort participants from the Coronary Artery Risk Development in Young Adults (CARDIA) study and is compliant with the Health Insurance Portability and Accountability Act (HIPAA). However, concern about a third-party website hosting study data was an important barrier for using SurveyGizmo. Assessment Center is a platform funded by the National Institutes of Health that was specifically created to collect PROs [7] and to reduce respondent burden. It is widely used by biomedical and behavioral research programs. REDCap is a consortium developed among various institutions for research data capture, including electronic surveys. Both Assessment Center and REDCap platforms are secure, are HIPAA compliant, and allow easy data export. Both Assessment Center and REDCap utilize email as a means of sending the survey link to participants.

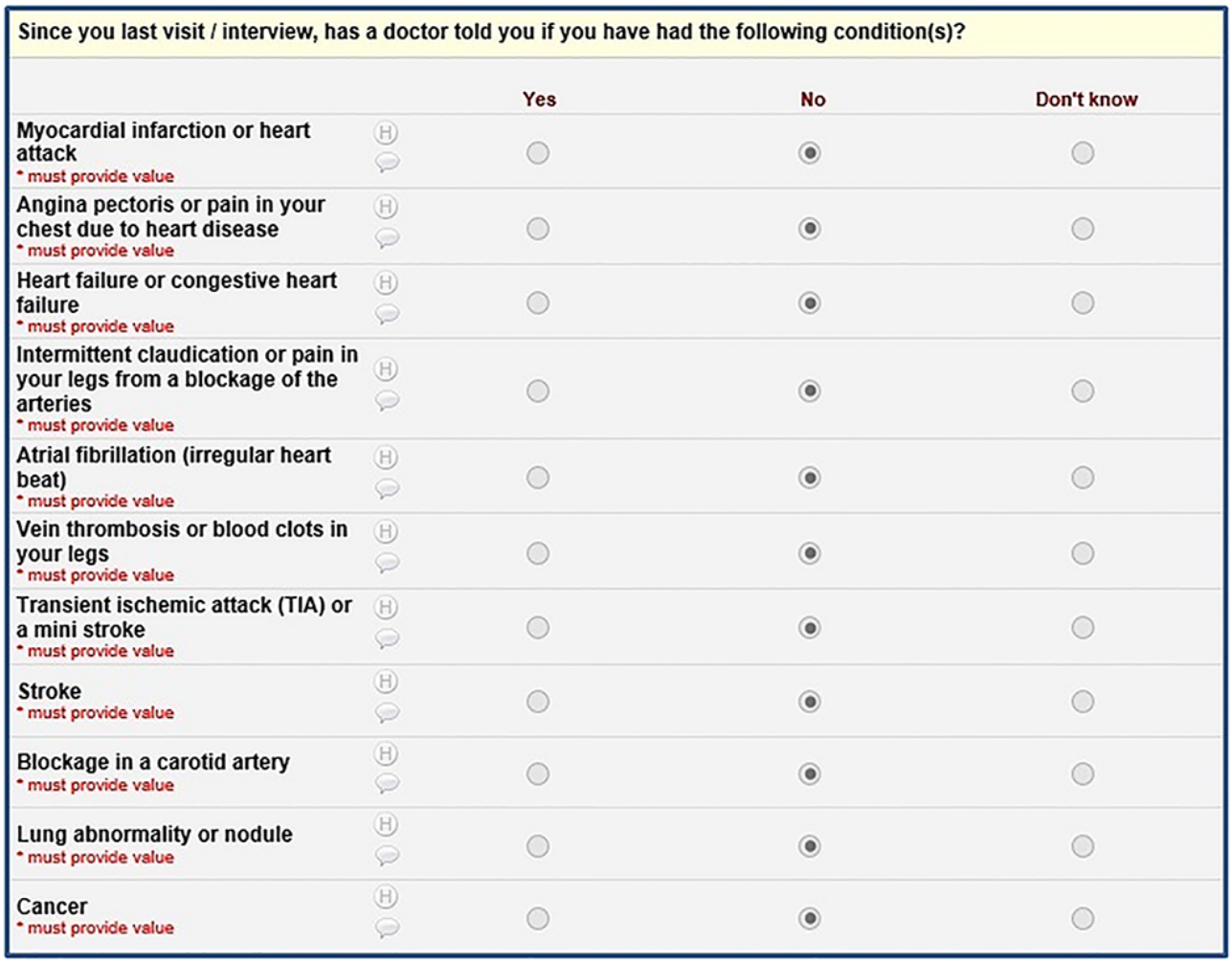
REDCap was chosen as the Web-based platform for the MASALA study because it had several necessary features and capabilities that were not available through Assessment Center, such as branching capacity and dynamic templates. Assessment Center can be customized, but the cost of customization was prohibitive for the MASALA study.

Development of Web-Based Survey

The MASALA annual follow-up survey used paper surveys and the TeleForm version 9.1 software system (Verity Inc, San Francisco, CA, USA) for automated data entry; the survey was converted by study staff into a Web-based survey in REDCap. If a participant reported a hospitalization, CVD event, or other cardiac testing, they were asked to provide further details on the event date, hospital or clinic, and physician's name so that MASALA staff could obtain the records for event adjudication. In addition to the 21 annual follow-up questions, we added three PRO measures (15 new questions on physical function, applied cognition, and satisfaction with social roles) from the static PRO short forms developed by the Patient-Reported Outcomes Measurement Information System (PROMIS) to the end of the Web-based follow-up survey. These questions were added to collect pilot data for future studies related to aging and cognition among MASALA participants (Figure 1).

We conducted beta testing of the Web-based electronic MASALA (e-MASALA) follow-up survey and PRO using REDCap with 10 South Asian men and women aged 27 to 77 years. Participants varied in their computer literacy and familiarity with the Internet. All participants were able to follow the on-screen instructions, complete the survey, and reported that they understood the questions and response options. When asked about preferences related to how the survey would be viewed in the browser, seven of 10 preferred a one-page survey. Participants also preferred using a matrix to answer questions that had the same stem rather than repeating the stem for each question. The first version of the Web questionnaire required approximately 240 hours of a research assistant's (RA) time to design, test, and implement.

Figure 1. Matrix included in the Web-based questionnaire.



Web Survey and Security

Participants received a link to the survey through their email. The survey linked to an online portal from which patients could gain access to a study-specific REDCap page. REDCap allows for secure Web authentication, data logging, and Secure Sockets Layer (SSL) encryption. REDCap is built around HIPAA guidelines, but is not suitable for clinical trials governed by the Federal Drug Administration because it is not compliant with 21 CFR Part 11 [8]. The participant's study ID and an acrostic were the only identifiers for completed surveys.

Protocol for Web-Based Survey Follow-Up

Before implementing the Web-based survey, annual follow-up of MASALA participants was completed by telephone using teleforms. If a participant was not reachable after six telephone calls, project staff would mail the teleforms, instructions, and a stamped envelope addressed to the site principal investigator so teleforms could be returned.

The Web-based follow-up survey was sent out to participants who were due for their annual follow-up on the first Friday morning of each month. Four weekly reminders were sent out every Friday if the participant did not complete the survey in the prior week. The participant's baseline clinical visit date determined when the annual follow-up survey was sent. During the initial 2 months of this pilot study, the Web-based survey was also sent to participants who had been unresponsive to telephone follow-up since their baseline visit. Participants who did not complete the Web-based survey after four reminders were contacted at the end of the month by telephone to complete their annual follow-up. If time allowed, the RA asked participants about reasons for not completing the Web-based survey.

Initially the participants received three emails over a 4-week period to complete the survey. After observing the first month's completion rate, a fourth and final reminder email was added. This fourth email resulted additional survey completions without any obvious increase in participant burden. We continued to send four emails and the final email for the month was sent with the subject heading: "Final reminder: Last chance to complete your annual MASALA follow-up survey via Internet." This subject heading used a deadline and time-sensitive language to create a sense of urgency in participants [9].

The participants were emailed on Friday each week. The decision to send the email link to the survey on a Friday was based on study staffs' prior experience contacting MASALA study participants. Previously, we found that participants were more likely to read study recruitment letters or respond to study phone calls on Fridays and over the weekend because they had more time. Thus, we used the same protocol for the Web survey.

RedCAP is equipped with a scheduling feature that can be used to schedule and automate scheduled email reminders on a particular day and time. This feature was important for reducing staff burden during holiday season and during long weekends while ensuring that participants received their emails reminders weekly.

Descriptive statistics were used to calculate the completion rate for the Web survey to compare Web responders to telephone responders and to calculate estimated costs of using a Web-based survey for follow-up data collection. Differences between Web responders and telephone responders were compared using unadjusted chi-square test and *t* test for age with a *P* value of .05 or less to determine statistical significance. Analyses were conducted using SAS version 9.4 software (SAS Institute, Inc, Cary, NC, USA).

Results

To date, we have completed 9 months of data collection using the Web-based platform at the Chicago field center of the MASALA study. A link to the follow-up survey has been emailed to 285 participants and the overall rate of completion was 47.7% (136/285) (Table 1). The majority of surveys were completed on the same day that the first email was sent. There were demographic differences in participants who completed the follow-up survey by Web or telephone. For example, Web responders were significantly younger and more likely to have higher education and incomes than telephone-only responders (Table 2). Two participants reported a CVD event using the Web-based survey.

Table 1. Completion rates of a Web-based follow-up survey in the Mediators of Atherosclerosis in South Asians Living in America (MASALA) study, Chicago field center, 2014 (N=285).

Month (2014)	Total surveys emailed, n	Weekly survey completion, n				Completed Web-based survey, n (%)
		Week 1	Week 2	Week 3	Week 4	
February	66	5	9	3	—[a]	20[b](33)
March	58	10	6	9	13	39 (67)
April	20	5	6	2	0	11 (55)
May	22	3	2	1	0	6 (27)
June	28	7	3	6	1	17 (60)
July	18	5	2	2	0	9 (50)
August	25	2	3	3	3	11 (44)
September	29	1	5	5	4	15 (52)
October	19	2	3	2	1	8 (42)

[a]Fourth email reminder added in March.

[b]Three follow-up surveys were completed by telephone when participants called us in response to e-MASALA.

Table 2. Characteristics of MASALA study participants in the electronic pilot study by response modality, 2014 (N=285).

Characteristics	Web survey (n=119)	Telephone (n=125)	No response (n=51)	*P*
Sex (female), n (%)	50 (42.0)	61 (48.8)	20 (39)	.41
Marital status, [a] n (%)				.02
Married	116 (97.4)	110 (88.0)	48 (94)	
Unmarried	3 (2.5)	15 (12.0)	3 (6)	
Age (years), mean (SD)	55.4 (9.5)	57.5 (9.0)	51.9 (9.0)	.002
Age group (years), n (%)				.02
35-44	18 (15.1)	13 (10.4)	15 (29)	
45-54	43 (36.1)	34 (27.2)	19 (37)	
55-64	35 (29.4)	49 (39.2)	10 (20)	
65-74	19 (15.9)	26 (20.8)	5 (10)	
75-84	4 (3.3)	3 (2.4)	2 (4)	
Education, n (%)				<.001
≤ High school	2 (1.6)	19(15.2)	4 (8)	
Some college/bachelors	35 (29.4)	54 (43.2)	21 (41)	
≥ Bachelors	82 (68.9)	52 (41.6)	26 (51)	
Income group (US$), n (%)				<.001
<50,000	16 (13.4)	43 (36.4)	13 (25)	
50,000-100,000	24 (20.1)	27 (22.8)	9 (18)	
100,000-200,000	36 (30.2)	35 (29.6)	15 (29)	
>200,000	41 (34.4)	13 (11.0)	14 (27)	

[a]Marital status of 21 nonrespondents is not known.

One-third (12/36) of participants who were unresponsive to telephone follow-up since their baseline exam (n=36) completed the Web-based survey. Some surveys were partially completed (n=8), where participants opened the link but did not complete the survey. A personal reminder from the site principal investigator was sent to participants who opened, but did not complete, the survey. After receiving the reminder email, six of eight participants revisited and completed the Web-based survey.

Among participants who were contacted by telephone to complete the follow-up survey and who were asked about reasons for not completing the Web survey (n=32), most (78%, 25/28) said it was because they were too busy, did not check their email regularly, or did not pay attention to the email. These participants said that they would try to complete the Web-based survey in the future because they were subsequently aware of it.

An RA developed and implemented the Web survey. During the initial development stages, the RA spent 20 hours per week for 8 weeks exploring different platforms and their capabilities (Table 3). This time was primarily spent on exploring different Web platforms and designing and implementing the Web-based survey. During survey development in REDCap, the RA spent 10 hours per week meeting with REDCap staff, designing the branching and skip patterns, and pretesting and modifying the Web survey.

Table 3. Comparison of approximate costs for telephone, Web-based, and mixed mode (50% Web-based and 50% telephone) follow-up.

Activity	Survey type (US$)		
	Telephone	Web-based	Mixed method
Development (exploration, instrument building, usability testing)	$8500 (5 teleform pages at $1700/page)	$3600 (at $15/hr)=$2400 (20 hr/wk for 2 months) + $1200 (10 hr/wk for 1 month)	$12,100/year
Operation and maintenance	$3120/year (4 hr/wk at $15/hr)	$2340/year (3 hr/wk at $15/hr)	$3120/year
Data management	$2340/year (at $45/wk)	Included in maintenance	$1170/year
Total annual cost	Year 1: $13,960; Year 2 onward: $5460	Year 1: $5940; Year 2 onward: $2340	Year 1: $16,480; Year 2 onward: $4290

Since its launch, the Web survey and platform required 3 hours per week of the research staff's time to build new batches of participants who are due for follow-up, send out the surveys, track survey completion, and send follow-up emails to participants who did not complete the survey in the prior week. The process of collecting annual follow-up information via telephone required research staff to make multiple attempts to contact participants, spend 5 to 10 minutes interviewing participants, and then fax the teleforms to the study's data management center. The annual cost of the telephone follow-up and data management of teleforms was US $13,960 annually (Table 3). During its first year of design and implementation, the annual cost of the Web survey was US $6660 and the projected cost of operating and maintaining the Web-based survey is expected to be US $2340 per year. REDCap provides automated export procedures for data, whereas the telephone survey required manual entry of data onto a teleform and data verification after the teleform was faxed to the data-coordinating center.

Discussion

This study found that a Web-based platform was feasible and at a lower cost than telephone follow-up for the collection of longitudinal follow-up data in the MASALA study cohort. Of participants who received a link to the Web survey, we found that 48% completed it. Differences between Web responders and telephone-only responders included age, sex, income, and education. Telephone follow-up of participants who did not respond to Web surveys was still required; however, the Web survey allowed research staff to spend far less time on follow-up. Web-based follow-up also lowered the number of telephone contacts between participants and study staff, which may in turn help to reduce participant burden. One important finding was that one-third of respondents who had not previously responded to the follow-up survey completed the Web survey, which suggests that a Web platform can help engage participants who may be difficult to reach by telephone. The majority of costs that were associated with development of a Web survey were for development, beta testing, and initial implementation. Since the initial implementation, the cost of maintaining the Web survey and follow-up data have been minimal compared to the costs of telephone follow-up and management of teleform data.

We had a higher completion rate of the Web survey compared to what was reported in the Black Women's Health Study; in 2007-2008, the investigators reported that approximately 25% of participants completed the Web survey [10]. However, they noted that completion of Web surveys among participants was increasing over time, suggesting that temporal trends in Internet use would lead to more individuals having access to the Internet and feeling more comfortable with Web surveys. The finding that age and socioeconomic status influenced mode of response has been reported by others [10-14].

In October 2014, the National Heart, Lung, and Blood Council (NHLBI) Board of External Experts Working Group's Recommendations to the NHLBI Advisory Council stated that, "NHLBI should actively engage in studies to establish the validity, reliability, and scalability of electronic tools for primary data collection" [3]. The board also recommended active support by NHLBI for the development, validation, and sharing of digital tools. Along with the Health eHeart [15] and the CARDIA cohort's recent experiences, these data represent some of the first describing the methods and findings from "e-epidemiology" in the United States. The primary difference between e-MASALA and studies such as Health eHeart is the lack of an in-person examination among the latter's participants. Other cohort studies, such as the Nurses' Health Studies [16] and others, have not included in-person examinations and have relied solely on telephone and postal mail to capture data. Such cohort studies can be efficient, but can also lack in-depth phenotyping with in-person examinations or advanced imaging.

It also remains uncertain how participant retention rates may differ, if at all, among participants who are recruited and followed in an Internet-based cohort compared to a traditional cohort study. A study of the association between communication strategies used for recruitment (offline, online, face-to-face) and follow-up participation in nine Internet-based cohorts found that follow-up participation ranged from 43% to 89% depending on the cohort. The study also found that participants who became aware of the study through an online communication campaign, compared with those through traditional offline media, seemed to have a lower follow-up participation in eight of nine cohorts [17].

Studies have also found associations between sociodemographics and participation in follow-up reporting. In the Influenzanet study, participants from seven European countries were asked to report weekly symptoms during influenza season using a Web-based reporting system [18]. Sociodemographic factors associated with lower participation in follow-up reporting included younger age, lower education, living in a household with children, and not being vaccinated for influenza. However, another Web-based cohort study found that individuals with lower self-reported computer skills and literacy were more positive toward the study and less concerned about the burden of study follow-up than those with higher education [14]. Given this information, it appears that any well-designed cohort study, regardless of how data are collected, should use a combination of Internet and non-Internet engagement and retention activities to enhance follow-up of all participants and to potentially reduce selection bias.

Strengths of this study include novel development, implementation, and evaluation of a Web-based survey instrument within a traditional cohort and inclusion of start-up and maintenance time and cost estimates to help researchers leading other longitudinal cohort studies. However, our study also has limitations. First, we piloted the Web-based follow-up study only among MASALA participants from the Chicago field center. However, we might expect even higher response to Web-based follow-up among the San Francisco-based participants because those participants tend to have higher education and income levels, which were associated with higher use of the Web-based follow-up instrument. This program was expanded to the San Francisco field center in January 2015. Second, our results are limited to South Asians in the United States and results from other race/ethnic groups and nationalities

may be different, particularly when differences in sex, education, and income are present. Our ability to demonstrate feasibility and lower costs with Web-based follow-up serve as an initial step toward more advanced methods of data capture.

We successfully implemented a Web-based survey for follow-up and collection of PRO measures among MASALA cohort participants. These results demonstrate the benefits of using Web-based methods for longitudinal follow-up in epidemiologic cohort studies and that a combination of modalities may be most effective. Although electronic follow-up will not be a panacea for cohort operations as hypothesized by some, it will serve as an adjunctive strategy to telephone follow-up for maximizing cohort retention, lower costs, and possibly lower participant and research staff burden. Other traditional cohort studies can adapt these methods for Web-based follow-up of research participants.

Acknowledgments

This study was funded by John M Eisenberg Foundation and the National Institutes of Health (R01HL093009).

Conflicts of Interest

None declared.

References

1. Kilburn LS, Banerji J, Bliss JM, NCRI Breast Clinical Studies Group. The challenges of long-term follow-up data collection in non-commercial, academically-led breast cancer clinical trials: the UK perspective. Trials 2014;15:379 [FREE Full text] [doi: 10.1186/1745-6215-15-379] [Medline: 25262026]
2. Uhlig CE, Seitz B, Eter N, Promesberger J, Busse H. Efficiencies of Internet-based digital and paper-based scientific surveys and the estimated costs and time for different-sized cohorts. PLoS One 2014;9(10):e108441 [FREE Full text] [doi: 10.1371/journal.pone.0108441] [Medline: 25313672]
3. Strategic Transformation of Population Studies: NHLBI Council/BEE Working Group's Recommendations to the NHLBI Advisory Council. 2014 Oct 22. URL: https://nhlbiepi.files.wordpress.com/2014/10/council-bee-epi-wg-presentation10-22-14-_pptx.pdf [accessed 2015-04-05] [WebCite Cache ID 6dmCRne7U]
4. Kanaya AM, Kandula N, Herrington D, Budoff MJ, Hulley S, Vittinghoff E, et al. Mediators of Atherosclerosis in South Asians Living in America (MASALA) study: objectives, methods, and cohort description. Clin Cardiol 2013 Dec;36(12):713-720 [FREE Full text] [doi: 10.1002/clc.22219] [Medline: 24194499]
5. Gershon R, Rothrock NE, Hanrahan RT, Jansky LJ, Harniss M, Riley W. The development of a clinical outcomes survey research application: Assessment Center. Qual Life Res 2010 Jun;19(5):677-685 [FREE Full text] [doi: 10.1007/s11136-010-9634-4] [Medline: 20306332]
6. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)-a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009 Apr;42(2):377-381 [FREE Full text] [doi: 10.1016/j.jbi.2008.08.010] [Medline: 18929686]
7. Gershon RC, Rothrock N, Hanrahan R, Bass M, Cella D. The use of PROMIS and assessment center to deliver patient-reported outcome measures in clinical research. J Appl Meas 2010;11(3):304-314 [FREE Full text] [Medline: 20847477]
8. Research Information Services & Computing. Collect data URL: https://rc.partners.org/research-apps-and-services/collect-data [accessed 2016-05-04] [WebCite Cache ID 6hGCYiEje]
9. Petrovčič A, Petrič G, Lozar Manfreda K. The effect of email invitation elements on response rate in a web survey within an online community. Comput Hum Behav 2016 Mar;56:320-329. [doi: 10.1016/j.chb.2015.11.025]
10. Russell CW, Boggs DA, Palmer JR, Rosenberg L. Use of a web-based questionnaire in the Black Women's Health Study. Am J Epidemiol 2010 Dec 1;172(11):1286-1291 [FREE Full text] [doi: 10.1093/aje/kwq310] [Medline: 20937635]
11. Smith B, Smith TC, Gray GC, Ryan MA, Millennium Cohort Study Team. When epidemiology meets the Internet: Web-based surveys in the Millennium Cohort Study. Am J Epidemiol 2007 Dec 1;166(11):1345-1354 [FREE Full text] [doi: 10.1093/aje/kwm212] [Medline: 17728269]
12. Kroth PJ, McPherson L, Leverence R, Pace W, Daniels E, Rhyne RL, et al. Combining web-based and mail surveys improves response rates: a PBRN study from PRIME Net. Ann Fam Med 2009;7(3):245-248 [FREE Full text] [doi: 10.1370/afm.944] [Medline: 19433842]
13. Callas PW, Solomon LJ, Hughes JR, Livingston AE. The influence of response mode on study results: offering cigarette smokers a choice of postal or online completion of a survey. J Med Internet Res 2010;12(4):e46 [FREE Full text] [doi: 10.2196/jmir.1414] [Medline: 20965873]
14. Pouchieu C, Méjean C, Andreeva VA, Kesse-Guyot E, Fassier P, Galan P, et al. How computer literacy and socioeconomic status affect attitudes toward a Web-based cohort: results from the NutriNet-Santé study. J Med Internet Res 2015;17(2):e34 [FREE Full text] [doi: 10.2196/jmir.3813] [Medline: 25648178]
15. The Health eHeart Study. URL: https://www.health-eheartstudy.org/ [accessed 2015-12-04] [WebCite Cache ID 6dWwiwG9a]

16. Belanger CF, Hennekens CH, Rosner B, Speizer FE. The nurses' health study. Am J Nurs 1978 Jun;78(6):1039-1040. [Medline: 248266]
17. Bajardi P, Paolotti D, Vespignani A, Eames K, Funk S, Edmunds WJ, et al. Association between recruitment methods and attrition in Internet-based studies. PLoS One 2014;9(12):e114925 [FREE Full text] [doi: 10.1371/journal.pone.0114925] [Medline: 25490045]
18. Bajardi P, Vespignani A, Funk S, Eames KT, Edmunds WJ, Turbelin C, et al. Determinants of follow-up participation in the Internet-based European influenza surveillance platform Influenzanet. J Med Internet Res 2014;16(3):e78 [FREE Full text] [doi: 10.2196/jmir.3010] [Medline: 24613818]

Abbreviations

CARDIA: Coronary Artery Risk Development in Young Adults Study
CVD: cardiovascular disease
e-MASALA: electronic MASALA
MASALA: Mediators of Atherosclerosis in South Asians Living in America Study
PRO: patient-reported outcomes
PROMIS: Patient-Reported Outcomes Measurement Information System
RA: research assistant
REDCap: Research Electronic Data Capture
SSL: Secure Sockets Layer

Edited by G Eysenbach; submitted 18.12.15; peer-reviewed by M Bass; comments to author 19.01.16; revised version received 29.02.16; accepted 21.03.16; published 08.06.16.

Please cite as:
Kandula NR, Puri-Taneja A, Victorson DE, Dave SS, Kanaya AM, Huffman MD
Mediators of Atherosclerosis in South Asians Living in America: Use of Web-Based Methods for Follow-Up and Collection of Patient-Reported Outcome Measures
JMIR Res Protoc 2016;5(2):e95
URL: http://www.researchprotocols.org/2016/2/e95/
doi:10.2196/resprot.5448
PMID:27278905

Original Paper

Enhancing the Return to Work of Cancer Survivors: Development and Feasibility of the Nurse-Led eHealth Intervention Cancer@Work

Sietske J Tamminga[1], PhD; Sanne van Hezel[1], MSc; Angela GEM de Boer[1], PhD; Monique HW Frings-Dresen[1], PhD

Coronel Institute of Occupational Health, Academic Medical Center, Amsterdam, Netherlands

Corresponding Author:
Sietske J Tamminga, PhD
Coronel Institute of Occupational Health
Academic Medical Center
Meibergdreef 9 / K0-110
Amsterdam, 1105 AZ
Netherlands
Phone: 31 205663279
Fax: 31 206977161
Email: s.j.tamminga@amc.nl

Abstract

Background: It is important to enhance the return to work of cancer survivors with an appropriate intervention, as cancer survivors experience problems upon their return to work but consider it an essential part of their recovery.

Objective: The objective of our study was to develop an eHealth intervention to enhance the return to work of cancer survivors and to test the feasibility of the eHealth intervention with end users.

Methods: To develop the intervention we 1) searched the literature, 2) interviewed 7 eHealth experts, 3) interviewed 7 cancer survivors, 2 employers, and 7 occupational physicians, and 4) consulted experts. To test feasibility, we enrolled 39 cancer survivors, 9 supervisors, 7 occupational physicians, 9 general physicians and 2 social workers and gave them access to the eHealth intervention. We also interviewed participants, asked them to fill in a questionnaire, or both, to test which functionalities of the eHealth intervention were appropriate and which aspects needed improvement.

Results: Cancer survivors particularly want information and support regarding the possibility of returning to work, and on financial and legal aspects of their situation. Furthermore, the use of blended care and the personalization of the eHealth intervention were preferred features for increasing compliance. The first version of the eHealth intervention consisted of access to a personal and secure website containing various functionalities for cancer survivors blended with support from their specialized nurse, and a public website for employers, occupational physicians, and general physicians. The eHealth intervention appeared feasible. We adapted it slightly by adding more information on different cancer types and their possible effects on return to work.

Conclusions: A multistakeholder and mixed-method design appeared useful in the development of the eHealth intervention. It was challenging to meet all end user requirements due to legal and privacy constraints. The eHealth intervention appeared feasible, although implementation in daily practice needs to be subject of further research.

ClinicalTrial: Dutch Trial Register number (NTR): 5190; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=5190 (Archived by WebCite at http://www.webcitation.org/6hm4WQJqC)

(JMIR Res Protoc 2016;5(2):e118) doi:10.2196/resprot.5565

KEYWORDS

cancer; return to work; eHealth; survivorship; feasibility studies; self-management

Introduction

Due to the improved survival rates for cancer in recent decades [1], remaining in or returning to work has become a relevant topic to address for people with a job when being treated for cancer. The number of people who have a job when diagnosed with cancer is expected to increase considerably in the coming years. This is mainly due to an increase in the retirement age, with the incidence of cancer within the working age group

predicted to increase by 45% with the inclusion of people aged 65–70 years [1].

Research done over the past 10 years has indicated that cancer survivors are more likely than cancer-free controls to be unemployed [2,3] and they also experience problems upon their return to work [4]. These adverse work outcomes need to be improved through an appropriate intervention, as returning to work is considered a key survivorship issue by cancer survivors [5]. It also contributes to their quality of life and reduces financial problems [6]. A few interventions with the potential to enhance the return to work of cancer survivors have been studied in randomized controlled trials, with some interventions showing positive results on sustainable return to work, while others did not [7]. Of these interventions, multidisciplinary interventions showed the most promising results [7].

An overview of the outcomes of these above-mentioned intervention studies, as well as studies of factors predicting the return to work of cancer survivors, led to the following main insights. First, it is both feasible and appreciated by cancer survivors to address the issue of return to work in an early stage of psycho-oncological cancer care [8,9], although the amount of time available to spend on this topic is limited [9]. Second, self-assessed work ability is an important prognostic factor, irrespective of clinical characteristics [10]. Third, cancer survivors differ considerably in the time needed before their return to work [11] and the amount and timing of support required, suggesting that support needs to be tailored to the individual [12]. Fourth, employers are important stakeholders who can facilitate or hamper the return to work [13], while at the same time it appears difficult to establish cooperation between primary care, occupational care, and the workplace [9]. These main findings led to 2 hypotheses: 1) that an intervention aimed at enhancing the return to work of cancer survivors could be based on the theory of self-management, which can address misconceptions about self-assessed work ability through the technique of cognitive restructuring; and 2) that cooperation between specialist cancer care, the general practitioner, and occupational health care might be improved with integrative care management [14,15].

Based on the assumption that information and support need to be tailored to the individual, a stepped-care eHealth intervention may be a suitable solution. Other advantages of eHealth interventions include that they are easy to access and to tailor to the individual, both of which are important, as information on the Internet can be overwhelming [16]. Furthermore, eHealth interventions can be delivered interactively and also be integrated with traditional health care visits, which is much needed, given the limited availability of time in the health care system. Such eHealth approaches have also demonstrated that they are suitable for delivering self-management interventions for cancer survivors [17] and self-management interventions to enhance the return to work [18]. Finally, eHealth has also been used to facilitate involvement of the employer [14]. Nevertheless, a few drawbacks of eHealth interventions have been reported, such as difficulties with patients' noncompliance, high dropout rates, and security and privacy issues [19,20].

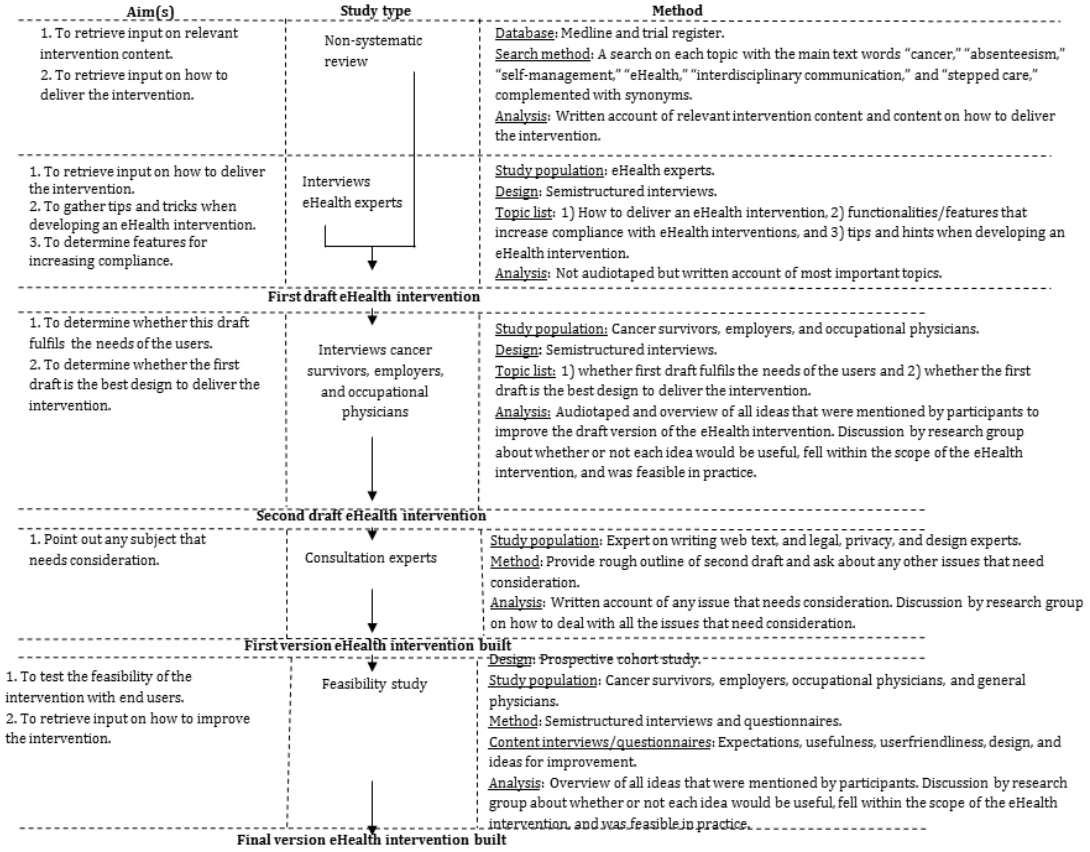
Based on all of the above-mentioned findings, we decided to develop an intervention that would be part of psycho-oncological care and be based on the theory of self-management and integrative care management. We decided to deliver the intervention as stepped care through eHealth. In this paper, we report on this process, specifically addressing the above-mentioned challenges to eHealth interventions, including noncompliance.

The objectives of this study were to develop an eHealth intervention to enhance the return to work of cancer survivors and to test the feasibility of the eHealth intervention with end users.

Methods

We sought ethical approval to interview cancer survivors, employers, and occupational physicians, as well as approval for the feasibility study, from the Medical Ethics Committee of the Academic Medical Center, Amsterdam, the Netherlands, which judged that ethical approval was not required for either of the 2 studies (METC number W13_028 and W13_122). Participants (with the exception of experts) gave either their oral or written informed consent before the interview took place, or their written informed consent before participating in the feasibility study. We executed the following steps for objective 1 (Figure 1).

Figure 1. Flowchart of the development of Cancer@Work and the feasibility study.



Objective 1: Development of the Intervention Cancer@Work

We conducted a stepwise development of the intervention (Figure 1). We developed a first draft based on 1) a nonsystematic literature review and 2) interviews with experts in an iterative manner. Thereafter, we undertook 3) semistructured interviews with end users (cancer survivors, employers, occupational physicians) to test whether this first draft fit the needs of the users and whether it was the best design to deliver the intervention. Subsequently, we adapted the first draft on the basis of the results of these interviews. Using this second draft, we built a first version of the website after 4) consultation with experts, including a legal expert.

Nonsystematic Literature Review

Methods

Our literature search was focused on self-management, integrative care management, stepped care, and eHealth in a nonsystematic manner. The aim of this search was to retrieve input on relevant intervention content and input on how to deliver the intervention. We restricted our search to MEDLINE, searching the trial register for relevant interventions. The search was carried out between March and May 2012. We completed a search for each topic using the main text words: "cancer," "absenteeism," "self-management," "eHealth," "interdisciplinary communication," and "stepped care," complemented with synonyms. We also searched references from relevant studies. The results of our search were analyzed on the basis of a written account of the relevant intervention content and relevant information on how to deliver the intervention.

Results

Several studies described self-management interventions that aimed to improve individuals' skills and confidence, helping them deal with their disease more effectively in daily life [21]. Research on self-management has shown that it has positive effects in cancer survivors dealing with survivorship issues [22], as well as in chronically ill patients dealing with work-related issues [23]. The key elements of self-management interventions are information and assignments. Self-management interventions can be based on problem-solving techniques or cognitive behavioral techniques, and have proven to be equally effective in treating patients with depression [24]. When addressing misconceptions about cancer and work, a cognitive behavioral component seems most appropriate, since the core focus of this technique is on cognitive reframing. In addition, to resolve a patient's work-related problems, a problem-solving component seems most appropriate, since this technique attempts to resolve patients' problems by teaching them structured problem-solving skills and how to generate achievable and simple action plans [26]. Moreover, one self-management intervention based on a problem-solving technique aimed at increasing the work functioning of employees with rheumatoid arthritis demonstrated its feasibility and was appreciated by both patients and care providers [27]. We therefore decided to include both components, offering problem-solving and cognitive behavioral techniques.

A few studies have tried to enhance collaboration between primary and occupational health care, but the level of effectiveness is still inconclusive. Some studies have shown positive results with respect to feasibility [28] and effectiveness [15], but others did not demonstrate any positive results [9,29]. One strategy that did prove feasible is integrative care management [15]. The goal of integrative care management is to establish the much-needed collaboration between all stakeholders (eg, the sick-listed employee, the occupational physician, the employer, the general physician, and the treating physician) to achieve a successful return to work of the sick-listed employee. A coordinator is ideally situated to establish this collaboration. However, collaboration can also be established using a secure website, where stakeholders can work together toward a common goal and share the necessary information to achieve this. In the eHealth intervention developed by Vonk Noordegraaf et al [14], almost half of the participants invited their supervisor to be involved in the eHealth intervention and that approximately 60% of the supervisors took this opportunity [30].

In a stepped-care intervention, all patients start with a low-intensity intervention, with the intensity increasing only if an intervention goal is not achieved at a certain point in time (eg, [31]). The advantages of a stepped-care intervention include the ability to deliver the right intensity of an intervention to each patient, lower intervention costs, and less time wasted by patients who participate [32]. The challenge for stepped-care intervention, however, is determining the cutoff value that indicates whether the intervention goal has been met and when a judgment can be made about whether the intervention goal has been met. When using a self-management intervention based on problem-solving techniques, it has been proposed that patients should be carefully selected to reduce noncompliance and dropout [27]. For this reason, a self-management intervention based on problem-solving techniques seems relevant only in cases where a patient experiences problems with his or her return to work, and it should therefore be offered only as a second step in an intervention.

Several eHealth intervention features are related to enhanced patient compliance: peer and counsellor support, email and phone contact, updates, record keeping, and individualized feedback [33,34]. Furthermore, eHealth interventions that are combined with face-to-face contact with a health care professional also showed enhanced patient compliance [35].

Interviews With Experts on eHealth Interventions

Methods

We approached approximately 10 experts based on the fact that they had recently developed an eHealth intervention for cancer survivors or an eHealth intervention aimed at increasing return to work of sick-listed employees. The first author (ST) undertook semistructured interviews based on a topic list. This list consisted of questions on 1) how to deliver an eHealth intervention, 2) features required to increase compliance with eHealth interventions, and 3) tips and tricks for developing an eHealth intervention. The interviews were held in August 2012. They were not audiotaped but the first author (ST) provided a written summary of the most important issues mentioned during the interview.

Results

In total, 7 eHealth experts were interviewed with the aim of 1) gaining input on how to deliver the intervention, 2) gathering tips and tricks for developing an eHealth intervention, and 3) determining features that increase compliance. These eHealth experts reported that the following elements were required to deliver an eHealth intervention: choose a modular or a structured form; and use a combination of text, film, and pictures. The following additional features that increase compliance with eHealth interventions were also suggested: sending reminders, and using blended care with a health care professional. Finally, the experts also noted that what was most important when developing an eHealth intervention was 1) to consider, before starting, what type of “track and trace data” would be required to study use and compliance, and 2) to consult an information technology expert at the beginning of the development of the intervention because they can give advice at an early phase about the functionalities that are possible given financial and practical constraints. As return-to-work trajectories vary across patients in terms of length [36] and needs, we decided to deliver the eHealth intervention in a modular form. As we considered the remainder of the above-mentioned suggestions to be valuable for our eHealth intervention, we decided to use them all. Based on the literature search and interviews with these experts, we created a first draft of the intervention (Multimedia Appendix 1,Multimedia Appendix 2,Multimedia Appendix 3).

First Draft

This first draft of the eHealth intervention consisted of access to a personal, tailored, and secure website containing various functionalities for cancer survivors, blended with support from their nurse, occupational physician, and employer (Multimedia Appendix 1,Multimedia Appendix 2,Multimedia Appendix 3). We presented this first draft as an online working environment. Blended care delivered by specialized nurse encompassed 1) answering questions, 2) monitoring and supervising use of the eHealth intervention, 3) providing personal feedback on assignments on the eHealth intervention, and 4) encouraging patients to comply with the intervention. Functionalities included providing insight into laws and regulations, a library, and a self-test to gain insight into opportunities to return to work (based on the problem-solving technique component), and redressing negative ideas concerning the possibilities to work after cancer, including the idea that one can return to work only after complete recovery (based on cognitive behavioral technique components). The occupational physician and employer had access to a specific part of the secure website that contained certain information, allowed them to access the cancer survivor’s return-to-work plan, and allowed them to add their suggestions to facilitate their employee’s return to work.

Interviews With Cancer Survivors, Employers, and Occupational Physicians

Methods

Cancer survivors were eligible to participate if they had been working at the time of diagnosis, were fluent in Dutch, and were

aged between 18 and 65 years. Occupational physicians and employers were eligible to participate if they had recently encountered an employee with cancer and were fluent in Dutch. We intended to interview 10 cancer survivors, 5 employers, and 5 occupational physicians. The first author (ST) undertook semistructured interviews after the interviewees had been given a rough outline of the first draft of the intervention. They were asked whether this first draft accorded with their needs and whether they thought the design was the most appropriate to deliver the intervention. The interviews were held in March 2013; they were audiotaped but not transcribed verbatim. We analyzed the interviews using a direct content analysis [37] in order to obtain an overview of all ideas mentioned by the participants that could improve the draft version of the intervention. Subsequently, 3 of the authors (ST, AdB, MF) discussed whether each idea would be useful, whether it fell within the scope of the intervention, and whether it was feasible in practice (eg, financial constraints).

Results

In total, we interviewed 7 cancer survivors, 2 employers, and 7 occupational physicians with the aim of determining whether this draft fulfilled the needs of the users and whether it was the best design for delivering the intervention. We added the following functionalities to the first draft for cancer survivors: assignments providing insight into possible financial consequences, a documentary called *Irrevocable*, and assignments providing insight into the individual importance of work (Multimedia Appendix 1). We added the assignments providing insight into possible financial consequences and the individual importance of work because cancer survivors mentioned that they would have benefited from such insight and that this information is not readily available. In addition, to meet the needs of cancer survivors for peer support, and given our financial constraints, we added the documentary, which follows the return-to-work trajectories of 3 cancer survivors. For employers, we added a functionality that addressed the need to involve colleagues. Finally, in relation to occupational physicians, we added advice for cancer survivors on how to remain in contact with their workplace and references to relevant guidelines. We altered or removed some functionalities of the first draft of the eHealth intervention (eg, the occupational physician's and employer's access to a specific part of the secure website containing certain information, and the possibility to see the cancer survivor's return-to-work plan and add their suggestions to facilitate their return to work). In addition, we excluded some suggested functionalities from the eHealth intervention due to legal, privacy, financial, or practical constraints (eg, the ability to obtain peer support from former cancer survivors) or because we did not consider them to be of added value (eg, teaching the user how to deal with the expectations of others) or within the scope of the intervention (eg, information on benefits from municipalities and on the long-term disability pension) (Multimedia Appendix 1). Based on these interviews, we developed a second draft (Multimedia Appendix 1,Multimedia Appendix 2,Multimedia Appendix 3).

Second Draft

The second draft consisted of access to a personal and secure website containing various functionalities for cancer survivors blended with support from their nurse, and a public website for occupational physicians, general physicians, and employers (Multimedia Appendix 1,Multimedia Appendix 2,Multimedia Appendix 3). Blended care delivered by specialized nurse encompassed 1) answering questions, 2) monitoring and supervising use of the eHealth intervention, 3) providing personal feedback on assignments on the eHealth intervention, and 4) encouraging patients to comply with the intervention. Functionalities for patients included support to draw up a strategy to manage specific personal problems that might inhibit their return to work, assignments providing insight into possible financial consequences of being on sick leave, support to draw up a return-to-work plan, and how to redress negative ideas concerning the possibilities of working after cancer, including the idea that one can return to work only after complete recovery (based on cognitive behavioral technique components).

Consultation With Experts on Writing Web Text and Website Design, Privacy, and Legal Aspects of Building an eHealth Intervention

Methods

We consulted an expert on writing text for websites and an expert on design, privacy, and legal aspects of building an eHealth intervention. They were given the rough outline of the second draft of the intervention and were asked to point out any issues that required further consideration.

Results

Consultation with an expert on writing Web text taught us that it is important to 1) draft a "tone of voice document," which reflects the key values of the intervention, and on the basis of which the text is written, 2) to write clear and concise sentences without ambiguity, and 3) to develop the website in such a way that it is personal, for example, by using quotes from former cancer survivors that include their name, age, and occupation. The key values for this intervention were reliability, activating, personal, confrontational, serious, and directed to work and income. The design expert showed us that it is essential to match the design of the website with the tone of voice and Web text. Based on the tone of voice we wanted, the design expert created style sheets (Multimedia Appendix 4,Multimedia Appendix 5). After consultation with privacy and legal experts, it appeared that some functionalities would not be possible due to privacy legislation and that we needed to add a disclaimer pointing out the risk of using two functionalities and provide more secure alternatives (Multimedia Appendix 1,Multimedia Appendix 2,Multimedia Appendix 3).

First Version

Based on consultations with these experts, we built a first version of the eHealth intervention, consisting of access to a personal and secure website containing various functionalities for cancer survivors blended with support from their nurse, and a public website for occupational physicians, general physicians, and employers (Multimedia Appendix 1,Multimedia Appendix 2,Multimedia Appendix 3). Functionalities for patients included

support in gaining insight into the individual importance of work, the ability to invite their employer, occupational physician, or general practitioner to use the public website (as a first step), and guidance in drawing up a strategy to manage specific personal problems that might inhibit their return to work (as a second step). Cancer survivors and specialized nurses were given a unique username and password to log in to the secure webpage, while verification would take place by text message.

Objective 2: Feasibility of the Intervention Cancer@Work

After developing the first version of the intervention, we tested its feasibility by interviewing 1) cancer survivors, 2) employers, occupational physicians, and general physicians, and 3) social workers. All of the interviews discussed below were audiotaped but not transcribed verbatim. We intended to interview 40 cancer survivors, 10 employers, 10 occupational physicians, and 10 general physicians. We analyzed the interviews using a direct content analysis [37] in order to obtain an overview of all of the ideas that were mentioned by participants that might improve the first version of the eHealth intervention. Subsequently, we discussed whether each idea would be useful, whether it fell within the scope of the eHealth intervention, and whether it was feasible in practice. The cancer survivors also filled in 2 questionnaires.

Feasibility of the Intervention for Cancer Survivors

Methods

To test the feasibility of the intervention for cancer survivors, 1) we invited cancer survivors who had taken part in previous research by our department and who had given their consent to be approached in future research on cancer and work, and 3) the treating physician also invited cancer survivors who were treated between 2012 and 2014 in the department of gynecological oncology of an academic medical center. Cancer survivors were eligible to participate if they had been working at the time of diagnosis, were fluent in Dutch, and were aged between 18 and 65 years. The patients were sent an informative letter about the study. If interested, they could return a consent form agreeing to telephone contact, whereupon 1 of the researchers contacted the patient by phone. During this conversation they could ask questions and decide whether they wanted to participate.

We used the following criteria to assess feasibility: 1) appropriateness of each functionality, 2) which functionalities needed improvement, 3) usefulness of the eHealth intervention, 4) user friendliness of the eHealth intervention, and 5) whether the eHealth intervention met their expectations. We considered the eHealth intervention feasible when at least 50% of the patients responded positively to each criterion.

After patients gave their informed consent, they filled in a questionnaire on their expectations of the intervention (eg, “What are your expectations regarding the Internet program Cancer@Work?”) and their need for support regarding their return to work (eg, “Do you need support on questions or problems regarding your work?”). After completing the questionnaire, they were given access to the eHealth intervention for 6 weeks, after which they filled in another questionnaire about the usefulness and user friendliness of the intervention (eg, “Which functionalities from Cancer@Work did you find useful?”) and whether the intervention met their expectations (eg, “Did Cancer@Work meet your expectations?”; “Cancer@Work did (not) meet my expectations because...”). All of the participants who filled in both questionnaires were invited to participate in a telephone interview by 1 of the researchers (SvH) to potentially gain greater insight into the answers to the questionnaire and to ask whether they had any further suggestions to improve the eHealth intervention and its functionalities. These interviews were held in June 2015. Based on these interviews, we developed a final version of the eHealth intervention for cancer survivors.

Results

Of the 177 cancer survivors invited to participate, 39 (22.0%) filled in the first questionnaire, while 20 filled in the second questionnaire (each participant was contacted by phone to remind them to fill in the questionnaire). We used the data of the 20 participants who filled in both questionnaires for our analysis. Table 1 details the participants’ characteristics. The main reason that 19 participants did not fill in the second questionnaire was that they did not feel the need to use the intervention because it was, on average, 3 years since they had received their cancer diagnosis and they had already returned to work.

Table 1. Characteristics of cancer survivors who participated in the feasibility study (n=20).

Variables	n (%) or mean (SD)
Sociodemographic variables	
Female, n (%)	18 (90)
Age in years, mean (SD)	49 (10)
Marital status, n (%)	
Married/living together	11 (55)
Single	5 (25)
Divorced	4 (4)
Educational level, n (%)	
Lower vocational education	1 (5)
Secondary vocational education	8 (40)
Intermediate vocational education	1 (5)
Higher professional education	6 (30)
University	4 (20)
Cancer diagnosis, n (%) [a]	
Breast cancer	8 (40)
Gynecological cancer	7 (35)
Lymphoma	1 (5)
Bowel cancer	2 (10)
Skin cancer	1 (5)
Hematological cancer	1 (5)
Cancer treatment, n (%) [a]	
Surgery	17 (85)
Chemotherapy	14 (70)
Radiotherapy	9 (45)
Hormonal therapy	7 (35)
No treatment	2 (10)
Work-related variables	
Current work status, n (%)	
Fully returned to work	16 (80)
Partially returned to work	1 (5)
Fully sick listed	1 (5)
Never sick listed	1 (5)
Data missing	1 (5)
Type of occupation, n (%)	
Physical heavy work	2 (10)
Type of employment contract, n (%)	
Permanent employment contract	15 (75)

[a]Numbers do not add up because of possibility of giving multiple answers.

Table 2. Results of questionnaire for cancer survivors who participated in the feasibility study (n=20).

Intervention-related questions	n (%)
Need for information on cancer and work	
A bit to very much	9 (45)
Need for support on cancer and work	
A bit to very much	7 (35)
Are you experiencing problems with returning to work?	
Yes	6 (30)
Reason for not using eHealth intervention Cancer@Work	
No need	4 (20)
Not up to it yet	1 (5)
No time	1 (5)
Forgot to log in	1 (5)
Other	3 (15)
Reason for using eHealth intervention Cancer@Work	
Useful program	1 (5)
My specialized nurse encouraged me to use Cancer@Work	0 (0)
My supervisor/occupational physician encouraged me to use Cancer@Work	0 (0)
Other	10 (50)
Did Cancer@Work meet your expectations?	
Yes	1 (5)
Yes, a little	3 (15)
No, not at all	1 (5)
Do not know/did not have any expectations	15 (75)
Reason why Cancer@Work met my expectations	
Receive information on cancer and work	2 (10)
Receive support for work-related problems	0 (0)
Get insight into my work-related problems	0 (0)
Get solutions to work-related problems	0 (0)
Get help from others	0 (0)
Other	2 (10)
Reason why Cancer@Work did not meet my expectations	
Did not receive information on cancer and work	0 (0)
Did not receive support for work-related problems	0 (0)
Did not get insight into my work-related problems	0 (0)
Did not get solutions for work-related problems	0 (0)
Did not get help from others	0 (0)
Other	1 (5)
Did Cancer@Work fit into daily use?	
Yes or somewhat	2 (10)
For whom is Cancer@Work appropriate? [a]	
For me	2 (10)
For all cancer survivors with a job	9 (45)
For all cancer survivors with cancer-related problems	13 (65)

Intervention-related questions	n (%)
For cancer survivors who lost their job	8 (40)
Do not know/no opinion	2 (10)
Other	5 (25)
Is Cancer@Work useful?	
Very useful	5 (25)
Useful	10 (50)
Not useful	5 (25)
Do not know/no opinion	0 (0)
Is Cancer@Work user friendly?	
Yes	12 (60)
No	1 (5)
Do not know/no opinion	7 (35)
Is it useful to be able to ask for support with the use of Cancer@Work?	
Yes	5 (25)
No	3 (15)
Do not know/no opinion	12 (60)

[a]Numbers do not add up because of possibility of giving multiple answers.

In total, 11 participants (55%) used the eHealth intervention. The other participants did not use the intervention either because they forgot to log in or they did not have any problems at work and thus did not feel the need to use the intervention. Table 2 details the results of the questionnaires. One of the participants' expectations regarding Cancer@Work were not met because she had already fully returned to work and did not have any work-related problems. Furthermore, 1 participant did not find the eHealth intervention user friendly because there was too much theoretical information and not enough opportunities to interact with other cancer survivors.

All of the 20 participants were invited for a telephone interview and 11 participated. The other 9 participants did not participate because of time constraints, practical issues, or lack of interest. During the interviews, the participants were positive about the intervention and its functionalities. They proposed several ideas to improve the intervention, such as making it easier to log in by using less-complicated passwords or not using text message authentication, or to make the intervention accessible for vision-impaired people by making it possible to enlarge the size of the text or to have the text read aloud. For an overview of all of the ideas that were proposed to improve the intervention, see Multimedia Appendix 1,Multimedia Appendix 2, and Multimedia Appendix 3. We did not use any of these ideas to improve the intervention in the final version, either because they did not meet the security or privacy regulations or because of practical constraints. Therefore, we made no changes and the first version became the final version of the intervention for cancer survivors.

Feasibility of the Intervention for Employers, Occupational Physicians, and General Physicians

Methods

Employers were eligible to participate if they had recently encountered an employee with cancer, while occupational physicians and general physicians did not need to have recent experience with a cancer patient or the associated work-related problems. All of the participants had to be fluent in Dutch. After giving informed consent, participants visited the eHealth intervention website designed for their respective profession and then participated in a semistructured interview to gather information on participants' experience with the intervention, its usefulness, and its user friendliness. The interviews were conducted in January and February 2015 by 1 of the authors (SvH) and they were audiotaped but not transcribed verbatim. Based on these interviews, we developed a final version of the intervention for employers, occupational physicians, and general practitioners.

Results

In total, 9 employers, 7 occupational physicians, and 6 general physicians participated in the interviews. For a full overview of the ideas that were mentioned, see Multimedia Appendix 1,Multimedia Appendix 2, and Multimedia Appendix 3. The main issue that arose from the interviews was that participants needed more detailed information, mainly on the different cancer diagnoses and treatments, and their possible effects on the employee's ability to return to work. The occupational physicians were least enthusiastic about the intervention, since they felt that they already had a lot of knowledge on this topic. Thus, the occupational physicians in particular indicated that more detailed information was required to make the intervention useful. As a result, in the final version of the intervention, we

added more detailed information on different cancer diagnoses and treatments and their possible effects on the employee's ability to return to work. In addition, we added many institutions to the list of support agencies they could consult.

When asked about the user friendliness, design, and practical usefulness of the intervention, almost all of the participants indicated that the intervention was easy to use (n=21, 96%), that the design matched the content and purpose of the website (n=20, 91%), and that they would recommend this intervention, for example, to their friends or colleagues if they had to deal with an employee, client, or patient with cancer (n=19, 86%). Thus, we made no changes regarding these aspects in the final version of the intervention (see Multimedia Appendix 1,Multimedia Appendix 2,Multimedia Appendix 3).

Feasibility of Blended Support From the Cancer Survivor's Specialized Nurse

Methods

We asked 2 social workers from a gynecology department of a Dutch hospital who had experience supporting cancer survivors in their return to work to visit the section of the eHealth intervention for specialized nurses and to participate in a semistructured interview with 1 of the authors (SvH). Based on this interview, we developed a final version of the section of the eHealth intervention for specialized nurses.

Results

A total of 2 social workers participated in 1 interview, on the basis of which we added information on financial and legal issues to the final version of the intervention in order to provide specialized nurses and social workers with access to the same information as that provided to the patients they are supporting (Multimedia Appendix 1,Multimedia Appendix 2,Multimedia Appendix 3). In this way, it would be easier for them to advise patients on financial and legal issues by referring to the intervention. Furthermore, the social workers indicated that the intervention was easy to use, and that they anticipated no problems in using the intervention in practice.

Discussion

The objectives of this study were to develop an eHealth intervention to enhance the return to work of cancer survivors and to test the feasibility of the eHealth intervention with end users. The results of our development study show that cancer survivors particularly want to receive information and support on opportunities to return to work, and on the financial and legal aspects of their position. Furthermore, we found that the use of blended care and the personalization of the eHealth intervention are preferred features for increasing compliance. The results of the feasibility study showed that the eHealth intervention was feasible; however, we adapted it slightly by adding more information on different types of cancer and its treatment and on the possible effects of these on the return to work.

Strengths and Limitations

The strengths of our study include the use of a multistakeholder and mixed-method design to develop our eHealth intervention. In this way, the content, design, and delivery of the eHealth intervention could best fulfill the needs of the end users and be the most suitable option to achieve the intervention goal, given Dutch law and our framework of psycho-oncological care. This also ensured that the risk of a type III error (ie, theory failure) was minimized [38].

We did not test the feasibility of the eHealth intervention in precisely the same conditions under which the intervention is intended to be used, as the feasibility study among cancer survivors was a prospective cohort study, with a short follow-up period of 6 weeks, that started on average 3 years after diagnosis, while the eHealth intervention is intended to be used from the initial cancer diagnosis until sustainable return to work. As a result, we are unable to draw firm conclusions about the usefulness of the content of the eHealth intervention, the features that enhance compliance, and the features that enhance integrative care management. We have partly overcome this drawback by consulting the literature, and interviewing experts and end users under our first objective. However, implementation of the eHealth intervention in daily practice should be the subject of further research. We were able to test the appropriateness of all the functionalities and the user friendliness, the usefulness, and the design of the eHealth intervention, for which we found positive results, so that the criteria for feasibility were met.

The employers, occupational physicians, and general practitioners who participated in the interviews and feasibility study were generally very interested in this subject for personal reasons, for example, as a cancer survivor. This was very useful for generating ideas about the content of the eHealth intervention, but it might have led to an overestimation of its future use by other members of their profession in daily practice. Implementation in daily practice should, for this reason, also be the subject of further research.

Interpretation of Findings

Cancer survivors, employers, occupational physicians, general practitioners, and specialized nurses were generally positive about the eHealth intervention. Not surprisingly, occupational physicians saw the least added value of the eHealth intervention for their own profession, as they thought that they were already applying the content in their daily practice. However, in their experience, they believed that employers would particularly benefit from the content, as they rarely have to deal with an employee with cancer, and cancer remains a difficult topic to address in the workplace [13,39]. We also added specific content to the eHealth intervention for general practitioners, for two reasons. First, patients themselves wanted more return-to-work guidance from their general practitioner, in addition to guidance from their occupational physician or in the absence of an occupational physician [25]. Second, general practitioners play a more prominent role in psycho-oncological care after primary treatment, including dealing with the possible effects on social outcomes such as being able to return to work [40]. We hope that we have equipped general practitioners with sufficient information and referral options. Apart from these issues, it seems important that future research examine what general practitioners specifically require to support cancer survivors in their return to work.

Although 97% of Dutch society has Internet access [41], Internet illiteracy is associated with a lower educational level [41]. At the same time, research indicates that self-management interventions are more effective in patients with a lower educational level [23]. Moreover, cancer survivors with a lower educational level are less likely to return to work [42], indicating that the intervention might be especially needed among this group. For these reasons, we spent additional time and effort to ensure that the eHealth intervention was very easy to use so that people with limited Internet literacy would be able to use the eHealth intervention as well. As appeared from both our quantitative study and our qualitative study, where we found that participants had very few problems using the eHealth intervention, we might have succeeded in this goal.

Due to legal regulations, we were obliged to add a disclaimer to two functionalities explaining the risk of using each of them and suggesting a more secure alternative, for example, in relation to inviting their employer, occupational physician, or general practitioner to view personal information via an email. The use of email is generally not considered a secure way to exchange information if you wish to keep the information completely confidential. Although we fully agree that it is our responsibility to inform patients about any possible harm, such warnings might cause unnecessary concern and discourage them from using the eHealth intervention at all, which might lead to otherwise preventable dropout. We therefore recommend that researchers engage the services of a legal adviser from the start when developing an eHealth intervention.

The process evaluation of the study by Bouwsma et al [30], which investigated an interactive eHealth intervention on the return to work of gynecological patients with benign tumors, showed that only half of the participants invited their employer to visit an anonymous section of the website. Most participants reported that the reason for not using this tool was “finding it unnecessary because of fast recovery and good relationship with employer” [30], while most employers reported being satisfied or very satisfied with the information provided [30]. As the return-to-work trajectories of patients with malignant tumors are significantly longer than for patients with benign tumors (median sick-leave days 102 vs 44) [43,44], we expect that there will be more substantial need to use this functionality among our population. We therefore decided to include a comparable functionality without alteration.

Implications for Further Research

One subject of further study should be the feasibility of the eHealth intervention in daily practice, and such a study should especially focus on the functionalities aimed at increasing compliance and integrative care, as we were unable to study them this feasibility study. In addition, the effectiveness of the eHealth intervention on a sustainable return to work should also be further studied, and the intermediate effect of the eHealth intervention on self-management skills and work-related self-efficacy should be analyzed (ie, a measure to study a change of ideas regarding possibilities to return to work). We are studying both of these in a multicenter randomized controlled trial.

Conclusion

A multistakeholder and mixed-method design appeared useful in the development of the eHealth intervention. However, it is challenging to meet all end users’ requirements due to legal and privacy constraints. The eHealth intervention appeared feasible, although implementation in daily practice requires further research.

Acknowledgments

This study is part of the research project Cancer@Work and was provided with a grand by the Stichting Alpe D’HuZes/KWF (Dutch Cancer Society), 2011-5061. This work was supported by COST Action IS1211 CANWON (AGEM De Boer and SJ Tamminga).

Conflicts of Interest

None declared.

Multimedia Appendix 1

Functionalities of Cancer@Work at different stages of development.

[PDF File (Adobe PDF File), 61KB - resprot_v5i2e118_app1.pdf]

Multimedia Appendix 2

Design of Cancer@Work at different stages of development.

[PDF File (Adobe PDF File), 39KB - resprot_v5i2e118_app2.pdf]

Multimedia Appendix 3

Features to increase compliance with Cancer@Work at different stages of development.

[PDF File (Adobe PDF File), 37KB - resprot_v5i2e118_app3.pdf]

Multimedia Appendix 4

Screenshot from the eHealth intervention - quiz.

[PNG File, 60KB - resprot_v5i2e118_app4.PNG]

Multimedia Appendix 5

Screenshot from the eHealth intervention - home page.

[PNG File, 135KB - resprot_v5i2e118_app5.png]

References

1. Netherlands Cancer Registry. 2016. URL: http://cijfersoverkanker.nl/ [accessed 2016-01-14] [WebCite Cache ID 6eWnxfIqv]
2. de Boer A, Taskila T, Ojajärvi A, van Dijk F, Verbeek J. Cancer survivors and unemployment: a meta-analysis and meta-regression. JAMA 2009 Feb 18;301(7):753-762. [doi: 10.1001/jama.2009.187] [Medline: 19224752]
3. Mehnert A. Employment and work-related issues in cancer survivors. Crit Rev Oncol Hematol 2011 Feb;77(2):109-130. [doi: 10.1016/j.critrevonc.2010.01.004] [Medline: 20117019]
4. Tiedtke C, de Rijk A, Dierckx de Casterlé B, Christiaens M, Donceel P. Experiences and concerns about 'returning to work' for women breast cancer survivors: a literature review. Psychooncology 2010 Jul;19(7):677-683. [doi: 10.1002/pon.1633] [Medline: 19823971]
5. Rasmussen DM, Elverdam B. The meaning of work and working life after cancer: an interview study. Psychooncology 2008 Dec;17(12):1232-1238. [doi: 10.1002/pon.1354] [Medline: 18623607]
6. Syse A, Tretli S, Kravdal O. Cancer's impact on employment and earnings: a population-based study from Norway. J Cancer Surviv 2008 Sep;2(3):149-158. [doi: 10.1007/s11764-008-0053-2] [Medline: 18792789]
7. de Boer AG, Taskila TK, Tamminga SJ, Feuerstein M, Frings-Dresen MH, Verbeek JH. Interventions to enhance return-to-work for cancer patients. Cochrane Database Syst Rev 2015;9:CD007569. [doi: 10.1002/14651858.CD007569.pub3] [Medline: 26405010]
8. Bains M, Munir F, Yarker J, Steward W, Thomas A. Return-to-work guidance and support for colorectal cancer patients: a feasibility study. Cancer Nurs 2011;34(6):E1-12. [doi: 10.1097/NCC.0b013e31820a4c68] [Medline: 21372705]
9. Tamminga SJ, de Boer AG, Bos MM, Fons G, Kitzen JJ, Plaisier PW, et al. A hospital-based work support intervention to enhance the return to work of cancer patients: a process evaluation. J Occup Rehabil 2012 Dec;22(4):565-578 [FREE Full text] [doi: 10.1007/s10926-012-9372-2] [Medline: 22699884]
10. de Boer AG, Verbeek JHAM, Spelten E, Uitterhoeve ALJ, Ansink A, de Reijke TM, et al. Work ability and return-to-work in cancer patients. Br J Cancer 2008 Apr 22;98(8):1342-1347 [FREE Full text] [doi: 10.1038/sj.bjc.6604302] [Medline: 18349834]
11. Roelen CA, Koopmans PC, Schellart AJ, van der Beek AJ. Resuming work after cancer: a prospective study of occupational register data. J Occup Rehabil 2011 Sep;21(3):431-440 [FREE Full text] [doi: 10.1007/s10926-010-9274-0] [Medline: 21153688]
12. Tamminga SJ, de Boer AG, Verbeek JH, Frings-Dresen MH. Breast cancer survivors' views of factors that influence the return-to-work process: a qualitative study. Scand J Work Environ Health 2012 Mar;38(2):144-154 [FREE Full text] [doi: 10.5271/sjweh.3199] [Medline: 21986836]
13. Tiedtke C, Donceel P, de Rijk A, Dierckx de Casterlé B. Return to work following breast cancer treatment: the employers' side. J Occup Rehabil 2014 Sep;24(3):399-409. [doi: 10.1007/s10926-013-9465-6] [Medline: 23982854]
14. Vonk Noordegraaf NA, Huirne JA, Brölmann HA, Emanuel M, van Kesteren PJ, Kleiverda G, et al. Effectiveness of a multidisciplinary care program on recovery and return to work of patients after gynaecological surgery; design of a randomized controlled trial. BMC Health Serv Res 2012;12:29 [FREE Full text] [doi: 10.1186/1472-6963-12-29] [Medline: 22296950]
15. Lambeek L, Bosmans J, Van Royen BJ, Van Tulder MW, Van Mechelen W, Anema J. Effect of integrated care for sick listed patients with chronic low back pain: economic evaluation alongside a randomised controlled trial. BMJ 2010;341:c6414 [FREE Full text] [Medline: 21118874]
16. Ruland C, Jeneson A, Andersen T, Andersen R, Slaughter L, Bente-Schjødt-Osmo, et al. Designing tailored Internet support to assist cancer patients in illness management. AMIA Annu Symp Proc 2007:635-639 [FREE Full text] [Medline: 18693913]
17. van den Berg SW, Gielissen MF, Custers JA, van der Graaf WT, Ottevanger PB, Prins JB. BREATH: Web-based self-management for psychological adjustment after primary breast cancer: results of a multicenter randomized controlled trial. J Clin Oncol 2015 Sep 1;33(25):2763-2771. [doi: 10.1200/JCO.2013.54.9386] [Medline: 26169621]
18. Volker D, Zijlstra-Vlasveld MC, Anema JR, Beekman AT, Brouwers EP, Emons WH, et al. Effectiveness of a blended web-based intervention on return to work for sick-listed employees with common mental disorders: results of a cluster randomized controlled trial. J Med Internet Res 2015;17(5):e116 [FREE Full text] [doi: 10.2196/jmir.4097] [Medline: 25972279]

19. Makai P, Perry M, Robben SH, Schers HJ, Heinen MM, Olde Rikkert MG, et al. Evaluation of an eHealth intervention in chronic care for frail older people: why adherence is the first target. J Med Internet Res 2014;16(6):e156 [FREE Full text] [doi: 10.2196/jmir.3057] [Medline: 24966146]
20. Ludden GD, van Rompay TJ, Kelders SM, van Gemert-Pijnen JE. How to increase reach and adherence of Web-based interventions: a design research viewpoint. J Med Internet Res 2015;17(7):e172 [FREE Full text] [doi: 10.2196/jmir.4201] [Medline: 26163456]
21. Barlow J, Wright C, Sheasby J, Turner A, Hainsworth J. Self-management approaches for people with chronic conditions: a review. Patient Educ Couns 2002;48(2):177-187. [Medline: 12401421]
22. Stanton A, Ganz P, Kwan L, Meyerowitz B, Bower J, Krupnick J, et al. Outcomes from the Moving Beyond Cancer psychoeducational, randomized, controlled trial with breast cancer patients. J Clin Oncol 2005 Sep 1;23(25):6009-6018 [FREE Full text] [doi: 10.1200/JCO.2005.09.101] [Medline: 16135469]
23. Detaille SI, Heerkens YF, Engels JA, van der Gulde JW, van Dijk FJ. Effect evaluation of a self-management program for Dutch workers with a chronic somatic disease: a randomized controlled trial. J Occup Rehabil 2013 Jun;23(2):189-199. [doi: 10.1007/s10926-013-9450-0] [Medline: 23690087]
24. Warmerdam L, van Straten A, Twisk J, Riper H, Cuijpers P. Internet-based treatment for adults with depressive symptoms: randomized controlled trial. J Med Internet Res 2008;10(4):e44 [FREE Full text] [doi: 10.2196/jmir.1094] [Medline: 19033149]
25. Buijs P. Huisarts en arbeid blinde vlek? Tijdschr Bedrijfs en Verzekeringsgeneeskunde 2013;21(6). [doi: 10.1007/s12498-013-0118-7]
26. Bodenheimer T, Lorig K, Holman H, Grumbach K. Patient self-management of chronic disease in primary care. JAMA 2002 Nov 20;288(19):2469-2475. [Medline: 12435261]
27. Hoving JL, Zoer I, van der Meer M, van der Straaten Y, Logtenberg-Rutten C, Kraak-Put S, et al. E-health to improve work functioning in employees with rheumatoid arthritis in rheumatology practice: a feasibility study. Scand J Rheumatol 2014;43(6):481-487. [doi: 10.3109/03009742.2014.914568] [Medline: 25178316]
28. Lambeek L, van Mechelen W, Buijs P, Loisel P, Anema J. An integrated care program to prevent work disability due to chronic low back pain: a process evaluation within a randomized controlled trial. BMC Musculoskelet Disord 2009;10:147 [FREE Full text] [doi: 10.1186/1471-2474-10-147] [Medline: 19943976]
29. Vlasveld MC, van der Feltz-Cornelis CM, Adèr HJ, Anema JR, Hoedeman R, van MW, et al. Collaborative care for sick-listed workers with major depressive disorder: a randomised controlled trial from the Netherlands Depression Initiative aimed at return to work and depressive symptoms. Occup Environ Med 2013 Apr;70(4):223-230. [doi: 10.1136/oemed-2012-100793] [Medline: 23112266]
30. Bouwsma EV, Vonk NA, Szlávik Z, Brölmann HA, Emanuel MH, Lips JP, et al. Process evaluation of a multidisciplinary care program for patients undergoing gynaecological surgery. J Occup Rehabil 2014 Sep;24(3):425-438 [FREE Full text] [doi: 10.1007/s10926-013-9475-4] [Medline: 24057871]
31. Jakicic JM, Tate DF, Lang W, Davis KK, Polzien K, Rickman AD, et al. Effect of a stepped-care intervention approach on weight loss in adults: a randomized clinical trial. JAMA 2012 Jun 27;307(24):2617-2626 [FREE Full text] [doi: 10.1001/jama.2012.6866] [Medline: 22735431]
32. van Straten A, Hill J, Richards DA, Cuijpers P. Stepped care treatment delivery for depression: a systematic review and meta-analysis. Psychol Med 2014 Mar 26:1-16. [doi: 10.1017/S0033291714000701] [Medline: 25065653]
33. van Ballegooijen W, Cuijpers P, van Straten A, Karyotaki E, Andersson G, Smit JH, et al. Adherence to Internet-based and face-to-face cognitive behavioural therapy for depression: a meta-analysis. PLoS One 2014;9(7):e100674 [FREE Full text] [doi: 10.1371/journal.pone.0100674] [Medline: 25029507]
34. Schubart JR, Stuckey HL, Ganeshamoorthy A, Sciamanna CN. Chronic health conditions and internet behavioral interventions: a review of factors to enhance user engagement. Comput Inform Nurs 2011 Feb;29(2 Suppl):TC9-T20. [doi: 10.1097/NCN.0b013e3182155274] [Medline: 21372645]
35. Spek V, Cuijpers P, Nyklícek I, Riper H, Keyzer J, Pop V. Internet-based cognitive behaviour therapy for symptoms of depression and anxiety: a meta-analysis. Psychol Med 2007 Mar;37(3):319-328. [doi: 10.1017/S0033291706008944] [Medline: 17112400]
36. Roelen CA, Koopmans PC, Groothoff JW, van der Klink JJ, Bültmann U. Return to work after cancer diagnosed in 2002, 2005 and 2008. J Occup Rehabil 2011 Sep;21(3):335-341 [FREE Full text] [doi: 10.1007/s10926-011-9319-z] [Medline: 21796373]
37. Hsieh H, Shannon SE. Three approaches to qualitative content analysis. Qual Health Res 2005 Nov;15(9):1277-1288. [doi: 10.1177/1049732305276687] [Medline: 16204405]
38. Green J. The role of theory in evidence-based health promotion practice. Health Educ Res 2000 Apr;15(2):125-129 [FREE Full text] [Medline: 10751371]
39. Amir Z, Wynn P, Chan F, Strauser D, Whitaker S, Luker K. Return to work after cancer in the UK: attitudes and experiences of line managers. J Occup Rehabil 2010 Dec;20(4):435-442. [doi: 10.1007/s10926-009-9197-9] [Medline: 19890619]
40. Ngune I, Jiwa M, McManus A, Hughes J. Do patients with long-term side effects of cancer treatment benefit from general practitioner support? A literature review. Int J Integr Care 2015;15:e023 [FREE Full text] [Medline: 26150761]

41. Statistics Netherlands. 2016. CBS URL: http://www.webcitation.org/6eWoFGysv [WebCite Cache ID 6eWoFGysv]
42. van Muijen P, Weevers NL, Snels IA, Duijts SF, Bruinvels DJ, Schellart AJ, et al. Predictors of return to work and employment in cancer survivors: a systematic review. Eur J Cancer Care (Engl) 2013 Mar;22(2):144-160. [doi: 10.1111/ecc.12033] [Medline: 23279195]
43. Vonk NA, Anema JR, van MW, Knol DL, van Baal WM, van Kesteren PJ, et al. A personalised eHealth programme reduces the duration until return to work after gynaecological surgery: results of a multicentre randomised trial. BJOG 2014 Aug;121(9):1127-35; discussion 1136 [FREE Full text] [doi: 10.1111/1471-0528.12661] [Medline: 24511914]
44. Tamminga SJ, Verbeek JH, Bos MM, Fons G, Kitzen JJ, Plaisier PW, et al. Effectiveness of a hospital-based work support intervention for female cancer patients: a multi-centre randomised controlled trial. PLoS One 2013 May;8(5):e63271 [FREE Full text] [doi: 10.1371/journal.pone.0063271] [Medline: 23717406]

Edited by G Eysenbach; submitted 26.01.16; peer-reviewed by J Verbeek, G Ludden, P Makai; comments to author 03.04.16; revised version received 28.04.16; accepted 19.05.16; published 10.06.16.

Please cite as:
Tamminga SJ, van Hezel S, de Boer AGEM, Frings-Dresen MHW
Enhancing the Return to Work of Cancer Survivors: Development and Feasibility of the Nurse-Led eHealth Intervention Cancer@Work
JMIR Res Protoc 2016;5(2):e118
URL: http://www.researchprotocols.org/2016/2/e118/
doi:10.2196/resprot.5565
PMID:27286819

Original Paper

Using Social Media Data to Identify Potential Candidates for Drug Repurposing: A Feasibility Study

Majid Rastegar-Mojarad[1,2], M Eng; Hongfang Liu[1], PhD; Priya Nambisan[2], PhD

[1]Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, United States

[2]Department of Health Informatics and Administration, UW-Milwaukee, Milwaukee, WI, United States

Corresponding Author:
Majid Rastegar-Mojarad, M Eng
Division of Biomedical Statistics and Informatics
Mayo Clinic
200 1st St SW
Rochester, MN, 55902
United States
Phone: 1 (414) 229 1122
Fax: 1 (507) 284 0745
Email: rastegar.83@gmail.com

Abstract

Background: Drug repurposing (defined as discovering new indications for existing drugs) could play a significant role in drug development, especially considering the declining success rates of developing novel drugs. Typically, new indications for existing medications are identified by accident. However, new technologies and a large number of available resources enable the development of systematic approaches to identify and validate drug-repurposing candidates. Patients today report their experiences with medications on social media and reveal side effects as well as beneficial effects of those medications.

Objective: Our aim was to assess the feasibility of using patient reviews from social media to identify potential candidates for drug repurposing.

Methods: We retrieved patient reviews of 180 medications from an online forum, WebMD. Using dictionary-based and machine learning approaches, we identified disease names in the reviews. Several publicly available resources were used to exclude comments containing known indications and adverse drug effects. After manually reviewing some of the remaining comments, we implemented a rule-based system to identify beneficial effects.

Results: The dictionary-based system and machine learning system identified 2178 and 6171 disease names respectively in 64,616 patient comments. We provided a list of 10 common patterns that patients used to report any beneficial effects or uses of medication. After manually reviewing the comments tagged by our rule-based system, we identified five potential drug repurposing candidates.

Conclusions: To our knowledge, this is the first study to consider using social media data to identify drug-repurposing candidates. We found that even a rule-based system, with a limited number of rules, could identify beneficial effect mentions in patient comments. Our preliminary study shows that social media has the potential to be used in drug repurposing.

(JMIR Res Protoc 2016;5(2):e121) doi:10.2196/resprot.5621

KEYWORDS

social media; drug repurposing; natural language processing; patient comments

Introduction

New drug development costs US $500 million to $2 billion and takes 10-15 years [1]. A well-known approach to reduce risk and cost of new drug development is drug repurposing (or drug repositioning) [2]. Drug repurposing (defined as discovering new indications for existing drugs) could play a significant role in drug development, considering the declining success rates of developing novel drugs. From 2007-2009, 30-40% of newly approved drugs were repurposed medications [3]. Considering the high cost of launching a new drug, this emphasis on repurposing could markedly affect drug development. Typically, a new indication for an available drug is identified by chance. However, new technologies and a large number of available

resources enable the development of systematic approaches to identify and validate drug repurposing candidates with considerably lower costs. Drug repurposing has been exhaustively studied, and various approaches have been used [3-5] to identify novel drug repurposing candidates, using clinical data [6], genetic information [7-9], and scientific literature [10-13].

Grau and Serbedzija [4] named two types of drug repurposing: (1) identification of off-target drug actions and (2) identification of relevance of a known drug target to a new disease. From an informatics perspective, freely available and relevant resources such as scientific literature, clinical trials, and biological resources can be used to conduct drug-repurposing studies. The compound database PubChem [14] has been used in several drug-repurposing studies [15]. Hoehndorf et al [16] implemented a system that inferred novel associations between drugs and diseases by linking drug-gene associations in the PharmGKB database to phenotype studies and animal models of disease. Moriaud et al [17] presented a computational method that mined the Protein Data Bank [18] to identify drug repositioning candidates. Several studies [10,11,16,17,19,20] considered literature mining for drug repurposing; this approach has been comprehensively reviewed elsewhere [21,22].

Social media provides a platform for patients to share their experiences with illnesses, medications, and also medical centers [23]. Patient posts, usually written in an informal language, contain hidden and valuable information. Owing to the massive amount of data derived from social media, computerized systems are needed to analyze and extract useful information from patient experience. Unlike scientific literature, these comments are usually written by non-experts users who do not have any obligation to follow proper grammar in their comments or report accurate observation. These differences make mining social media more complicated and challenging compared to scientific literature. Nevertheless, there have been several attempts to extract knowledge from social media. Leaman et al [24] examined comments posted in a medical forum to identify reported adverse drug events. After manually annotating a corpus of patient posts, they used natural language processing methods to develop a system that extracted adverse drug reactions from the text. Chee et al [25] studied patient posts on Health and Wellness Yahoo! groups and applied common natural language processing methods to predict adverse drug events and identify medications that might require further scrutiny by the Food and Drug Administration. Freifeld et al [26] evaluated the correlation between adverse drug events reported in Twitter (where statements are limited to 140 characters) and spontaneous reports received by a regulatory agency. Rastegar et al [27] implemented a binary classifier to identify adverse drug reactions in tweets. Sharif et al [28] proposed a sentiment classification framework to detect adverse drug reactions in medical blogs and forums. Recently, Karimi et al [29] provided a corpus of 1321 medical forum posts on patient-reported adverse drug events, which allows researchers to develop and evaluate pharmacovigilance systems.

Although patients mostly use medically oriented social media to describe adverse events associated with drugs [30,31], their experiences may help others to conceive of new indications for existing medications if their descriptions also include beneficial effects. A well-known example is Zolpidem, an insomnia medication that, through social media and patient reviews, was subsequently used for brain injury [32]. Leaman at el [24] identified 157 beneficial effects, in 3600 patient posts that could lead to drug repurposing. The accuracy of these reported beneficial effects in social media may be questionable, but considering the value of drug repurposing and huge amount of available social media data, it is worthwhile to study this type of information and investigate the possibility of identifying potential drug-repurposing candidates. In this study, we assessed the feasibility of using social media data in identifying potential drug repurposing candidates. Our hypothesis is that this imperfect resource could lead to drug repurposing.

Methods

Data Sources

In this study, we used data from four public resources: WebMD [33], DrugBank [34], SIDe Effect Resource (SIDER) [35], and Unified Medical Language System (UMLS) [36]. Below are brief descriptions of the resources and their uses in this research.

WebMD is an US corporation that provides Web-based health-related services, including a forum for patients to share their experiences with medications. The comments are entered as free text, and the length of comments is not subject to a character or word count limit. WebMD [33] allows users to score three different aspects of the medication in their reviews: (1) effectiveness, (2) ease of use, and (3) satisfaction. WebMD provides some basic information about the users such as age, sex, and duration of treatment. The patient comments from WebMD were the main material used in this study.

DrugBank is a bioinformatics and cheminformatics resource that provides drug information, such as indication, synonyms, gene target, drug interactions, and structure. This database was used to identify known indications of drugs.

SIDER, developed by Kuhn et al [35], contains information about 1430 marketed medications and 5880 side effects (140,064 drug-side effect pairs) extracted from public documents and package inserts. SIDER retrieved adverse drug reaction and disease names from UMLS to generate a dictionary of side effects. We used SIDER to detect known side effects of drugs mentioned in the comments.

UMLS [36] integrates medical terminology and coding standards to help researchers and developers create interoperable biomedical information systems. We used UMLS resources to create a dictionary of disease names. The dictionary contains all spelling variants of diseases provided in UMLS. The dictionary includes 239,227 entries for 86,839 unique diseases.

Method

In the first step, we generated a list of the top 180 most frequently searched medications on WebMD. All patient comments pertaining to these drugs were retrieved. Through DrugBank, we collected known and approved indications related to those medications. To locate the drugs in DrugBank, we searched synonyms and brand name entries in addition to drug

name entry. In the next step, a list of known side effects for each drug is retrieved from SIDER.

We next developed a natural language processing system to identify beneficial or adverse effects. Any mention of disorders in the reviews was tagged by using two disease named entity recognition (NER) approaches: (1) dictionary-based and (2) machine learning. In the dictionary-based approach, a list of disease names from UMLS was retrieved and a string-matching technique was applied to identify diseases mentioned in the comments. The dictionary-based approach did not consider any grammatical or semantic reasoning or spelling errors. For the machine-learning NER approach, we used MetaMap [37], a tool to recognize UMLS concepts (eg, diseases) in the text. Unlike the dictionary-based method, MetaMap uses natural language processing and computational linguistic techniques to incorporate semantic and grammatical reasoning in the identification task.

We discarded comments that contained only known indications or adverse effects for related medication. We then manually reviewed some of the remaining comments to develop a list of textual patterns commonly used to report beneficial effects or indications. We developed a rule-based system to tag the comments containing at least one of those patterns. In the final step, the tagged comments were manually reviewed to identify potential drug repurposing candidates.

Results

We retrieved 64,616 patient posts from the top 180 most commonly searched drugs in WebMD (mean number of posts per drug was 358). Lisinopril (an angiotensin-converting enzyme inhibitor used to treat high blood pressure and heart failure) had the most comments (n=2931), whereas metoclopramide (used to treat gastric esophageal reflux disease) had the fewest comments (n=8). Table 1 shows the top 10 reviewed medications and includes the three most frequently named diseases in the respective comments.

The dictionary-based NER approach identified 2178 disease names in the comments, whereas MetaMap identified 6171 disease mentions. Table 2 shows the 10 most commonly named diseases in the comments (after disambiguated terms were removed manually). Of the 180 drugs, 164 (91.1%) were listed in DrugBank but only 74 (41.1%) were listed in SIDER. We filtered comments to remove text describing known indications and adverse drug events from the list of recognized disease names; frequently named diseases from the text that remained are shown in Table 3 (note the overlap with Table 1).

Table 1. Most-reviewed medications in WebMD and most frequently named diseases in the reviews.

Drug name	Reviews, n	Disease names, n		Most frequent disease names	
		Dictionary-based	MetaMap	Dictionary-based	MetaMap
Lisinopril	2931	288	1135	Itch	Blood pressure
				High blood pressure	Cough
				Rash	Dry cough
Hydrocodone-acetaminophen	2684	320	987	Arthritis	Pain
				Itch	Back pain
				Chronic pain	Arthritis
Phentermine	1931	207	860	Dry mouth	Dry mouth
				Depression	Weight loss
				Obese	Blood pressure
Cymbalta	1651	320	1063	Depression	Depression
				Itch	Anxiety
				Fibromyalgia	Weight gain
Lexapro	1609	269	864	Depression	Depression
				Itch	Weight gain
				Panic attack	Anxiety
Effexor	1568	290	943	Depression	Depression
				Itch	Dizziness
				Panic attack	Anxiety
Tramadol	1404	261	826	Arthritis	Pain
				Fibromyalgia	Back pain
				Migraine	Dizziness
Trazodone	1305	226	701	Depression	Insomnia
				Dry mouth	Depression
				Chronic insomnia	Anxiety
Topamax	1191	271	840	Migraine	Migraine
				Gist	Headaches
				Memory loss	Tingling
Percocet	1125	245	713	Itch	Pain
				Chronic pain	Abuse
				Arthritis	Back pain

Table 2. Most frequently named diseases in reviews.

Dictionary-based		MetaMap	
Disease	Count	Disease	Count
Depression	5602	Pain	9990
Itch	3594	Depression	4921
Migraine	1610	Blood pressure	4016
Dry mouth	1269	Weight gain	3778
Infection	1218	Dizziness	3484
Panic attack	1174	Anxiety	3323
Rash	1086	Headache	2216
Arthritis	905	Nausea	1977
Fibromyalgia	850	Relief	1671
Mood swing	730	Dry mouth	1279

Table 3. Most-reviewed medications in WebMD and most frequently named diseases in the reviews after removing known indications and adverse drug events.

Drug name	Disease names, n		Most frequent disease names	
	Dictionary-based	MetaMap	Dictionary-based	MetaMap
Lisinopril	280	1124	Itch	Blood pressure
			High blood pressure	Cough
			Rash	Dry cough
Hydrocodone-acetaminophen	320	987	Arthritis	Pain
			Itch	Back pain
			Chronic pain	Arthritis
Phentermine	195	834	Depression	Weight loss
			Obese	Blood pressure
			High blood pressure	Sleeping
Cymbalta	320	1063	Depression	Depression
			Itch	Anxiety
			Fibromyalgia	Weight gain
Lexapro	269	864	Depression	Depression
			Itch	Weight gain
			Panic attack	Anxiety
Effexor	290	943	Depression	Depression
			Itch	Dizziness
			Panic attack	Anxiety
Tramadol	200	670	Fibromyalgia	Pain
			Chronic pain	Back pain
			Migraine	Headache
Trazodone	196	609	Chronic insomnia	Depression
			Migraine	Anxiety
			Fibromyalgia	Headache
Topamax	271	840	Migraine	Migraine
			Gist	Headaches
			Memory loss	Tingling
Percocet	245	713	Itch	Pain
			Chronic pain	Abuse
			Arthritis	Back pain

Textual Patterns

The frequency of ten common textual patterns, used to report beneficial effects, were counted in the comments and shown in Table 4. Table 5 shows the frequency of the patterns after removing the comments, which mentioned only known side effects or indication. A manual review of the remaining comments identified five drugs with potential for repurposing (see Table 6).

Table 4. Textual patterns to identify drug-repurposing candidates.

Pattern	Count	Example drugs and comments[a]
I use * for	307	Methadone: I use this for diabetic neuopathy. works well with very little side effects.
		Percocet: I use this for M.S. pain
		Percocet: I use this med for peripheral neuropathy pain.
I use it for	42	Cymbalta: My use of Cymbalta is two fold. I use it for depression and fibromyalgia pain.
		Spironolactone: I use it for acne. Go figure it works
		Promethazine: I use it for gastroparesis. I also use it for sleep 4 or 5 times a month
It helps with	131	Nucynta: It helps with my pain from surgery
		Percocet: it helps with my back pain, better then any drug
		Klonopin: I like this medication it helps with my anxiety.
It help with	11	OxyContin: it help with muscle spasms
		Neurontin: i had drop foot and much pain. it help with the pain along with the 3 epidurals i receiveed in my spine.
		Cymbalta: i started this medication years ago. not only did it help my depression, it help with my auto immune, muscle and nerve pain.
I take it	1,161	Nucynta: I take it for severe headache and neck pain from arthritis, bulging disks, and bone spur in my neck (cervical spine)
		Methadone: I take it for chronic pain it helps a lot
		Flexeril: I take it for muscle spasms related to fibromyalgia.
I take it for	91	Methadone: I take it for chronic pain it helps a lot
		Methadone: I take it for degenertive disk deteration in my neck.
		Hydrocodone-acetaminophen: i take it for my scholiosis of my back
It works for	258	Methocarbamol: It works for my muscle tension, but gives me a headache.
		Diazepam: it works for my pain weal good
		Tramadol: It works for my Arthritis Pain.
It is useful for	0	…
Useful for	18	Methadone: very useful for chronic and severe pain associated with fibromyalgia/rheumatoid arthritis.
		Effexor: I have been reading the reviews of this med. I have been using it for 1.5 yrs and has been very useful for my depression.
		Ultram: this med has been very useful for my hip and back pain.
Prescribed for	319	Percocet: I was prescribed for kidney stones. definately took the pain away and very high.
		Zoloft: I feel like the antidepressant is used in conjunction with my cymbalta which I am prescribed for both depression and fibromayalgia.
		Celebrex: I was prescribed for knee pain following surgery for torn muniscus.

[a]Consumer comments are shown exactly as they appeared on the WebMD site.

Table 5. Frequency of common textual patterns after removing known indications and adverse drug effects.

Pattern	Count	Example drugs and comments[a]
I use * for	171	Flector: it's not so bad. I use them for stress headaches only if I have a mild headache
		Hydroxyzine: I use this drug for itching attacks and it works fast and effective for me.
		Elavil: I use this medication for restless leg syndrom
I use it for	23	Promethazine: I use it for gastroparesis.i also use it for sleep 4 or 5 times a month
		Amitriptyline: I use it for ic
		Seroquel: I m in love with seroquel its amazing! I use it for sleep and I wake up refreshed
It helps with	72	Neurontin: it helps with numbness in my legs and arms
		Neurontin: I was diagnosed with rsd in from a fall on the ice. It helps with controlling the pain;
		Seroquel: although it helps with my depression I have gained over 50lbs
It help with	6	Oxycontin: it help with muscle spasms
		Hydrocodone-acetaminophen: it is ok I think and it help with my back pian.
		Neurontin: I had drop foot and much pain. It help with the pain along with the 3 epidurals I receiveed in my spine.
I take it	729	Methadone: I take it for chronic pain it helps alot
		Pristiq: I take it for depression and ptsd as well as for chronic pain from failed cervical fusion.
		Zoloft: I have taken it for three years almost and when I take it my depression worsens rather in the summer when I wouldnt take it I was the happiest
I take it for	48	Percocet: I take it for pain after a shoulder surgery and it works
		Buspar: I take it for stress.
		Effexor: I take it for depression.
It works for	155	Pristiq: I do not think it works for me makes me very consipated and I think it makes the back of my legs hurt in the muscle part.
		Metformin: I take it before bed no sideeffect so for taking one month hope it works for me yes I am scared
		Flexeril: back problems healed up then came right back. overall it works for a little while.
Useful for	13	Effexor: I have been reading the reviews of this med. I have been using it for 1.5 yrs and has been very useful for my depression.
		Hydrocodone-acetaminophen: this med. is useful for short term relief of pain.
		Ultram: this med has been very useful for my hip and back pain.
Prescribed for	0	…

[a]Consumer comments are shown exactly as they appeared on the WebMD site.

Table 6. Example comments suggesting the possibility of drug repurposing.

Medication	Indication	Adverse effect	Patient comments[a]
Methadone	Dry cough, drug withdrawal syndrome, opioid type drug dependence, and pain	Amenorrhea, phlebitis, sneezing, suffering, withdrawn, hypomagnesemia, urticaria, rhinorrhea, fever, spasm, …	I use this for diabetic neuopathy. Works well with very little side effects.
Elavil	Depression, chronic pain, irritable bowel syndrome, sleep disorders, diabetic neuropathy, agitation and insomnia, and migraine prophylaxis	None in SIDER	elavil is an old school antidepressant that is now considered a dirty drug because of its undesired side effects. one of the unintended side effects is to relax the skeletal muscle tissue. I use elavil off label to treat my tmj
Spironolactone	Low-renin hypertension, hypokalemia, and Conn syndrome	Hyperkalemia, amenorrhea, urticaria, epidermal necrolysis, anaphylaxis, fever, toxic epidermal necrolysis, lethargy, nausea, …	I use it for acne. go figure it works
Strattera	Attention-deficit/hyperactivity disorder, alone or in combination with behavioral treatment	None in SIDER	I was prescribed this medication for slight adhd with off label anxiety help.
Viibryd	Acute episodes of major depression	None in SIDER	It even helps my migraines somewhat (maybe it will be off label in the future for migraine prophylaxis)

[a]Consumer comments are shown exactly as they appeared on the WebMD site.

Discussion

Comparison of MetaMap Versus Dictionary-Based Approach

MetaMap is a sophisticated tool that uses natural language processing and machine learning methods; thus, it is more accurate than the dictionary-based approach. MetaMap, to some extent, tackled some general concerns such as disambiguation, misspelling, and word normalization, but none of these is addressed in the dictionary-based approach. For example, in the phrase "My stomach and back hurts to sit, lay down, or stand," the dictionary-based approach would tag "down" as a disease because of overlap with the "genetic disorder down syndrome." As Table 2 shows, MetaMap recognized about three times the number of disease names than the dictionary-based approach. The main reason for this difference is word normalization in MetaMap. The dictionary-based approach is limited by its requirement for exact matches—for example, a dictionary that contains only "dizzy" would not detect "dizziness" as a relevant word. In contrast, MetaMap uses stemming and lemmatization to normalize words. The main advantage of dictionary-based mapping over MetaMap is speed (the dictionary-based approach is considerably faster).

Using Patient Comments for Drug Repurposing

The reviews commonly described general disorders such as pain, itching, and headache. This is expected because comments usually are not authored by medical experts. We observed that patients tend to report adverse drug events instead of beneficial effects, as some of the previous studies reported a similar trend [24]. For example, in the corpus provided by Leaman et al [24], they annotated 157 beneficial effects in 3600 posts, while they found 1260 adverse drug events. Nevertheless, some patient comments contain beneficial effects of medication, which makes social media a useful resource for drug repurposing. This imbalance distribution makes identifying beneficial effects more difficult, especially for training a classifier. Our results (see Tables 4,5, and 6) suggest that an effective approach for this task is to recognize the textual patterns that people used to report beneficial effects (eg, "I use [*drug*] for [*disease*]"). For example, in a review of Viibryd , a user mentioned, "It even helps my migraines somewhat," clearly noting a beneficial effect of the drug, which could be captured by our rule-based system. Similar to other computational drug repurposing approaches, these findings need to be reviewed manually by experts and then confirmed or rejected by laboratory tests or clinical trials. But as these reviews provided by non-expert users, compared to other drug repurposing studies, which use resources provided or generated by experts such as clinical data or biomedical literature, our findings need more validation before going through clinical trials or laboratory tests.

Limitations

We acknowledge some limitations to this study. Analysis of the patient comments, which are written in an informal manner, obviously needs a system that can handle spelling and grammatical errors. Our current implementation does not address these issues.

Our system covered only simple textual patterns, although examples in Tables 4 and 5 highlight the need to decode complex patterns. A simple pattern-matching system obviously is insufficient for a statement such as "I use it for nose allergies and it does not clear up my nostrils." A system should be able to handle negation and coreference.

Another limitation of this study was that comments originated from only one forum. Other social media sites such as Yahoo! Answers, PatientsLikeMe [38], and even Twitter have similar information, which can be studied and added to our corpus. In

addition, using only one resource for known side effects and one for indication was another limitation. In Table 3, there are several known indications and adverse drug events, which highlight this limitation.

In this study, we were not able to evaluate our system precisely and provide common performance metrics because of the lack of an annotated corpus. As future work, we plan to annotate a corpus of comments from various forums, to allow us to explore this valuable resource extensively and implement and evaluate different approaches.

Conclusion

We assessed the feasibility of using social media to identify drug-repurposing candidates. After collecting patient reviews of medications from WebMD, we used dictionary-based and MetaMap approaches to identify disorders mentioned in the reviews. Reviews describing known indications or known adverse drug events were excluded, and the remaining reviews were searched for textual patterns commonly used to report beneficial effects. Although the most commonly reported disorders were nonspecific (eg, pain, itching, headache), we nevertheless showed that consumer comments contain beneficial effects of medication and have the potential to be used for drug repurposing. Our textual patterns were able to capture some beneficial effects, but there is a need for a more complex and sophisticated system to identify beneficial effects in social media.

Acknowledgments

This work was supported in part by the National Institute of General Medical Sciences R01 GM102282 and National Library of Medicine R01 LM011934.

Conflicts of Interest

None declared.

References

1. Adams CP, Brantner VV. Estimating the cost of new drug development: is it really 802 million dollars? Health Aff (Millwood) 2006;25(2):420-428 [FREE Full text] [doi: 10.1377/hlthaff.25.2.420] [Medline: 16522582]
2. Tobinick EL. The value of drug repositioning in the current pharmaceutical market. Drug News Perspect 2009 Mar;22(2):119-125. [doi: 10.1358/dnp.2009.22.2.1303818] [Medline: 19330170]
3. Jin G, Wong STC. Toward better drug repositioning: prioritizing and integrating existing methods into efficient pipelines. Drug Discov Today 2014 May;19(5):637-644 [FREE Full text] [doi: 10.1016/j.drudis.2013.11.005] [Medline: 24239728]
4. Grau D, Serbedzija G. Innovative strategies for drug repurposing. Drug Discovery & Development 2005.
5. Dudley JT, Deshpande T, Butte AJ. Exploiting drug-disease relationships for computational drug repositioning. Brief Bioinform 2011 Jul;12(4):303-311 [FREE Full text] [doi: 10.1093/bib/bbr013] [Medline: 21690101]
6. Xu H, Aldrich MC, Chen Q, Liu H, Peterson NB, Dai Q, et al. Validating drug repurposing signals using electronic health records: a case study of metformin associated with reduced cancer mortality. J Am Med Inform Assoc 2015 Jan;22(1):179-191 [FREE Full text] [doi: 10.1136/amiajnl-2014-002649] [Medline: 25053577]
7. Sanseau P, Agarwal P, Barnes MR, Pastinen T, Richards JB, Cardon LR, et al. Use of genome-wide association studies for drug repositioning. Nat Biotechnol 2012 Apr;30(4):317-320. [doi: 10.1038/nbt.2151] [Medline: 22491277]
8. Rastegar-Mojarad M, Ye Z, Kolesar JM, Hebbring SJ, Lin SM. Opportunities for drug repositioning from phenome-wide association studies. Nat Biotechnol 2015 Apr;33(4):342-345. [doi: 10.1038/nbt.3183] [Medline: 25850054]
9. Moosavinasab S, Patterson J, Strouse R, Rastegar-Mojarad M, Regan K, Payne PRO, et al. 'RE:fine drugs': an interactive dashboard to access drug repurposing opportunities. Database (Oxford) 2016 [FREE Full text] [doi: 10.1093/database/baw083] [Medline: 27189611]
10. Wei CP, Chen KA, Chen LC. Mining Biomedical Literature and Ontologies for Drug Repositioning Discovery. Advances in Knowledge Discovery and Data Mining 2014:384.
11. Rastegar-Mojarad M, Komandur Elayavilli R, Li D, Prasad R, Liu H. A new method for prioritizing drug repositioning candidates extracted by literature-based discovery. Bioinformatics and Biomedicine (BIBM) 2015:669-674.
12. Liu H, Rastegar-Mojarad M. Literature-Based Knowledge Discovery. In: Big Data Analysis for Bioinformatics and Biomedical Discoveries. Boca Raton, FL: CRC Press; 2016:233-248.
13. Rastegar-Mojarad M, Komandur Elayavilli R, Li D, Liu H. Assessing the Need of Discourse-Level Analysis in Identifying Evidences for Drug-Disease Relations in Scientific Literature. In: 15th World Congress on Health and Biomedical Informatics. 2015 Presented at: MEDINFO 2015; Aug. 19-23, 2015; Sao Paulo, Brazil.
14. Wang Y, Suzek T, Zhang J, Wang J, He S, Cheng T, et al. PubChem BioAssay: 2014 update. Nucleic Acids Res 2014 Jan;42(Database issue):D1075-D1082 [FREE Full text] [doi: 10.1093/nar/gkt978] [Medline: 24198245]
15. Cheng T, Pan Y, Hao M, Wang Y, Bryant SH. PubChem applications in drug discovery: a bibliometric analysis. Drug Discov Today 2014 Nov;19(11):1751-1756 [FREE Full text] [doi: 10.1016/j.drudis.2014.08.008] [Medline: 25168772]

16. Hoehndorf R, Oellrich A, Rebholz-Schuhmann D, Schofield PN, Gkoutos GV. Linking PharmGKB to phenotype studies and animal models of disease for drug repurposing. Pac Symp Biocomput 2012:388-399 [FREE Full text] [Medline: 22174294]
17. Moriaud F, Richard SB, Adcock SA, Chanas-Martin L, Surgand JS, Ben Jelloul M, et al. Identify drug repurposing candidates by mining the protein data bank. Brief Bioinform 2011 Jul;12(4):336-340 [FREE Full text] [doi: 10.1093/bib/bbr017] [Medline: 21768131]
18. Moriaud F, Doppelt-Azeroual O, Martin L, Oguievetskaia K, Koch K, Vorotyntsev A, et al. Computational fragment-based approach at PDB scale by protein local similarity. J Chem Inf Model 2009 Feb;49(2):280-294. [doi: 10.1021/ci8003094] [Medline: 19434830]
19. Rajpal DK, Qu XA, Freudenberg JM, Kumar VD. Mining emerging biomedical literature for understanding disease associations in drug discovery. Methods Mol Biol 2014;1159:171-206. [doi: 10.1007/978-1-4939-0709-0_11] [Medline: 24788268]
20. Tari LB, Patel JH. Systematic drug repurposing through text mining. Methods Mol Biol 2014;1159:253-267. [doi: 10.1007/978-1-4939-0709-0_14] [Medline: 24788271]
21. Xu R, Wang Q. Large-scale extraction of accurate drug-disease treatment pairs from biomedical literature for drug repurposing. BMC Bioinformatics 2013;14:181 [FREE Full text] [doi: 10.1186/1471-2105-14-181] [Medline: 23742147]
22. Deftereos SN, Andronis C, Friedla EJ, Persidis A, Persidis A. Drug repurposing and adverse event prediction using high-throughput literature analysis. Wiley Interdiscip Rev Syst Biol Med 2011;3(3):323-334. [doi: 10.1002/wsbm.147] [Medline: 21416632]
23. Rastegar-Mojarad M, Ye Z, Wall D, Murali N, Lin S. Collecting and Analyzing Patient Experiences of Health Care From Social Media. JMIR Res Protoc 2015;4(3):e78 [FREE Full text] [doi: 10.2196/resprot.3433] [Medline: 26137885]
24. Leaman R, Wojtulewicz L, Sullivan R, Skariah A, Yang J, Gonzalez G. Towards internet-age pharmacovigilance: extracting adverse drug reactions from user posts to health-related social networks. In: BioNLP. 2010 Presented at: BioNLP; 2010; Stroudsburg, PA p. 117-125.
25. Chee BW, Berlin R, Schatz B. Predicting adverse drug events from personal health messages. AMIA Annu Symp Proc 2011;2011:217-226 [FREE Full text] [Medline: 22195073]
26. Freifeld CC, Brownstein JS, Menone CM, Bao W, Filice R, Kass-Hout T, et al. Digital drug safety surveillance: monitoring pharmaceutical products in twitter. Drug Saf 2014 May;37(5):343-350 [FREE Full text] [doi: 10.1007/s40264-014-0155-x] [Medline: 24777653]
27. Rastegar-Mojarad M, Komandur Elayavilli R, Yu Y, Hiu H. Detecting signals in noisy data - can ensemble classifiers help identify adverse drug reaction in tweets? In: Proceedings of the Social Media Mining Shared Task Workshop. 2015 Presented at: Pacific Symposium on Biocomputing; Jan. 4-8, 2015; Big Island, HI.
28. Sharif H, Zaffar F, Abbasi A, Zimbra D. Detecting Adverse Drug Reactions Using a Sentiment Classification Framework. Academy of Science and Engineering 2014.
29. Karimi S, Metke-Jimenez A, Kemp M, Wang C. Cadec: A corpus of adverse drug event annotations. J Biomed Inform 2015 Jun;55:73-81. [doi: 10.1016/j.jbi.2015.03.010] [Medline: 25817970]
30. Harpaz R, DuMouchel W, Shah NH, Madigan D, Ryan P, Friedman C. Novel data-mining methodologies for adverse drug event discovery and analysis. Clin Pharmacol Ther 2012 Jun;91(6):1010-1021 [FREE Full text] [doi: 10.1038/clpt.2012.50] [Medline: 22549283]
31. Yang C, Yang H, Jiang L, Zhang M. Social media mining for drug safety signal detection. 2012 Presented at: International Workshop on Smart Health and Wellbeing; 2012; New York, NY p. 33-40.
32. Boggan S. The Guardian. The miracle treatment that's bringing the brain-damaged back to life URL: https://www.theguardian.com/science/2006/sep/12/health.healthandwellbeing [accessed 2016-05-25] [WebCite Cache ID 6hlsT18dn]
33. WebMD. WebMD Drugs & Medications - Medical information on prescription drugs, vitamins and over-the-counter medicines URL: http://www.webmd.com/drugs/index-drugs.aspx [accessed 2016-05-25] [WebCite Cache ID 6hlsa2B5O]
34. Knox C, Law V, Jewison T, Liu P, Ly S, Frolkis A, et al. DrugBank 3.0: a comprehensive resource for 'omics' research on drugs. Nucleic Acids Res 2011 Jan;39(Database issue):D1035-D1041 [FREE Full text] [doi: 10.1093/nar/gkq1126] [Medline: 21059682]
35. Kuhn M, Campillos M, Letunic I, Jensen LJ, Bork P. A side effect resource to capture phenotypic effects of drugs. Mol Syst Biol 2010;6:343 [FREE Full text] [doi: 10.1038/msb.2009.98] [Medline: 20087340]
36. Bodenreider O. The Unified Medical Language System (UMLS): integrating biomedical terminology. Nucleic Acids Res 2004 Jan 1;32(Database issue):D267-D270 [FREE Full text] [doi: 10.1093/nar/gkh061] [Medline: 14681409]
37. Aronson AR. Effective mapping of biomedical text to the UMLS Metathesaurus: the MetaMap program. Proc AMIA Symp 2001:17-21 [FREE Full text] [Medline: 11825149]
38. PatientsLikeMe. URL: https://www.patientslikeme.com/ [accessed 2016-05-25] [WebCite Cache ID 6hlsohsRw]

Abbreviations

NER: named entity recognition

SIDER: SIDe Effect Resource
UMLS: Unified Medical Language System

Edited by G Eysenbach; submitted 08.02.16; peer-reviewed by M Torii, C Freifeld; comments to author 28.03.16; revised version received 14.04.16; accepted 15.04.16; published 16.06.16.

Please cite as:
Rastegar-Mojarad M, Liu H, Nambisan P
Using Social Media Data to Identify Potential Candidates for Drug Repurposing: A Feasibility Study
JMIR Res Protoc 2016;5(2):e121
URL: http://www.researchprotocols.org/2016/2/e121/
doi:10.2196/resprot.5621
PMID:27311964

Original Paper

Electronic Adherence Monitoring in a High-Utilizing Pediatric Asthma Cohort: A Feasibility Study

Chén Collin Kenyon[1], MD, MSc; Joyce Chang[2], MD; Sheri-Ann Wynter[3], MD; Jessica C Fowler[2], MD, MPH; Jin Long[2], PhD; Tyra C Bryant-Stephens[2], MD

[1]Center for Pediatric Clinical Effectiveness and PolicyLab, Department of Pediatrics, The Children's Hospital of Philadelphia, Philadelphia, PA, United States

[2]Department of Pediatrics, The Children's Hospital of Philadelphia, Philadelphia, PA, United States

[3]Department of Pediatrics, New York University School of Medicine, New York, NY, United States

Corresponding Author:
Chén Collin Kenyon, MD, MSc
Center for Pediatric Clinical Effectiveness and PolicyLab
Department of Pediatrics
The Children's Hospital of Philadelphia
3401 Civic Center Blvd, CHOP North
15th floor, Rm 1509
Philadelphia, PA, 19104
United States
Phone: 1 267 426 6339
Fax: 1 215 590 1269
Email: kenyonc@email.chop.edu

Abstract

Background: Inner-city, minority children with asthma have the highest rates of morbidity and death from asthma and the lowest rates of asthma controller medication adherence. Some recent electronic medication monitoring interventions demonstrated dramatic improvements in adherence in lower-risk populations. The feasibility and acceptability of such an intervention in the highest-risk children with asthma has not been studied.

Objective: Our objective was to assess the feasibility and acceptability of a community health worker-delivered electronic adherence monitoring intervention among the highest utilizers of acute asthma care in an inner-city practice.

Methods: This was a prospective cohort pilot study targeting children with the highest frequency of asthma-related emergency department and hospital care within a local managed care Medicaid plan. The 3-month intervention included motivational interviewing, electronic monitoring of controller and rescue inhaler use, and outreach by a community health worker for predefined medication alerts. We measured acceptability by using a modified technology acceptability model and changes in asthma control using the Asthma Control Test (ACT). Given prominent feasibility issues, we describe qualitative patterns of medication use at baseline only.

Results: We enrolled 14 non-Hispanic black children with a median age of 3.5 years. Participants averaged 7.8 emergency or hospital visits in the year preceding enrollment. We observed three distinct patterns of baseline controller use: 4 patients demonstrated sustained use, 5 patients had periodic use, and 5 patients lapsed within 2 weeks. All participants initiated use of the electronic devices; however, no modem signal was transmitted for 5 or the 14 participants after a mean of 45 days. Of the 9 (64% of total) caregivers who completed the final study visit, all viewed the electronic monitoring device favorably and would recommend it to friends, and 5 (56%) believed that the device helped to improve asthma control. ACT scores improved by a mean of 2.7 points (P=.05) over the 3-month intervention.

Conclusions: High-utilizer, minority families who completed a community health worker-delivered electronic adherence intervention found it generally acceptable. Prominent feasibility concerns, however, such as recruitment, data transmission failure, and lost devices, should be carefully considered when designing interventions in this setting.

(JMIR Res Protoc 2016;5(2):e132) doi:10.2196/resprot.5362

KEYWORDS

electronic medication monitoring; adherence; beta-agonists; inhaled steroids; motivational interviewing; community health workers

Introduction

Inner-city children with asthma experience high morbidity and mortality from persistent asthma [1-3]. Compared with their white counterparts, non-Hispanic black children have four times the rate of asthma-related emergency department visits, three times the rate of hospitalization, and five times the mortality. These disparities in adverse asthma outcomes have persisted over time despite advances in treatment [4].

Inhaled corticosteroids (ICS) remain the mainstay of therapy for persistent asthma [5]. However, suboptimal adherence to ICS regimens is a major barrier to achieving asthma control [6]. Self-reported adherence is unreliable and consistently overestimates medication use [7,8]. Actual ICS adherence rates measured using electronic monitoring in clinical studies are low for both adults and children [9-11]. Poor adherence to controller regimens is associated with poor asthma control [12], increased utilization of emergency and hospital care [13,14], and higher mortality from asthma [15,16]. Urban minority youth in particular demonstrate some of the lowest rates of adherence, ranging from 11% to 45% of prescribed doses [11,17-19]. Better strategies to improve adherence are needed to engage this patient population, especially for those experiencing high levels of asthma morbidity. In this setting, interventions involving community health workers have demonstrated great promise [20-22].

Electronic monitoring is a strategy used in a variety of settings to measure and increase medication adherence among patients with chronic conditions [23-26]. Studies in adults with asthma have shown that electronic monitoring interventions can increase adherence to ICS regimens [27-29]. In the few pilot studies of electronic monitoring interventions done in children, behavior modification strategies that included direct feedback about electronically monitored adherence were thought to be critical components of the strategies' success [30-34]. Motivational interviewing is a behavior modification strategy that has also been shown to improve medication adherence [35,36], and it helps address barriers to adherence such as parental beliefs about medications [37]. Thus far, electronic monitoring studies have not focused on the highest utilizers of emergency and hospital care among inner-city, minority children with asthma. By targeting this highest-risk group, an electronic adherence intervention could have a greater impact on health care utilization, cost of care, health disparities, and quality of life [38].

In this study, we sought to assess the acceptability and feasibility of an intervention that combined the community health worker strength of family engagement and the technologic benefits of electronic medication monitoring in a high morbidity patient cohort. Prior to developing large-scale trials, we posited that first exploring acceptability and feasibility issues in this high-risk population would be critical, especially given the complex social, economic, and cultural factors. In this study, we sought to assess caregiver attitudes toward monitoring and ease of use of the devices, as well as acceptable modes and frequency of feedback, in the families of children with the highest health care utilization for asthma.

Methods

We conducted a single-center, prospective cohort study of children with moderate to severe persistent asthma to assess the feasibility of a larger-scale intervention to improve adherence to asthma medications. The protocol for the conduct of this study was approved by The Children's Hospital of Philadelphia Institutional Review Board.

Study Participants

Eligible participants were children aged 3 through 16 years who received their primary care at an academic primary care clinic in West Philadelphia affiliated with The Children's Hospital of Philadelphia, Philadelphia, PA, USA. Additional inclusion criteria were 1) enrollment in a local Medicaid managed care plan (Keystone First, Philadelphia, PA, USA), and 2) identification as a "high utilizer" of hospital and emergency services for asthma. For the purposes of this study, we defined a high utilizer as a patient whose frequency of emergency department and hospital use for asthma-related reasons was in the top 50 in the year preceding the study. Our target enrollment was 15 to 20 patients for this feasibility study. Patients were excluded from the study if they were ≥17 years of age, or had congenital heart disease, neurologic disorders, cystic fibrosis, or other chronic respiratory conditions and structural abnormalities of the upper or lower airway. Children younger than 3 years were excluded, as other wheezing illnesses may confound the diagnosis of asthma in this age group.

Recruitment

We identified 50 potentially eligible participants using health insurance claims for the preceding year provided by the Medicaid managed care organization. An asthma navigator (a community health worker with background expertise and training in the care of children and families with asthma) contacted eligible families sequentially until 20 patients were scheduled for an initial visit. A total of 15 patients had an initial visit and 14 were enrolled in the study.

Intervention

The study intervention included 1) motivational interviewing, 2) electronic monitoring of adherence to prescribed inhaler regimens (controller and rescue medications), and 3) outreach by the asthma navigator based on specific, predefined inhaler use criteria.

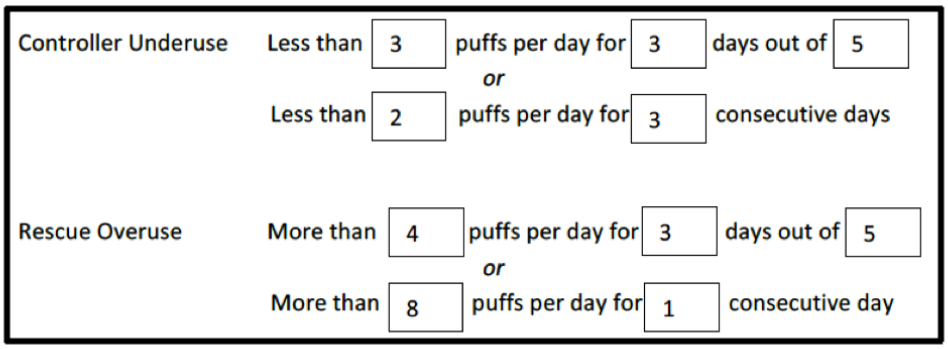
Prior to study participant enrollment, study staff members (including the asthma navigator and the study physicians) received two training sessions in motivational interviewing by experts experienced in this technique. These sessions included lectures, videos, role play of modeled behaviors, and feedback.

Participant families were asked to list their three primary barriers to medication adherence at the initial study visit; these barriers were addressed using motivational interviewing techniques by the asthma navigator and, if necessary, a study physician (CK, JC, SW, or JF). Examples of such barriers were not remembering to take medications, concerns about ICS side effects, and perceptions about the severity of the child's asthma that differed from the perceptions of the child's clinical team. Counseling techniques for the initial visit and follow-up calls were based on strategies outlined in a review of brief motivational interviewing for asthma medication adherence by Borrelli et al [39]. To ensure fidelity of delivery, the research team developed prompts to standardize the initial portion of the telephone encounters and participated in intermittent direct observation of counseling by the asthma navigator.

Each family received SmartTouch (Adherium, Auckland, New Zealand) electronic monitoring devices for both the controller and rescue medication. SmartTouch monitors are electronic adherence monitors that can be affixed to the exterior of patients' inhalers. Previous versions of these devices have shown both good reliability and validity in monitoring daily inhaler use [38]. Study staff affixed these devices to participants' rescue and controller inhalers. In the case that participants did not bring their inhalers to the first study visit or had less than a month's supply remaining, we provided participants with new rescue (albuterol) and controller inhalers (fluticasone or fluticasone-salmeterol) to ensure availability. The electronic devices transmitted inhaler usage information to a cellular modem in the home, which we also provided. Medication usage data were then uploaded to a US Food and Drug Administration-approved, Health Insurance Portability and Accountability Act-compliant website [50]. Medication usage alerts were registered for overuse of rescue medications and underuse or overuse of controller medications at predetermined frequencies (Figure 1). Families were encouraged at enrollment to take their controller medications as directed by their primary care doctor and to continue with daily and rescue asthma care as they usually would. We provided them with chargers for the devices, and instructed them on how to monitor battery life and to charge the devices when battery life was low (indicated by a red light).

The asthma navigator and a study physician (CK) actively monitored the electronic monitoring website for medication alerts. The asthma navigator contacted families after the initial study visit to ensure the study modem was connected and that the system was transmitting inhaler usage data to the monitoring website. Study staff made no subsequent contact with families for the first month to allow participants' medication use patterns to return to their baseline. After this observation period and for the subsequent 2 months, when alerts were triggered for controller medication underuse, the asthma navigator contacted families and used motivational interviewing techniques to address suboptimal adherence. The asthma navigator monitored the site daily, except on weekends. For those with persistent daily alerts beyond 2 consecutive days, calls were attempted twice weekly. In the case of rescue medication overuse, the family was instructed to call the clinic triage nurse to determine whether a clinic appointment was needed for an asthma exacerbation. We provided basic cell phones with unlimited minutes and text messaging to families to facilitate communication with study staff during the study period.

Figure 1. Thresholds for asthma medication alerts (based on controller schedule of 2 puffs twice a day).



Outcomes

The primary outcomes for this study were acceptability and feasibility. To measure acceptance of the electronic monitoring technology, we assessed the perceived ease of use, result demonstrability, and perceived usefulness of the new technology using these subscales from the previously validated technology acceptance model instrument [40,41]. For our evaluation of feasibility, we assessed the functionality of the technology, initiation and duration of use of the electronic monitors by the caregivers of study participants, and the ability to contact study participants in response to adherence alerts.

Secondary outcomes were asthma control and daily adherence. We assessed parental perception of asthma control with the Asthma Control Test (ACT) [42]. An ACT score of ≤19 is consistent with uncontrolled asthma. ACT questionnaires were completed by participants with the asthma navigator at the initial visit and follow-up visit, and scores were recorded for comparison at the end of the study. Daily adherence was captured using the electronic monitoring devices.

Analysis

We used descriptive statistics to characterize study participants' demographic composition, prior health care utilization, and responses to the modified technology acceptance model

questionnaire. We identified qualitative patterns of daily controller use in the month preceding asthma navigator contact with the family based on two criteria: the percentage of days in the observation window with controller actuations; and runs of consecutive days with controller actuations (see Patterns subsection of Results section). We used both paired *t* tests and Wilcoxon signed rank sum test to compare ACT scores at the start of the study with scores at the completion of the study based on the assumption of the data with and without normality. The American Thoracic Society suggests that the minimally clinically significant ACT score change is 3 points [43].

Results

Of the 50 highest utilizers of emergency asthma care, we enrolled 14 patients for this study, of whom 6 (43%) were female. Their median age was 3.5 years (range 3–9), and all families identified their race as non-Hispanic black. Enrolled participants had a mean of 7.8 (range 5–15) combined emergency visits and hospitalizations in the preceding year, and the mean ACT score at the first visit was 15.9 (range 9–24) (Table 1).

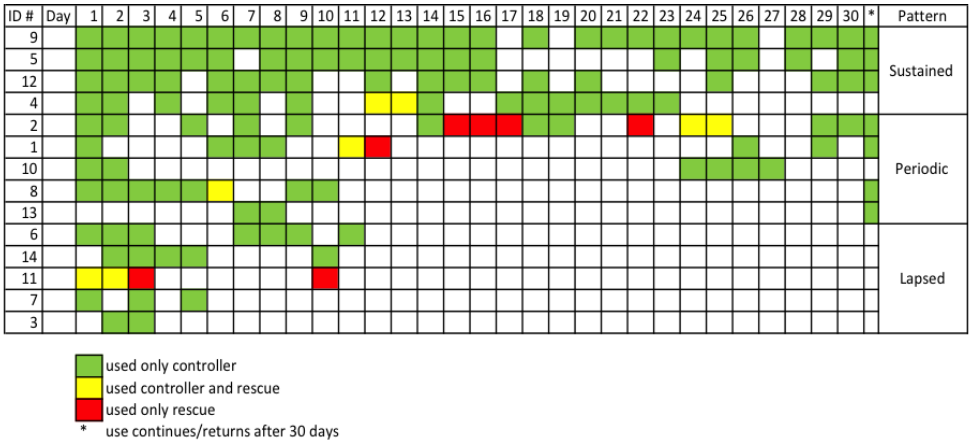
Table 1. Participant characteristics (n=14).

Characteristics	Median (range) or n (%)
Age in years, median (range)	3.5 (3–9)
Female, n (%)	6 (43)
Race/ethnicity non-Hispanic black, n (%)	14 (100)
Prior emergency visits and hospitalizations, mean (range)	7.8 (5–15)
Asthma Control Test score, mean (range)	15.9 (9–24)
Baseline adherence pattern, n (%)	
Sustained	4 (29)
Periodic	5 (36)
Lapsed	5 (36)

Baseline Patterns

We identified distinct patterns of controller use over the first 30 days of the study interval (Figure 2): 4 patients had sustained use (>50% of days with use and <7 consecutive days of missed doses), 5 patients had periodic use (<50% of days with use with >7 consecutive days with no use), and 5 patients had lapsed use (<50% of days with use and no return of use after 14 days).

Figure 2. Patterns of asthma controller and rescue medication use in the first 30 days of the study. ID#: participant identification number.



Acceptability

Of the 14 caregivers, 9 (64%) completed the modified technology acceptance model questionnaire at the final study visit. All 9 found the electronic monitoring devices to be easy to use, saw clear benefit in the devices, and would recommend the devices to others, and 5 (56%) of these caregivers felt that the device itself actually helped to improve asthma control. A total of 8 families (89%) felt that the devices were small enough to carry easily.

Feasibility

All 14 participants initiated use of the electronic monitors; however, no modem signal was transmitted for 5 of them after a mean of 45 days. Of the 9 caregivers who completed the final study visit, 2 had lost one of the monitoring devices; we were not able to retrieve the 10 devices from the 5 caregivers who did not complete the final study visit. Thus, in total, 16 of the 28 electronic monitoring devices were returned, and 10 of them (63%) were either uncharged or no longer responding to a charge. Families who disconnected their cellular modems noted competition for use of the electrical outlets and concerns about

the additional use of electricity contributing to their electricity bills. Because of these issues with data capture during the intervention window, we report adherence data for only the first 30 days of the intervention, when all participants had a transmitting modem signal.

Telephone contact was achieved with all participants (up to 2 calls per week for those with frequent adherence alerts) and ranged from short messages on their answering services to 10-minute calls to troubleshoot device issues or adherence lapses. Of the 9 caregivers who completed the final study visit, all were happy with the relationship they had with the asthma navigator, none felt that she contacted them too frequently, and 8 of them (89%) believed calls from the asthma navigator helped to avoid missing doses.

Limited Efficacy

Though the study was not powered to detect a change in asthma control, mean ACT score improved by 2.7 points (95% CI 0–5.5, *P*=.05) over the duration of the study, just below the minimally significant ACT change threshold of 3 points.

Loss to Follow-Up

The 5 caregivers who did not complete the final study visit were either unable to be contacted or unable to schedule and complete the final study visit following at least five attempts by the study team. Of these 5 participants, 3 were female, their median age was 3, and mean baseline ACT was 17.8 points, none of which were statistically significantly different from the characteristics of those who completed the final study visit.

Discussion

In this study, we partnered with a local managed care Medicaid plan to assess the feasibility of an electronic monitoring intervention for high-risk inner-city minority children with asthma. To our knowledge, this is the first study to assess the acceptability and feasibility of an electronic monitoring intervention delivered by a community health worker in the highest-risk children with asthma. With respect to feasibility, our findings demonstrate several prominent challenges in the delivery and sustainability of this intervention. While all 9 of the caregivers who completed the final study visit found the technology and monitoring devices acceptable, we were not able to complete the survey for 5 families (36%). And while all of the families initiated use of the monitoring technology, half of the caregivers either unplugged the cellular modem or lost the monitoring devices, leading to difficulty in interpretation of adherence data beyond the initial observation month. Despite these challenges, we noted a trend toward improved asthma control over the study interval, and we noted some qualitatively distinct patterns of ICS use from the observation period of this study that may inform future inquiry and interventions in high-risk asthma populations.

Studies have demonstrated that electronic monitoring of ICS adherence with some form of feedback can improve medication adherence in selected populations. In a recent randomized trial of patients ages 14–65 years with poorly controlled asthma in Australia, patients who received inhaler reminders and feedback demonstrated adherence rates of 73% compared with 46% in the groups that had usual care or personalized adherence discussions [29]. A randomized trial of electronic monitoring with an audiovisual reminder in children 6–15 years old conducted in New Zealand demonstrated rates of adherence of 84% in the intervention group compared with 30% in the control [34]. An earlier review of electronic monitoring of inhaler use described the accuracy and reliability of newer electronic monitoring devices and efficacy of monitoring and feedback interventions, but highlighted feasibility concerns in vulnerable populations, including “the patient’s ability and willingness to use electronic monitoring devices” [38]. Our study offers a first glimpse of feasibility issues in a high-utilizer, inner-city minority cohort of children in the United States.

One of our primary concerns prior to launching this study was that inner-city minority families might feel that electronic monitoring interventions are overly intrusive and, thus, unacceptable. In this small study, we found no evidence to suggest this, though only 9 families (64%) completed the acceptability survey. A total of 5 (36%) families did not complete the final study visit and, though we cannot be sure of the reasons why they did not follow-up, this relatively high rate of loss to follow-up could be interpreted as their revealed lack of acceptability.

Another prominent feasibility question was whether families would initiate and maintain use of the devices. Our findings show that, while all the enrolled families effectively set up and began to use the electronic monitoring systems, there were challenges in maintaining the devices and data transmission. Several families unplugged the modem devices either temporarily or permanently, noting competition for available electrical outlets and concerns about electricity bills. Also, many of the monitoring devices that were returned had no remaining charge. These issues might have been mitigated at the onset of the study by including a power strip and communicating the negligible daily use of electricity of the cellular modem and charging devices.

With respect to outcomes, while the study was not designed to detect an improvement in asthma control, we found a statistically, but just short of clinically, significant improvement in ACT score over the course of the study for those who completed both study visits. It is important to note, however, that the study was uncontrolled; improvements in parental perception of asthma control may reflect regression to the mean or a placebo effect. We also noted distinct patterns of medication use over the first month of the study, prior to the initiating outreach for adherence alerts. Different patterns of daily medication use have been noted in one prior study of asthma in adults [44], as well as in pediatric conditions such as epilepsy [45], inflammatory bowel disease [46], and cancer [47]. While these categories have different labels in each prior study, further research should be directed at learning which potentially modifiable factors drive more sustained use patterns; this may assist families with lapsed or periodic use patterns in improving the consistency and duration of their controller medication use.

Based on the findings of this feasibility study, we offer a few considerations for future studies seeking to use electronic medication monitoring to improve the care of high-risk

populations. Investigators should 1) establish regular communication with the electronic device company and gain assurance that there is robust technological support to troubleshoot technological issues that arise during the intervention, 2) consider practical issues such as competition for electrical outlets within the house and cellular or wireless coverage in the community of interest that might affect data transmission, and 3) include team members with knowledge and credibility in the community (such as community health workers) who can assist in recruitment and outreach and help elicit subtle reasons for changes in medication use or data transmission.

Our study has a few limitations. First, since this was a feasibility study, the sample size was small and restricted to one clinic population. Thus, the feasibility concerns we present may not be representative of high-risk populations in other settings. Second, the families who agreed to participate in the study (and completed the final study visit) may have been more open to and accepting of any type of intervention, inclusive of electronic monitoring, than other high utilizers or the general population. Participants' ratings of acceptability may have been further enhanced by the receipt of a cellular phone with unlimited minutes and by social desirability bias, as this outcome was collected by a member of the study team (the asthma navigator). The feasibility of wide-scale provision of cellular phones for high-risk families would depend on the cost effectiveness of similar interventions, an outcome beyond the scope of this study. With respect to our assessment of asthma control, we assessed parental perception of asthma control using the ACT, since the median age of patients in our cohort was 3.5 years and there are no validated measures of asthma control in children younger than 4 years. More broadly, the children in our cohort were young, with the oldest child enrolled being 9 years old. Because of this, our results may not be generalizable to older children, who tend to have greater responsibility for administering their medication [48].

With respect to adherence outcomes, we used different adherence categories than an earlier adult asthma study [44] for two reasons: 1) we were not able to capture multiple inhaler actuations occurring in the same minute in the first month of the study, and 2) even with our most conservative estimate, none of our participating patients met their criteria for "compliance" (75% of prescribed doses). Lastly, our assessment of adherence beyond 1 month was substantially limited by incomplete data resulting from causes such as unplugged cellular modems and uncharged monitoring devices. Therefore, we have presented medication use data for only the first month of the study prior to the onset of these issues, but also prior to the onset of the outreach intervention.

As payers, health systems, and providers seek new approaches to improving the care of high-risk populations, new or adapted technologies for "automated hovering" offer the potential to influence the 5000 hours that patients spend outside of the reach of the health care system [49]. While some electronic ICS monitoring interventions have shown promise in other populations, our findings demonstrate some of the prominent feasibility challenges of implementation in adapting such an intervention to a vulnerable patient cohort, even despite the strength of having a community-based peer as our effector arm. The findings of this study can be used to both anticipate challenges when planning future interventions and specify areas of future inquiry germane to understanding medication use behaviors of high-risk populations.

Acknowledgments

This work was supported by funding from and program staff at Keystone First. The authors have no financial disclosures. We thank Andrew Weinstein, MD, Meg Grant, Lily Higgins, MD, Steven Dinsmore, and John Holland, PhD, for their assistance in the conception and development of the study protocol and review of manuscript drafts. We thank Charmaine Braxton for her work in the execution of the study and commitment to improving the health of children with asthma in West Philadelphia.

Conflicts of Interest

None declared.

References

1. Rand CS, Butz AM, Kolodner K, Huss K, Eggleston P, Malveaux F. Emergency department visits by urban African American children with asthma. J Allergy Clin Immunol 2000 Jan;105(1 Pt 1):83-90. [Medline: 10629457]
2. Thakur N, Martin M, Castellanos E, Oh SS, Roth LA, Eng C, et al. Socioeconomic status and asthma control in African American youth in SAGE II. J Asthma 2014 Sep;51(7):720-728 [FREE Full text] [doi: 10.3109/02770903.2014.905593] [Medline: 24654704]
3. Bryant-Stephens T. Asthma disparities in urban environments. J Allergy Clin Immunol 2009 Jun;123(6):1199-206; quiz 1207. [doi: 10.1016/j.jaci.2009.04.030] [Medline: 19501229]
4. Akinbami L, Moorman J, Garbe P, Sondik E. Status of childhood asthma in the United States, 1980-2007. Pediatrics 2009 Mar;123 Suppl 3:S131-S145. [doi: 10.1542/peds.2008-2233C] [Medline: 19221156]
5. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J Allergy Clin Immunol 2007 Nov;120(5 Suppl):S94-138. [doi: 10.1016/j.jaci.2007.09.043] [Medline: 17983880]

6. Williams LK, Peterson EL, Wells K, Ahmedani BK, Kumar R, Burchard EG, et al. Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid nonadherence. J Allergy Clin Immunol 2011 Dec;128(6):1185-1191.e2 [FREE Full text] [doi: 10.1016/j.jaci.2011.09.011] [Medline: 22019090]
7. Bender B, Bartlett S, Rand C, Turner C, Wamboldt F, Zhang L. Impact of interview mode on accuracy of child and parent report of adherence with asthma-controller medication. Pediatrics 2007 Sep;120(3):e471-e477. [doi: 10.1542/peds.2006-3457] [Medline: 17698578]
8. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005 Aug 4;353(5):487-497. [doi: 10.1056/NEJMra050100] [Medline: 16079372]
9. Milgrom H, Bender B, Ackerson L, Bowry P, Smith B, Rand C. Noncompliance and treatment failure in children with asthma. J Allergy Clin Immunol 1996 Dec;98(6 Pt 1):1051-1057. [Medline: 8977504]
10. Naimi D, Freedman T, Ginsburg K, Bogen D, Rand C, Apter A. Adolescents and asthma: why bother with our meds? J Allergy Clin Immunol 2009 Jun;123(6):1335-1341 [FREE Full text] [doi: 10.1016/j.jaci.2009.02.022] [Medline: 19395075]
11. Bender B, Wamboldt F, O'Connor SL, Rand C, Szefler S, Milgrom H, et al. Measurement of children's asthma medication adherence by self report, mother report, canister weight, and Doser CT. Ann Allergy Asthma Immunol 2000 Nov;85(5):416-421. [Medline: 11101187]
12. Jentzsch N, Camargos P, Sarinho ESC, Bousquet J. Adherence rate to beclomethasone dipropionate and the level of asthma control. Respir Med 2012 Mar;106(3):338-343 [FREE Full text] [doi: 10.1016/j.rmed.2011.12.001] [Medline: 22188844]
13. Ordoñez GA, Phelan PD, Olinsky A, Robertson CF. Preventable factors in hospital admissions for asthma. Arch Dis Child 1998 Feb;78(2):143-147 [FREE Full text] [Medline: 9579156]
14. Farber HJ, Chi FW, Capra A, Jensvold NG, Finkelstein JA, Lozano P, et al. Use of asthma medication dispensing patterns to predict risk of adverse health outcomes: a study of Medicaid-insured children in managed care programs. Ann Allergy Asthma Immunol 2004 Mar;92(3):319-328. [doi: 10.1016/S1081-1206(10)61569-4] [Medline: 15049395]
15. Birkhead G, Attaway N, Strunk R, Townsend M, Teutsch S. Investigation of a cluster of deaths of adolescents from asthma: evidence implicating inadequate treatment and poor patient adherence with medications. J Allergy Clin Immunol 1989 Oct;84(4 Pt 1):484-491. [Medline: 2794293]
16. Robertson C, Rubinfeld A, Bowes G. Pediatric asthma deaths in Victoria: the mild are at risk. Pediatr Pulmonol 1992 Jun;13(2):95-100. [Medline: 1495863]
17. Celano M, Linzer J, Demi A, Bakeman R, Smith C, Croft S, et al. Treatment adherence among low-income, African American children with persistent asthma. J Asthma 2010 Apr;47(3):317-322. [doi: 10.3109/02770900903580850] [Medline: 20394517]
18. Farber H, Johnson C, Beckerman R. Young inner-city children visiting the emergency room (ER) for asthma: risk factors and chronic care behaviors. J Asthma 1998;35(7):547-552. [Medline: 9777881]
19. Rohan J, Drotar D, McNally K, Schluchter M, Riekert K, Vavrek P, et al. Adherence to pediatric asthma treatment in economically disadvantaged African-American children and adolescents: an application of growth curve analysis. J Pediatr Psychol 2010 May;35(4):394-404 [FREE Full text] [doi: 10.1093/jpepsy/jsp074] [Medline: 19710251]
20. Krieger JW, Takaro TK, Song L, Weaver M. The Seattle-King County Healthy Homes Project: a randomized, controlled trial of a community health worker intervention to decrease exposure to indoor asthma triggers. Am J Public Health 2005 Apr;95(4):652-659. [doi: 10.2105/AJPH.2004.042994] [Medline: 15798126]
21. Bryant-Stephens T, Kurian C, Guo R, Zhao H. Impact of a household environmental intervention delivered by lay health workers on asthma symptom control in urban, disadvantaged children with asthma. Am J Public Health 2009 Nov;99 Suppl 3:S657-S665. [doi: 10.2105/AJPH.2009.165423] [Medline: 19890172]
22. Fisher E, Strunk R, Highstein G, Kelley-Sykes R, Tarr K, Trinkaus K, et al. A randomized controlled evaluation of the effect of community health workers on hospitalization for asthma: the asthma coach. Arch Pediatr Adolesc Med 2009 Mar;163(3):225-232. [doi: 10.1001/archpediatrics.2008.577] [Medline: 19255389]
23. Creary S, Gladwin M, Byrne M, Hildesheim M, Krishnamurti L. A pilot study of electronic directly observed therapy to improve hydroxyurea adherence in pediatric patients with sickle-cell disease. Pediatr Blood Cancer 2014 Jun;61(6):1068-1073. [doi: 10.1002/pbc.24931] [Medline: 24436121]
24. Shellmer D, Zelikovsky N. The challenges of using medication event monitoring technology with pediatric transplant patients. Pediatr Transplant 2007 Jun;11(4):422-428 [FREE Full text] [doi: 10.1111/j.1399-3046.2007.00681.x] [Medline: 17493224]
25. Burgess S, Sly P, Morawska A, Devadason S. Assessing adherence and factors associated with adherence in young children with asthma. Respirology 2008 Jun;13(4):559-563. [doi: 10.1111/j.1440-1843.2008.01292.x] [Medline: 18422868]
26. Smith SR, Rublein JC, Marcus C, Brock TP, Chesney MA. A medication self-management program to improve adherence to HIV therapy regimens. Patient Educ Couns 2003 Jun;50(2):187-199. [Medline: 12781934]
27. Foster J, Smith L, Usherwood T, Sawyer S, Rand C, Reddel H. The reliability and patient acceptability of the SmartTrack device: a new electronic monitor and reminder device for metered dose inhalers. J Asthma 2012 Aug;49(6):657-662. [doi: 10.3109/02770903.2012.684253] [Medline: 22741746]

28. Onyirimba F, Apter A, Reisine S, Litt M, McCusker C, Connors M, et al. Direct clinician-to-patient feedback discussion of inhaled steroid use: its effect on adherence. Ann Allergy Asthma Immunol 2003 Apr;90(4):411-415. [doi: 10.1016/S1081-1206(10)61825-X] [Medline: 12722963]
29. Foster JM, Usherwood T, Smith L, Sawyer SM, Xuan W, Rand CS, et al. Inhaler reminders improve adherence with controller treatment in primary care patients with asthma. J Allergy Clin Immunol 2014 Dec;134(6):1260-1268.e3. [doi: 10.1016/j.jaci.2014.05.041] [Medline: 25062783]
30. Otsuki M, Eakin M, Rand C, Butz A, Hsu V, Zuckerman I, et al. Adherence feedback to improve asthma outcomes among inner-city children: a randomized trial. Pediatrics 2009 Dec;124(6):1513-1521. [doi: 10.1542/peds.2008-2961] [Medline: 19948623]
31. Bartlett S, Lukk P, Butz A, Lampros-Klein F, Rand C. Enhancing medication adherence among inner-city children with asthma: results from pilot studies. J Asthma 2002 Feb;39(1):47-54. [Medline: 11883739]
32. Burgess S, Sly P, Devadason S. Providing feedback on adherence increases use of preventive medication by asthmatic children. J Asthma 2010 Mar;47(2):198-201. [doi: 10.3109/02770900903483840] [Medline: 20170329]
33. Kahana S, Drotar D, Frazier T. Meta-analysis of psychological interventions to promote adherence to treatment in pediatric chronic health conditions. J Pediatr Psychol 2008 Jul;33(6):590-611 [FREE Full text] [doi: 10.1093/jpepsy/jsm128] [Medline: 18192300]
34. Chan AHY, Stewart A, Harrison J, Camargo C, Black P, Mitchell E. The effect of an electronic monitoring device with audiovisual reminder function on adherence to inhaled corticosteroids and school attendance in children with asthma: a randomised controlled trial. Lancet Respir Med 2015 Mar;3(3):210-219. [doi: 10.1016/S2213-2600(15)00008-9] [Medline: 25617215]
35. Weinstein A. The potential of asthma adherence management to enhance asthma guidelines. Ann Allergy Asthma Immunol 2011 Apr;106(4):283-291. [doi: 10.1016/j.anai.2011.01.016] [Medline: 21457876]
36. Riekert K, Borrelli B, Bilderback A, Rand C. The development of a motivational interviewing intervention to promote medication adherence among inner-city, African-American adolescents with asthma. Patient Educ Couns 2011 Jan;82(1):117-122 [FREE Full text] [doi: 10.1016/j.pec.2010.03.005] [Medline: 20371158]
37. Drotar D, Bonner M. Influences on adherence to pediatric asthma treatment: a review of correlates and predictors. J Dev Behav Pediatr 2009 Dec;30(6):574-582. [doi: 10.1097/DBP.0b013e3181c3c3bb] [Medline: 19996903]
38. Chan AHY, Reddel HK, Apter A, Eakin M, Riekert K, Foster JM. Adherence monitoring and e-health: how clinicians and researchers can use technology to promote inhaler adherence for asthma. J Allergy Clin Immunol Pract 2013;1(5):446-454. [doi: 10.1016/j.jaip.2013.06.015] [Medline: 24565615]
39. Borrelli B, Riekert K, Weinstein A, Rathier L. Brief motivational interviewing as a clinical strategy to promote asthma medication adherence. J Allergy Clin Immunol 2007 Nov;120(5):1023-1030. [doi: 10.1016/j.jaci.2007.08.017] [Medline: 17904625]
40. Wilson EV, Lankton NK. Modeling patients' acceptance of provider-delivered e-health. J Am Med Inform Assoc 2004;11(4):241-248 [FREE Full text] [doi: 10.1197/jamia.M1475] [Medline: 15064290]
41. Venkatesh V, Davis F. A theoretical extension of the technology acceptance model: Four Longitudinal Field Studies. Manag Sci 2000 Feb;46(2):186-204.
42. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol 2004 Jan;113(1):59-65. [doi: 10.1016/j.jaci.2003.09.008] [Medline: 14713908]
43. Schatz M, Kosinski M, Yarlas AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the Asthma Control Test. J Allergy Clin Immunol 2009 Oct;124(4):719-23.e1. [doi: 10.1016/j.jaci.2009.06.053] [Medline: 19767070]
44. Lacasse Y, Archibald H, Ernst P, Boulet LP. Patterns and determinants of compliance with inhaled steroids in adults with asthma. Can Respir J 2005;12(4):211-217. [Medline: 16003458]
45. Modi A, Rausch J, Glauser T. Patterns of nonadherence to antiepileptic drug therapy in children with newly diagnosed epilepsy. JAMA 2011 Apr 27;305(16):1669-1676 [FREE Full text] [doi: 10.1001/jama.2011.506] [Medline: 21521848]
46. Greenley R, Karazsia B, Schurman J, Gumidyala A, Nguyen E, Thomason M, et al. Trajectories of oral medication adherence in youth with inflammatory bowel disease. Health Psychol 2015 May;34(5):514-521. [doi: 10.1037/hea0000149] [Medline: 25222087]
47. Rohan J, Drotar D, Alderfer M, Donewar C, Ewing L, Katz E, et al. Electronic monitoring of medication adherence in early maintenance phase treatment for pediatric leukemia and lymphoma: identifying patterns of nonadherence. J Pediatr Psychol 2015;40(1):75-84 [FREE Full text] [doi: 10.1093/jpepsy/jst093] [Medline: 24365698]
48. Asch D, Muller R, Volpp K. Automated hovering in health care--watching over the 5000 hours. N Engl J Med 2012 Jul 5;367(1):1-3. [doi: 10.1056/NEJMp1203869] [Medline: 22716935]
49. Orrell-Valente J, Jarlsberg L, Hill L, Cabana M. At what age do children start taking daily asthma medicines on their own? Pediatrics 2008 Dec;122(6):e1186-e1192. [doi: 10.1542/peds.2008-0292] [Medline: 19047221]
50. AMC Health. Real-Time Virtual Care. New York, NY: AMC Health; 2016. URL: http://www.amchealth.com/ [accessed 2016-06-10] [WebCite Cache ID 6iAaxZe1C]

Abbreviations

ACT: Asthma Control Test
ICS: inhaled corticosteroids

Edited by G Eysenbach; submitted 21.11.15; peer-reviewed by A Chan, K Riekert; comments to author 03.04.16; revised version received 30.04.16; accepted 19.05.16; published 22.06.16.

Please cite as:
Kenyon CC, Chang J, Wynter SA, Fowler JC, Long J, Bryant-Stephens TC
Electronic Adherence Monitoring in a High-Utilizing Pediatric Asthma Cohort: A Feasibility Study
JMIR Res Protoc 2016;5(2):e132
URL: http://www.researchprotocols.org/2016/2/e132/
doi:10.2196/resprot.5362
PMID:27335355

Original Paper

Feasibility of an Electronic Survey on iPads with In-Person Data Collectors for Data Collection with Health Care Professionals and Health Care Consumers in General Emergency Departments

Shannon D Scott[1], PhD, RN; Lauren Albrecht[1], MEd; Lisa M Given[2], PhD; Danielle Arseneau[3], BScN; Terry P Klassen[4], FRCPC, MD, MSc

[1]University of Alberta, Faculty of Nursing, Edmonton, AB, Canada

[2]Charles Sturt University, School of Information Studies, New South Wales, Australia

[3]University of British Columbia, Faculty of Medicine, Vancouver, BC, Canada

[4]Children's Hospital Research Institute of Manitoba, Winnipeg, MB, Canada

Corresponding Author:
Shannon D Scott, PhD, RN
University of Alberta
Faculty of Nursing
3rd floor, Edmonton Clinic Health Adacemy
11405 87 Ave
Edmonton, AB, T6G 1C9
Canada
Phone: 1 7804921037
Fax: 1 7804922551
Email: ss14@ualberta.ca

Abstract

Background: Translating Emergency Knowledge for Kids was established to bridge the research-practice gap in pediatric emergency care by bringing the best evidence to Canadian general emergency departments (EDs). The first step in this process was to conduct a national needs assessment to determine the information needs and preferences of health professionals and parents in this clinical setting.

Objective: To describe the development and implementation of two electronic surveys, and determine the feasibility of collecting electronic survey data on iPads with in-person data collectors in a busy clinical environment.

Methods: Two descriptive surveys were conducted in 32 general EDs. Specific factors were addressed in four survey development and implementation stages: survey design, survey delivery, survey completion, and survey return. Feasibility of the data collection approach was determined by evaluating participation rates, completion rates, average survey time to completion, and usability of the platform. Usability was assessed with the in-person data collectors on five key variables: interactivity, portability, innovativeness, security, and proficiency.

Results: Health professional participation rates (1561/2575, 60.62%) and completion rates (1471/1561, 94.23%) were strong. Parental participation rates (974/1099, 88.63%) and completion rates (897/974, 92.09%) were excellent. Mean time to survey completion was 28.08 minutes for health professionals and 43.23 minutes for parents. Data collectors rated the platform "positively" to "very positively" on all five usability variables.

Conclusions: A number of design and implementation considerations were explored and integrated into this mixed-mode survey data collection approach. Feasibility was demonstrated by the robust survey participation and completion rates, reasonable survey completion times, and very positive usability evaluation results.

(JMIR Res Protoc 2016;5(2):e139) doi:10.2196/resprot.5170

KEYWORDS

survey development; electronic survey; survey implementation; needs assessment; pediatric emergency medicine

Introduction

The Translating Emergency Knowledge for Kids (TREKK) project aims to bridge the research-to-practice gap in pediatric emergency medicine, and reduce variable emergency care, by ensuring that practitioners in general emergency departments (EDs) have access to and apply the latest research evidence in their pediatric practice [1]. The first phase of the TREKK project (the *Needs Assessment*) surveyed health care professionals and parents seeking care for their children in general EDs, to determine information needs and preferences to guide the development of knowledge translation tools on key child health topics. Given the well-documented challenges of survey research [2], particularly in health research [3-9], specific factors were addressed in four survey development and implementation stages, including survey design, survey delivery, survey completion, and survey return. The aim of this research was to increase data quality (ie, increasing participation rates, reducing item nonresponse, and reducing dropouts) [10].

Despite a wealth of research, much debate remains regarding the superiority of electronic and/or mailed paper surveys [4,11]. Recent studies indicate that the future of survey research involves mixed-mode approaches (ie, two or more modes of administration including mail, web, telephone, and/or in-person) [12] and/or additional recruitment techniques to generate higher response rates [13-15]. However, further research is recommended to describe variations in survey content and administration, and effects on participation rates and data quality [12]. In this paper, we describe electronic survey development and implementation using iPads and in-person data collectors. We also detail the feasibility of this novel mixed-mode approach to survey research by providing survey response rate results, average length of time for survey completion, and the results of a usability evaluation with data collectors.

Methods

Survey Design

Given the complexity of the ED environment (ie, fast-paced, high volume, high acuity), traditional paper-based surveys were too cumbersome and resource-intensive for this study. An electronic survey was determined to be the most appropriate method to meet study timelines, due to ease of implementation across a large geographic area, and decreased administrative costs [5,12,14,16]. To be included in the survey, each participant was either a health care professional working in a participating general ED, or a parent seeking care for a child in the EDs. Participants were excluded if they were unable to read or write English or French.

Survey questions were developed using relevant research literature [3] and in consultation with content experts in pediatric emergency medicine, nursing, and information science. The surveys underwent several iterations, and face validity was determined through team meetings and pilot testing within the research team. Both surveys were developed in English and translated into French. The *Health Care Professional Needs Assessment* survey collected demographic information, current information-seeking practices, information needs related to caring for children in the ED, and preferences for receiving new information related to caring for children in the ED (Multimedia Appendix 1). The *Parent Needs Assessment* survey collected demographic information, information about the current visit to the ED, and health information needs and preferences (Multimedia Appendix 2).

In addition to survey content, six features affecting response rate of web-based surveys were considered: (1) general format, (2) length, (3) disclosure of survey progress, (4) visual presentation, (5) interactivity, and (6) question/response format [17]. A screen design format was selected to display one question per page, as this design has been shown to have lower item nonresponse than scrolling designs [17]. Much thought was given to survey length, and the surveys were constructed to achieve an average survey completion time of approximately 20 minutes. This target aimed to mitigate busyness as a barrier to health care professional participation [18], and to maximize the opportunity for parents to complete the survey in the waiting room before being brought into an examination room. Disclosure of survey progress has shown limited effect on response rates, so we did not incorporate this feature in our surveys [17]. In terms of visual presentation of the survey, a plain visual presentation approach with selective use of color was used, based on research indicating higher completion rates and later dropouts using this design [17]. *Sans serif* font was selected for ease of readability on a screen [19], questions and responses were numbered, and bolding, shading, italics, and color were used in a consistent fashion, with the aim to enhance understandability. Arrows were used to direct participants to subsequent screens. Interactivity was also incorporated, as it has been linked to lower item nonresponse [17]. This feature included automatic jumps to questions based on previous answers, and a *missing data* message was displayed when an item was left blank; however, responses were not forced due to the association of this option with higher dropout rates [17]. Four question/response formats were used throughout the surveys, and included single and multi-touch responses with radio buttons, sliding scales, and drag and drop boxes in which responses could be dragged to a new column and rank ordered (Multimedia Appendix 3).

Survey Delivery

Consistent hardware was used at each site to streamline training and mitigate technological issues in survey delivery [5]. iPads were selected as the most effective survey delivery and data collection device because of their functionality and participant preference. iPads are lightweight devices that are easy to transport and hand to participants. The iPad interface is user-friendly and the touch screen technology, which has been shown to reduce mean time for patients completing questionnaires [20], enabled new and interesting approaches to survey question design [21]. In addition, previous research has demonstrated that both health care professionals and parental respondents preferred participation on a tablet compared to paper-based surveys [22-25], and found these devices easy to use [23,25]. Furthermore, electronic tablets have been shown to be a viable method of collecting patient self-report data in pediatric waiting rooms [26] and in rural settings [24].

Survey Completion

External validity has been identified as a methodological issue of concern in survey research [3-5,27,28]; we attempted to address this issue by having in-person data collectors accompany the technology while conducting on-site recruitment. Census sampling aimed to recruit all health care professionals, and convenience sampling was used to recruit parents. The protocol for recruitment involved approaching all staff and parents to introduce TREKK and determine study eligibility. iPads were provided to interested parties to review the electronic consent form; once consent was indicated, participants automatically proceeded to the electronic survey. Data collectors were available throughout survey recruitment and completion to answer questions and assist with overcoming any technological barriers, including comfort with web browsers and touch screen technology. This consideration was based on research suggesting that the amount of contact and length of time in the field are important factors in health care professional response rates [4]. Surveys could be kept open for any length of time and were closed when the *Submit* button was indicated at the end of the survey, or the browser window was closed. The survey was designed with this flexibility, as data collection occurred in unpredictable and busy EDs.

Survey Return & Technical Issues

The electronic survey platform incorporated synchronous and asynchronous data collection capability, meaning that data could be collected online and automatically uploaded to a secure server when a wireless connection was present, and data could also be collected offline, safely stored on the device, and later uploaded to a secure server once a wireless connection was available. This feature was particularly important in the ED setting, as many hospitals do not provide wireless internet and 3G/4G connectivity is limited or non-existent in rural and remote regions. This approach also addressed previously identified security concerns with cloud-based data storage [29,30]. Automatic data upload also eliminated the need for data entry, thus reducing the potential for error, and allowed the research team to monitor data quality via a secure, password-protected portal to provide feedback or additional training to data collectors. This functionality required enhanced device security; however, iPads are equipped with the appropriate security features to meet this need, including passcodes and restrictions to limit access and usage, encryption to protect information stored on the device, GPS technology to track the device, and remote and automatic data wiping capabilities (in the event that the device is lost or stolen) [31].

Usability Evaluation of Data Collection Platform

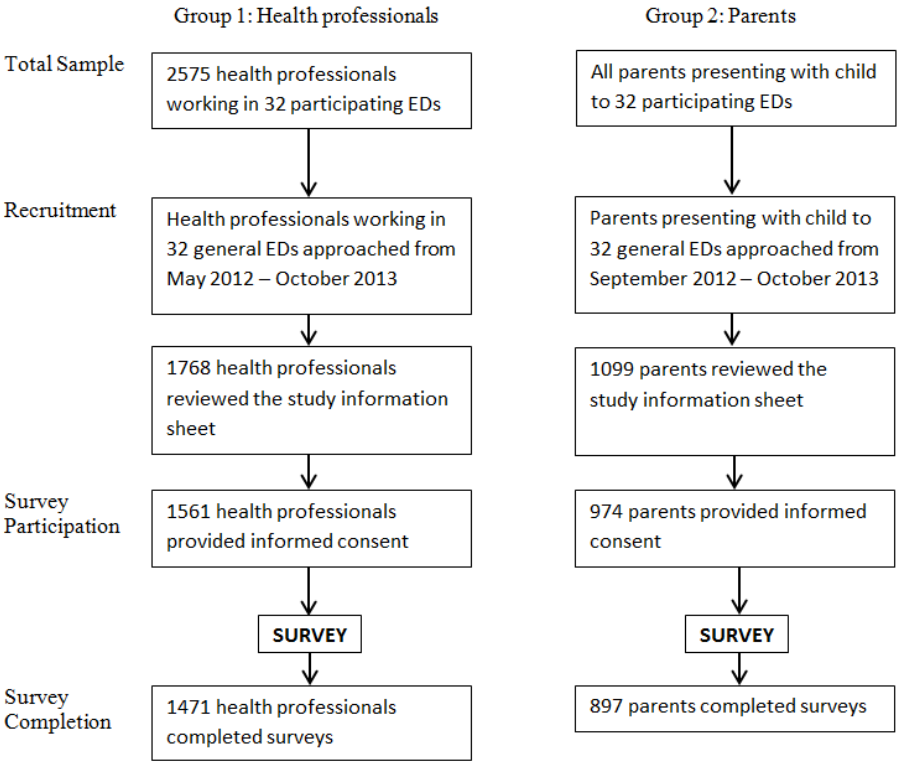
A usability evaluation was conducted with data collectors using an anonymous 20-question electronic survey. The content of the survey was theoretically informed on the basis of a small-scale review of previous studies employing electronic platforms for data collection and the National Institutes of Health's Usability Guidelines [32]. These guidelines outline key features of visual design and user experience, including interactivity, portability, innovativeness, security, and proficiency. The usability survey ranked features of the electronic survey and iPad on a five-point scale according to how positively or negatively these features affected their experience collecting data for the *TREKK Needs Assessment* (Multimedia Appendix 4). Face validity was determined via team meetings and pilot testing within the research team.

Results

Survey Participation & Completion Rates

The recruitment rate for health care professionals was 68.66% (1768/2575) and participation rate was 60.62% (1561/2575), and among participants the survey completion rate was 94.23% (1471/1561). Among parents the recruitment rate could not be determined because the eligible population was dependent on people coming into the general EDs; however, the participation rate was 88.63% (974/1099) and among participants the survey completion rate was 92.09% (897/974). See Figure 1 for recruitment and participation details for both populations.

Figure 1. Survey recruitment, participation & completion.



Length of Time for Survey Completion

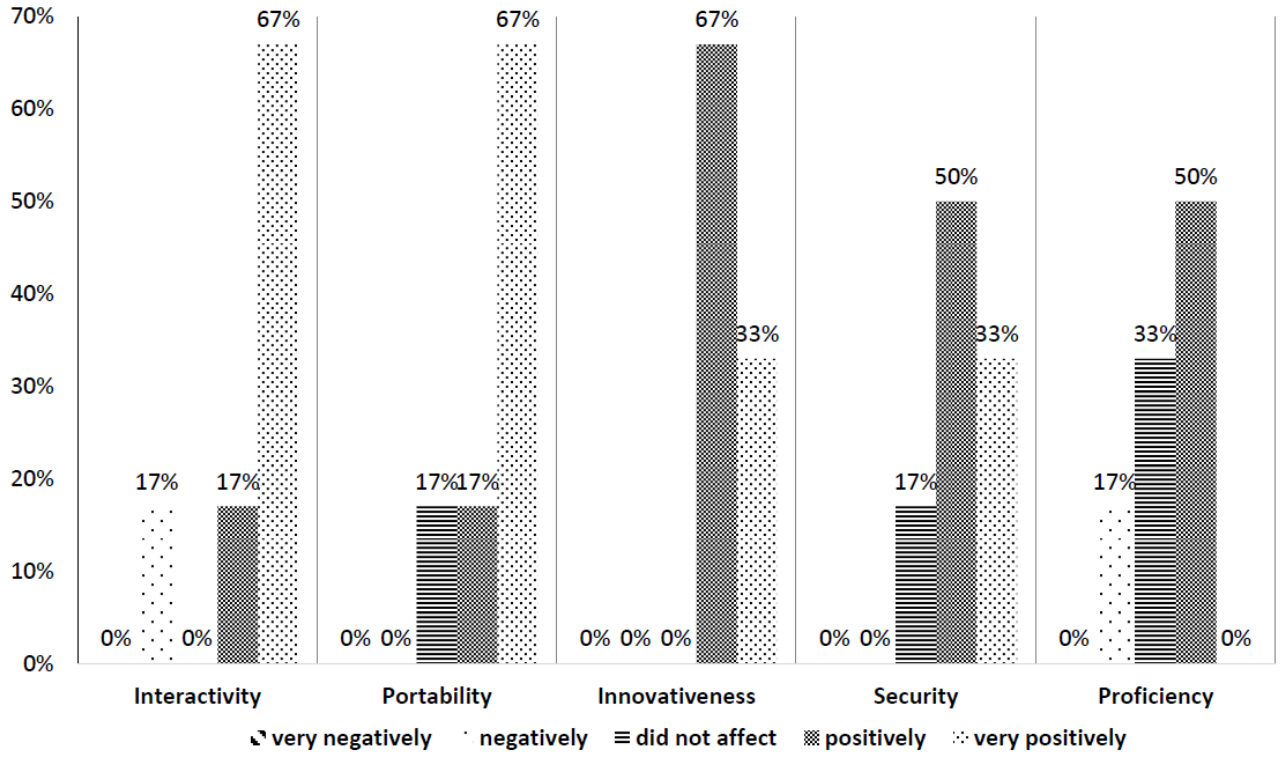
Of the 1471 health care professional surveys included in the final analysis, 79 surveys did not have a time stamp (ie, participants did not press *Submit* at the end of the survey) and were not included in the calculation of average survey completion time. Of the 1391 surveys with a time stamp, the mean time to survey completion was 28.08 minutes (standard deviation = 118.54 minutes). This estimate includes participants that left the survey open and returned to complete it at a later time (eg, 9 surveys were open for more than 1000 minutes).

Of the 897 parental surveys included in the final analysis, 25 did not have a time stamp and were not included in the calculation for average survey completion time. Of the 872 surveys with a time stamp, the mean time to survey completion was 43.23 minutes (standard deviation = 691.25 minutes). This estimate includes participants that left the survey open and returned to complete it at a later time (eg, 4 surveys were open for more than 1000 minutes).

Usability Evaluation of Data Collection Platform

Eight data collectors were approached to participate in the usability evaluation, six of whom agreed to participate and complete the survey (75% participation and completion rate). On a five-point scale, responses were largely *positive* (score=4) to *very positive* (score=5) on the five usability measures (see Figure 2). Additionally, respondents could enter free text information to describe, in detail, their perspectives on the strengths and weaknesses of iPads as a data collection tool. Respondents noted that the professional look and feel of the survey created a sense of trustworthiness and legitimacy of the research study, as demonstrated by the following excerpt, “With a unique online survey specific for TREKK, it appears more trustworthy as a legitimate research study, rather than having… paper surveys.” However, respondents illuminated some drawbacks to this approach, such as, “The only real negative of using the iPad relates to the survey participants [sic] level of comfort with technology, but not to such an extent that it affects participation - only initial comfort.”

Figure 2. Data collectors' (n=6) ratings on 5 variables to evaluate the data collection platform.



Discussion

Our findings make an important contribution to the web-based survey literature by addressing calls for research to examine web-based survey response and completion issues [10]. Generally, web-based surveys are correlated with low response rates [10], with estimates suggesting an average 10% decrease in response rates compared to traditional paper-based surveys. Given that 68.66% of health care professionals that were approached in our study reviewed the consent, and 94.23% of those who consented completed the survey, it is apparent that our mixed-mode approach mitigated these commonly accepted disadvantages of web-based surveys.

Utilizing data collectors to approach potential survey participants, and explain the study, eliminated the need for email or web-based invitations and completion reminders, and significantly enhanced survey participation and completion rates. We suggest that the addition of in-person data collectors offered the benefits of personal connection, and caused potential survey participants to make an active decision to participate in the study. In-person data collectors were also able to engage with potential participants and answer any questions the potential participants had about the study or the technology. Deploying a web-based survey without a mixed-mode approach allows potential participants to easily ignore electronic invitations to participate in survey research. With a mixed-mode approach, we were able to capitalize on the many benefits of web-based surveys, including improved data quality and the ability to immediately begin data analysis, while simultaneously mitigating previously reported downfalls of web-based surveys, including lower response rates and lower completion rates.

Vicente and Reis itemized six areas to consider when designing and implementing web-based surveys [17], and our usability findings support five of these recommendations (general structure, survey length, visual presentation, interactivity, and question/response format). Specifically, the usability findings collected by our in-person data collectors were largely *positive* to *very positive* for interactivity, portability, innovativeness, security, and proficiency. Free text responses further strengthened these findings by highlighting that the general structure, visual presentation, and question/response format of our survey helped to legitimize and enhance the credibility of our study. These findings highlight the importance of the investment of time and resources into survey design and implementation elements. Our participation and completion rates, and survey usability findings, are evidence that attention to survey design and implementation is strategic.

Conclusions

This study provides strong evidence for the feasibility of a mixed-mode approach to survey data collection using iPads and in-person data collectors, based on strong response rates, reasonable survey completion times, and very positive usability evaluation results. This study also details survey development and implementation considerations that will be useful to survey researchers working with a variety of populations. Great potential exists for utilizing a mixed-mode approach for future survey research in clinical settings.

Acknowledgments

TREKK is funded by the Networks of Centers of Excellence – Knowledge Mobilization initiative, and supported (either financially or through in-kind contributions) by the following agencies and institutions: Pediatric Emergency Research Canada, Children's Hospital Research Institute of Manitoba, University of Manitoba, Research Manitoba, ManitobaCPD.com, Cochrane Child Health Field, Alberta Children's Hospital Research Institute, Children's Hospital of Eastern Ontario, Ontario ED Local Health Integration Network Leads, Alberta Health Services, and Women and Children's Health Research Institute. SDS is a Canada Research Chair (tier II) for knowledge translation in child health and a Population Health Investigator with Alberta Innovates – Health Solutions (formerly Alberta Heritage Foundation for Medical Research). LA is supported by Alberta Innovates – Health Solutions Graduate Studentship and Women & Children's Health Research Institute Graduate Studentship.

We would like to acknowledge and thank the TREKK Team, including the Board of Directors, Prioritization Committee, Nodal Leaders, and Pediatric Emergency Research Canada Representatives, Coordinators, and Administrative staff for their dedication to this project.

Authors' Contributions

TPK and SDS obtained research funding. SDS conceptualized and led the research study. SDS, LA and LMG designed the electronic surveys. LA conducted data collection and data analysis for the *Needs Assessment*. SDS and DA conceptualized the small-scale iPad evaluation project. DA conducted data collection and data analysis for this evaluation. SDS and LA wrote the manuscript. All authors provided substantive feedback and approved the manuscript prior to submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1

TREKK Needs Assessment Healthcare Professional Survey.

[PDF File (Adobe PDF File), 51KB - resprot_v5i2e139_app1.pdf]

Multimedia Appendix 2

TREKK Needs Assessment Parent Survey.

[PDF File (Adobe PDF File), 49KB - resprot_v5i2e139_app2.pdf]

Multimedia Appendix 3

Electronic survey question design.

[PDF File (Adobe PDF File), 219KB - resprot_v5i2e139_app3.pdf]

Multimedia Appendix 4

TREKK Usability Survey with In-person Data Collectors.

[PDF File (Adobe PDF File), 34KB - resprot_v5i2e139_app4.pdf]

References

1. Translating Emergency Knowledge for Kids. Translating Emergency Knowledge for Kids. 2015. URL: http://trekk.ca/about [accessed 2015-08-26] [WebCite Cache ID 6b4Z6X9Ij]
2. Shih TH, Fan X. Comparing response rates from web and mail surveys: a meta-analysis. Field Methods 2008 Mar 03;20(3):249-271. [doi: 10.1177/1525822X08317085]
3. Burns KE, Duffett M, Kho M, Meade M, Adhikari NK, Sinuff T, et al. A guide for the design and conduct of self-administered surveys of clinicians. CMAJ 2008 Jul 29;179(3):245-252 [FREE Full text] [doi: 10.1503/cmaj.080372] [Medline: 18663204]
4. VanGeest JB, Johnson TP, Welch VL. Methodologies for improving response rates in surveys of physicians: a systematic review. Eval Health Prof 2007 Dec;30(4):303-321. [doi: 10.1177/0163278707307899] [Medline: 17986667]
5. Braithwaite D, Emery J, De Lusignan S, Sutton S. Using the Internet to conduct surveys of health professionals: a valid alternative? Fam Pract 2003 Oct;20(5):545-551 [FREE Full text] [Medline: 14507796]
6. Morris M, Edwards P, Doyle P, Maconochie N. Women in an infertility survey responded more by mail but preferred a choice: randomized controlled trial. J Clin Epidemiol 2013 Feb;66(2):226-235. [doi: 10.1016/j.jclinepi.2012.10.003] [Medline: 23257153]

7. Golnik A, Ireland M, Borowsky IW. Medical homes for children with autism: a physician survey. Pediatrics 2009 Mar;123(3):966-971. [doi: 10.1542/peds.2008-1321] [Medline: 19255027]
8. Rodriguez H, von Glahn T, Rogers W, Chang H, Fanjiang G, Safran D. Evaluating patients' experiences with individual physicians: a randomized trial of mail, Internet, and interactive voice response telephone administration of surveys. Med Care 2006 Feb;44(2):167-174. [Medline: 16434916]
9. Yusuf TE, Baron TH. Endoscopic transmural drainage of pancreatic pseudocysts: results of a national and an international survey of ASGE members. Gastrointest Endosc 2006 Feb;63(2):223-227. [doi: 10.1016/j.gie.2005.09.034] [Medline: 16427925]
10. Fan W, Yan Z. Factors affecting response rates of the web survey: a systematic review. Comp Human Behav 2010 Mar;26(2):132-139. [doi: 10.1016/j.chb.2009.10.015]
11. Cunningham CT, Quan H, Hemmelgarn B, Noseworthy T, Beck CA, Dixon E, et al. Exploring physician specialist response rates to web-based surveys. BMC Med Res Methodol 2015 Apr;15:32 [FREE Full text] [doi: 10.1186/s12874-015-0016-z] [Medline: 25888346]
12. Beebe TJ, Locke GR, Barnes SA, Davern ME, Anderson KJ. Mixing web and mail methods in a survey of physicians. Health Serv Res 2007 Jun;42(3 Pt 1):1219-1234 [FREE Full text] [doi: 10.1111/j.1475-6773.2006.00652.x] [Medline: 17489911]
13. Raziano DB, Jayadevappa R, Valenzula D, Weiner M, Lavizzo-Mourey R. E-mail versus conventional postal mail survey of geriatric chiefs. Gerontologist 2001 Dec 01;41(6):799-804. [doi: 10.1093/geront/41.6.799] [Medline: 11723348]
14. Potts HW, Wyatt JC. Survey of doctors' experience of patients using the Internet. J Med Internet Res 2002;4(1):e5 [FREE Full text] [doi: 10.2196/jmir.4.1.e5] [Medline: 11956037]
15. Dykema J, Jones NR, Piché T, Stevenson J. Surveying clinicians by web: current issues in design and administration. Eval Health Prof 2013 Sep;36(3):352-381. [doi: 10.1177/0163278713496630] [Medline: 23975760]
16. VanDenKerkhof EG, Parlow JL, Goldstein DH, Milne B. In Canada, anesthesiologists are less likely to respond to an electronic, compared to a paper questionnaire. Can J Anaesth 2004 May;51(5):449-454. [Medline: 15128630]
17. Vicente P, Reis E. Using questionnaire design to fight nonresponse bias in web surveys. Soc Sci Comput Rev 2010 May 10;28(2):251-267. [doi: 10.1177/0894439309340751]
18. Thompson DS, O'Leary K, Jensen E, Scott-Findlay S, O'Brien-Pallas L, Estabrooks CA. The relationship between busyness and research utilization: it is about time. J Clin Nurs 2008 Feb;17(4):539-548. [doi: 10.1111/j.1365-2702.2007.01981.x] [Medline: 18205684]
19. Josephson S. Keeping your readers' eyes on the screen: an eye-tracking study comparing sans serif and serif typefaces. Vis Comm Q 2011 Jan 20;15(1-2):67-79. [doi: 10.1080/15551390801914595]
20. Salaffi F, Gasparini S, Ciapetti A, Gutierrez M, Grassi W. Usability of an innovative and interactive electronic system for collection of patient-reported data in axial spondyloarthritis: comparison with the traditional paper-administered format. Rheumatology (Oxford) 2013 Nov;52(11):2062-2070 [FREE Full text] [doi: 10.1093/rheumatology/ket276] [Medline: 23955646]
21. Linder LA, Ameringer S, Erickson J, Macpherson CF, Stegenga K, Linder W. Using an iPad in research with children and adolescents. J Spec Pediatr Nurs 2013 Apr;18(2):158-164. [doi: 10.1111/jspn.12023] [Medline: 23678681]
22. Aiello EJ, Taplin S, Reid R, Hobbs M, Seger D, Kamel H, et al. In a randomized controlled trial, patients preferred electronic data collection of breast cancer risk-factor information in a mammography setting. J Clin Epidemiol 2006 Jan;59(1):77-81. [doi: 10.1016/j.jclinepi.2005.07.007] [Medline: 16360564]
23. Tscholl DW, Weiss M, Spahn DR, Noethiger CB. How to conduct multimethod field studies in the operating room: the iPad combined with a survey app as a valid and reliable data collection tool. JMIR Res Protoc 2016 Jan;5(1):e4 [FREE Full text] [doi: 10.2196/resprot.4713] [Medline: 26732090]
24. Newell SM, Logan HL, Guo Y, Marks JG, Shepperd JA. Evaluating tablet computers as a survey tool in rural communities. J Rural Health 2015;31(1):108-117 [FREE Full text] [doi: 10.1111/jrh.12095] [Medline: 25243953]
25. Fanning J, McAuley E. A comparison of tablet computer and paper-based questionnaires in healthy aging research. JMIR Res Protoc 2014 Jul;3(3):e38 [FREE Full text] [doi: 10.2196/resprot.3291] [Medline: 25048799]
26. Anand V, McKee S, Dugan TM, Downs SM. Leveraging electronic tablets for general pediatric care: a pilot study. Appl Clin Inform 2015 Jan;6(1):1-15 [FREE Full text] [doi: 10.4338/ACI-2014-09-RA-0071] [Medline: 25848409]
27. Akl EA, Maroun N, Klocke RA, Montori V, Schünemann HJ. Electronic mail was not better than postal mail for surveying residents and faculty. J Clin Epidemiol 2005 Apr;58(4):425-429. [doi: 10.1016/j.jclinepi.2004.10.006] [Medline: 15862729]
28. Granello D, Wheaton J. Online data collection: strategies for research. J Couns Dev 2004;82(4):387-393. [doi: 10.1002/j.1556-6678.2004.tb00325.x]
29. Wilcox AB, Gallagher KD, Boden-Albala B, Bakken SR. Research data collection methods: from paper to tablet computers. Med Care 2012 Jul;50 Suppl:S68-S73. [doi: 10.1097/MLR.0b013e318259c1e7] [Medline: 22692261]
30. Wilcox AB, Gallagher K, Bakken S. Security approaches in using tablet computers for primary data collection in clinical research. EGEMS (Wash DC) 2013 Feb;1(1):1008 [FREE Full text] [doi: 10.13063/2327-9214.1008] [Medline: 25848559]
31. Apple Inc.. iOS Security. 2015 Jun. URL: http://www.apple.com/business/docs/iOS_Security_Guide.pdf [accessed 2015-08-26] [WebCite Cache ID 6b4ZWjOQV]

32. U.S. Department of Health & Human Services. Research-Based Web Design & Usability Guidelines, Enlarged/Expanded edition. Washington: U.S. Government Printing Office; 2006. URL: https://www.usability.gov/sites/default/files/documents/guidelines_book.pdf [accessed 2015-08-26] [WebCite Cache ID 6iX9YZ3Kk]

Abbreviations

ED: emergency department
TREKK: Translating Emergency Knowledge for Kids

Edited by G Eysenbach; submitted 28.09.15; peer-reviewed by J Avis, P Muller, P Paulo Tanaka; comments to author 10.02.16; revised version received 13.04.16; accepted 07.05.16; published 29.06.16.

Please cite as:
Scott SD, Albrecht L, Given LM, Arseneau D, Klassen TP
Feasibility of an Electronic Survey on iPads with In-Person Data Collectors for Data Collection with Health Care Professionals and Health Care Consumers in General Emergency Departments
JMIR Res Protoc 2016;5(2):e139
URL: http://www.researchprotocols.org/2016/2/e139/
doi:10.2196/resprot.5170
PMID:27358205

Corrigenda and Addenda

Metadata and Title Correction: Online Focus Group Discussion is a Valid and Feasible Mode When Investigating Sensitive Topics Among Young Persons With a Cancer Experience

Lena Wettergren[1], PhD, RN; Lars E Eriksson[2,3,4], RN, MSc, PhD; Jenny Nilsson[1], RN, MSc (Nursing); Anna Jervaeus[1], RN, MSc, PhD; Claudia Lampic[1], Lic Psych, PhD

[1]Division of Nursing, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Huddinge, Sweden

[2]Medical Management Center (MMC), Department of Learning, Informatics, Management and Ethics (LIME), Karolinska Institutet, Stockholm, Sweden

[3]Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden

[4]School of Health Sciences, City University London, London, United Kingdom

Corresponding Author:
Lena Wettergren, PhD, RN
Division of Nursing
Department of Neurobiology, Care Sciences and Society
Karolinska Institutet
23 300
Huddinge, SE-141 83
Sweden
Phone: 46 524 836 50
Fax: 46 524 888 50
Email: lena.wettergren@ki.se

Related Article:

Correction of: http://www.researchprotocols.org/2016/2/e86/

(JMIR Res Protoc 2016;5(2):e92) doi:10.2196/resprot.5971

The title of the paper originally entitled “Content Analysis of Online Focus Group Discussions is a Valid and Feasible Mode When Investigating Sensitive Topics Among Young Persons With a Cancer Experience” (JMIR ResProtoc 2016 May 9; 5(2):e86) was corrected to read “Online Focus Group Discussion is a Valid and Feasible Mode When Investigating Sensitive Topics Among Young Persons With a Cancer Experience”. The error was introduced by the editor in the final proofreading process to remove a grammatical issue, but the authors feel that “content analysis” in the title is incorrect because content analysis was not the method used for analyzing data in the present study. The advantages and disadvantages with the mode of data collection was judged by analyzing characteristics of those who participated, interactions during discussions and the participants’ evaluation of the focus group discussions. Secondly, there was also an incorrect affiliation footnote reading “null” associated with author Lena Wettergren, which has now been removed from the metadata. These errors have been corrected in the online version of the paper on the JMIR website on May 10 and May 12, 2016, respectively, together with publishing this correction notice. There are no changes to the contents of the paper. A correction notice has been sent to PubMed. This was done before submission to Pubmed Central and other full-text repositories.

Edited by G Eysenbach; submitted 12.05.16; ###Reviewer names will be inserted here### published 12.05.16.

Please cite as:
Wettergren L, Eriksson LE, Nilsson J, Jervaeus A, Lampic C
Metadata and Title Correction: Online Focus Group Discussion is a Valid and Feasible Mode When Investigating Sensitive Topics Among Young Persons With a Cancer Experience
JMIR Res Protoc 2016;5(2):e92
URL: http://www.researchprotocols.org/2016/2/e92/
doi:10.2196/resprot.5971
PMID:27183496

Original Paper

The Good Food Junction: a Community-Based Food Store Intervention to Address Nutritional Health Inequities

Rachel Engler-Stringer[1], PhD; Nazeem Muhajarine[1], PhD; Tracy Ridalls[2], MA; Sylvia Abonyi[1], PhD; Hassan Vatanparast[3], MD, PhD; Susan Whiting[4], PhD; Ryan Walker[5], PhD

[1]Community Health and Epidemiology and Saskatchewan Population Health and Evaluation Research Unit, University of Saskatchewan, Saskatoon, SK, Canada

[2]Saskatchewan and Population Health and Evaluation Research Unit, Saskatoon, SK, Canada

[3]College of Pharmacy and Nutrition and School of Public Health, University of Saskatchewan, Saskatoon, SK, Canada

[4]College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, SK, Canada

[5]Department of Geography and Planning, University of Saskatchewan, Saskatoon, SK, Canada

Corresponding Author:
Rachel Engler-Stringer, PhD
Community Health and Epidemiology and Saskatchewan Population Health and Evaluation Research Unit
University of Saskatchewan
107 Wiggins Road
Saskatoon, SK, S7N5E5
Canada
Phone: 1 3069667839
Fax: 1 9667920
Email: rachel.engler-stringer@usask.ca

Abstract

Background: This is a 2-year study to assess the early impacts of a new grocery store intervention in a former food desert.

Objective: The purpose of the study is to understand the early health effects of the introduction of a large-scale food and nutrition-focused community-based population health intervention, the Good Food Junction (GFJ) Cooperative Store, in a geographically bounded group of socially disadvantaged neighborhoods (the “core neighborhoods”) in a midsized Canadian city. The GFJ grocery store was tasked with improving the access of residents to healthy, affordable food. The 5 research questions are: (1) What is the awareness and perception of the GFJ store among residents of the core neighborhoods? (2) Are there differences in awareness and perception among those who do and do not shop at the GFJ? (3) Will healthy food purchasing at the GFJ by residents of the core neighborhoods change over time, and what purchases are these individuals making at this store? (4) What early impact(s) will the GFJ have on key health-related outcomes (such as household food security status, vegetable and fruit intake, key aspects of self-reported mental health, self-reported health)? and (5) Are the effects of the intervention seen for specific vulnerable population groups, such as Aboriginal people, seniors (65 years old or older) and new immigrants (settled in Saskatoon for less than 5 years)?

Methods: The research project examined initial impacts of the GFJ on the health of the residents in surrounding neighborhoods through a door-to-door cross-sectional survey of food access and household demographics; an examination of GFJ sales data by location of shoppers' residences; and a 1-year, 3-time-point longitudinal study of self-reported health of GFJ shoppers.

Results: Analyses are on-going, but preliminary results show that shoppers are using the store for its intended purpose, which is to improve access to healthy food in a former food desert.

Conclusions: To our knowledge this is the first large-scale study of a full-service grocery store intervention in a former food desert in Canada that has used multiple data sources, as well as longitudinal analyses, to examine its effects. Its findings will contribute significantly to the knowledge base on food environment interventions.

(JMIR Res Protoc 2016;5(2):e52) doi:10.2196/resprot.5303

KEYWORDS

food environments; intervention; natural experiment

Introduction

North American lifestyles generally promote food that is packed with calories (ie, energy-dense food) and offer little incentive for being active [1], particularly in low-income neighborhoods [2]. Specifically, food environments are increasingly recognized as a critical determinant of community and population health [3-5]. Townshend and Lake stated that the food environment "can be broadly conceptualized to include any opportunity to obtain food…. This definition of the food environment can include physical, sociocultural, economic, and policy factors at both micro- and macro-levels" [6].

The presence and accessibility of supermarkets and grocery stores has been linked to improved fruit and vegetable consumption [7], general improvement in healthier food intake [8], and lower body weight [9]. Using national-level data, one US study reported that higher prices for vegetables and fruit are significantly associated with greater gains in BMIs in children between kindergarten and the third grade [10]. There is increasing evidence that poor food environments—such as greater access to fast food and convenience stores and limited access to full-service grocery stores—are more likely to be located in neighborhoods with a lower than average socioeconomic status [9,11-14]. Poor food environments may partly explain why individuals of lower socioeconomic status are more likely to be obese.

While early studies focused primarily on characterizing food environments using geographical and other methods [15], more recent research examined food environment interventions, such as healthy corner store studies [16,17] and the health impacts of opening new supermarkets in "food deserts" (ie, neighborhoods where affordable and nutritious foods are unavailable, requiring residents to travel outside of their neighborhood to access nutritious foods) [18-20]. The body of food environment interventions literature is still very limited in Canada, and results from outside of Canada are contradictory [21-23]. As such, there is a need to conduct larger scale, more systematic, and in particular longitudinal intervention research on food environments.

There have been mixed outcomes in previous research examining food store interventions. Wrigley et al [24] offered the first "before and after" study of a new grocery store development in Leeds, England, in a low-income neighborhood with poor retail access to healthy food. The store was a large-scale chain supermarket. Using fruit and vegetable consumption as a proxy for healthy diet, the authors noted that the introduction of a full-service grocery store significantly improved consumption. Cummins et al [19] also studied the impacts of the opening of a for-profit retail grocery store but showed the intervention had little effect on fruit and vegetable consumption. However, they later argued [25] that the community was not a true food desert and had some access to healthy food. They noted that positive consequences of the grocery store opening included community economic regeneration, increased employment, and a "net reduction in poor psychological health for those who directly engaged with the intervention" [26]. Overall there is uncertainty as to whether grocery store interventions impact healthy eating behavior or other aspects of health.

Drawing on the literature, this study was developed to contribute to the emerging field assessing the impacts of new food access points in low socioeconomic status communities that have previously been characterized as having particularly poor food environments [22,23]. The study is being conducted to assess the early impacts of a new grocery store in a community that had been identified as a food desert [27,28]. The goal of the study is to understand how the introduction of a large-scale food- and nutrition-focused community-based population health intervention (the Good Food Junction Cooperative Store) may impact the health of individuals and families in a geographically bounded group of neighborhoods.

Intervention and Setting

This study is being conducted in Saskatoon, Saskatchewan, a city of just over 250,000 people. The study is focused on neighborhoods surrounding the Good Food Junction Cooperative grocery store. These are known as the "core neighborhoods," a set of 7 low socioeconomic status neighborhoods in Saskatoon (Figure 1). The core neighborhoods have several characteristics in common. First, they are located on the west side of the South Saskatchewan River, a river that flows through the center of the city (Figure 1). Second, they are older neighborhoods, built between 1900 and 1930, and finally, they are relatively low-income when compared to the Saskatoon median. These neighborhoods have a relatively high concentration of residents who (1) rent their homes, (2) do not own a vehicle, (3) identify as Aboriginal, (4) are newcomers, or (5) are seniors with fixed incomes [29]. Saskatoon has a large Aboriginal population, compared to other Canadian urban centers, and over half of this population is young (10% of the people living in Saskatoon identify as Aboriginal compared to 3.8% for Canada, and 55% are ≤ 24 y) [30,31]. (The term "Aboriginal" refers to the Indigenous peoples of Canada, descendants of the original inhabitants of this country. It is the legal term used in the Constitution Act of 1982 to refer to First Nations, Métis, and Inuit peoples.)

In September 2012, the Good Food Junction Cooperative Store (GFJ) opened as a result of an 8-year consultation and planning process focused on meeting the food needs of the people living in the area. This grocery store was tasked with improving the access of residents to healthy, affordable food. It is geographically located in the center of a former food desert [27] in the heart of one of the lowest income neighborhoods in the city. The 4900-square-foot store offers a wide range of fresh, frozen, and packaged foods.

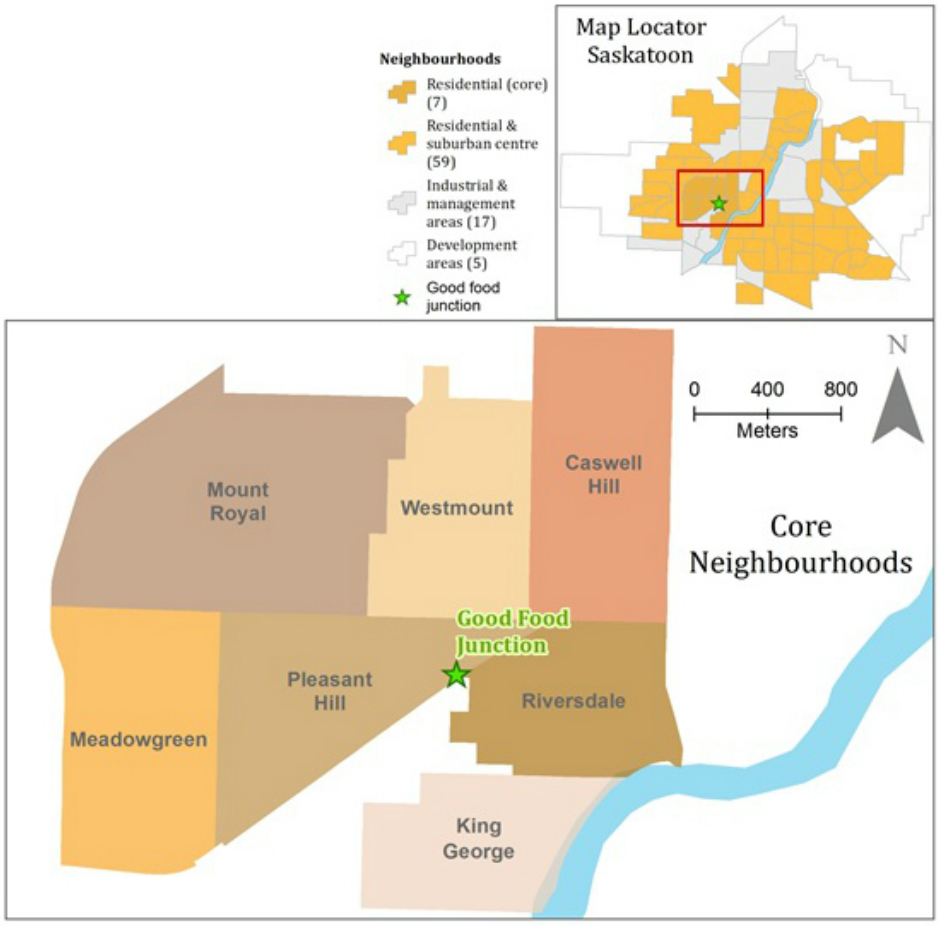
The core neighborhoods have had no major chain grocery stores since the mid-1990s, when the last such store closed [28]. The area also saw a loss of small local grocers, going from 12 local grocery stores in 1984 to 5 by 2004 [28]. A 2010 assessment found that residents of the core neighborhoods live much closer to fast food restaurants than to grocery stores, when compared to the citywide average [27].

The GFJ grocery store is housed in a building called Station 20 West [27]. Station 20 West includes the GFJ [32], a community

kitchen space, a coffee shop, community meeting space, and several offices for community-based organizations, health services and programming, and community-based research [33].

The goal of this research is to understand and model how the introduction of a large-scale food and nutrition-focused community-based population health intervention (the GFJ) may impact the health of individuals and families in a geographically bounded group of neighborhoods. The study proposal was peer-reviewed and funded by the Canadian Institutes for Health Research, through the Population Health Intervention Research funding stream (grant #127084).

Figure 1. Location of the Good Food Junction Grocery Store.



Methods

The study employed 3 approaches to data collection that roughly correspond to the 5 research questions stated below. There was (1) a cross-sectional door-to-door survey of household food access and demographics (research questions 1 and 2), (2) an analysis of food purchasing sales data obtained directly from the grocery store linked to unique membership numbers (research question 3), and (3) a year-long longitudinal 3-time-point study of food access and self-reported health of GFJ shoppers (research questions 4 and 5). Data collection was conducted from July 2013 through November 2014.

The following research questions informed the study:

1. What is the awareness and perception of the GFJ among residents of the core neighborhood?
2. Are there differences in awareness and perception among those who do and do not shop at the GFJ?
3. Will healthy food purchasing at the GFJ by residents of the core neighborhood change over time, and what purchases are these individuals making at this store?
4. What early impact(s) will the GFJ have on key health-related outcomes (such as household food security status, vegetable and fruit intake, key aspects of self-reported mental health, self-reported health)?
5. Are the effects of the intervention seen for specific vulnerable population groups, such as Aboriginal people, seniors (65 years or older), and new immigrants (settled in Saskatoon for less than 5 years)?

This complex, community-based study of the early impacts of the opening of a full-service grocery store in a former food desert has required a great deal of careful thought, flexibility, and willingness to adapt to the challenges of this type of research with a marginalized and difficult-to-access population. One of the goals of this paper, in addition to describing the research protocol, is to highlight some of the challenges experienced in conducting it and some of the ways in which the study was adapted due to circumstances outside of our control in studying the natural experiment that is the GFJ grocery store.

The project has received ethical approval from the University of Saskatchewan's Human Behavioural Research Ethics Board (#13-168, approval date: May 30, 2013). Informed consent was

obtained from all study participants. Participants have received detailed information outlining study goals and requirements. We have taken due care to inform participants regarding the purpose and the manner in which the data will be collected, used, and secured.

Cross-sectional Household Food Procurement Survey

In order to answer the first and second research questions, from July of 2013 to November 2013, a cross-sectional survey was administered. A team composed of 4 trained interviewers conducted the door-to-door survey administration in teams of 2. One of the 4 interviewers was a woman who lived adjacent to Station 20 West and was involved in the local community, and the other 3 were women who worked in or were otherwise involved in the community.

The intent of this quantitative survey was to examine the awareness and use of the GFJ grocery store approximately 1 year after opening and other food sources by individuals who lived within walking distance of the store.

With ArcGIS software, a road network of a 750-meter radius (with the GFJ at the center) formed the geographic boundaries for the study. All residential locations within this radius were considered to be within the sample. The distance of 750 meters from the GFJ was chosen to simulate a reasonable walking distance.

Drawing on information from the City of Saskatoon, a total of 1459 residences were considered to be within the 750-meter radius. Of this number, 271 locations were excluded as they were determined to be nonresidential, inaccessible, unsafe, vacant, or nonexistent. We did not want overlap between those who participated in the cross-sectional household food procurement survey and those participating in the longitudinal study described below. Therefore, given that the recruitment period for the 2 components of the research overlapped somewhat, we asked potential participants if they were already participating the longitudinal research. If they answered to the affirmative they were excluded from this component of the research (n=47 participants). The remaining 1141 households were contacted through door-to-door recruitment over a period of 5 months.

Individuals were eligible to participate in the short interviewer-administered survey if they were over 18 years of age, lived in the residence, and were the person primarily responsible for purchasing food for the household.

Topics covered in the survey included whether the participant was aware of the GFJ; if the participant had shopped at the GFJ; which grocery store was their primary grocer; and what mode/s of transportation the participant used to travel to said primary grocery store. Information regarding whether participants accessed a wide range of food programs provided by local nonprofits was also gathered, as well as sociodemographic and household composition information.

Initially, residences within the geographic boundary were randomly sampled for inclusion in the research, but it soon became clear that in order to cover more ground and efficiently collect data, it would be necessary to contact all households within the geographic boundaries of the study area. Interviewers worked in pairs and approached households until the successful completion of a survey, a direct refusal by a resident, or the third unsuccessful attempt to connect with a household member. Appointments were arranged with individuals who wanted to participate but were unable at the initial time of contact. Interviewers left printed door hangers on residences if no one was home, informing residents of the study and ways to participate.

For management of the data collection, the targeted geographical area was divided into 4 quadrants. Visits were systematically recorded on a log sheet, and these sheets were updated before each new round of outreach to potential participants. The schedule for conducting on-the-doorstep outreach was designed to ensure that residences were visited on different days, and at different times. For example, if there had been no one home during a weekday, the following visit was conducted on a weekend or in the early evening.

Of the residences approached, there were 180 refusals and 596 nonresponses after 3 visits. A total of 365 households within the 750-meter radius participated in the survey, which was 32% of all “eligible” households. The average length of interview was 10 minutes. Individuals who participated in the cross-sectional household survey were provided with a $10 gift card to the GFJ as compensation for their time.

All quantitative data for the door-to-door survey was entered and cleaned by study research staff and then analyzed using SPSS version 22 (IBM).

One peer-reviewed paper on this data has been published to date [34] but without description of full methodology as presented here, and full analysis is on-going.

Multilevel Cross-Sectional Analysis of GFJ Sales Data

In order to answer the third research question, the GFJ shared their sales data to allow the research team to track food sales data by postal code for analysis through a multilevel cross-sectional analytical design.

Since GFJ is a cooperative, members who shop at the store can be tracked to understand their purchasing behavior. For a period of 5 months, from May 1, 2013, to September 30, 2013, the research project paid the membership cost for any shoppers who wished to be a member of the GFJ cooperative. Each GFJ member is assigned a unique membership number, which is recorded at checkout. Food purchasing can be tracked through these membership numbers, as the store records a history of purchases made by each member. Through this database it is possible to analyze the patterns of food purchasing over a period of time.

One limitation with the GFJ sales data is that the membership database contains minimal information (eg, only the members’ postal codes and linked purchasing habits). Individual socioeconomic position is not recorded, but each member’s neighborhood’s socioeconomic position was derived using data from the 2006 Canadian Census, according to Pampalon’s deprivation index [35].

To date, the sales data have been used to observe the food purchasing habits of store members over a 1-year period in order to see whether shoppers living near the GFJ (the "targets" of the intervention) have different shopping patterns compared to GFJ members who live farther away from the GFJ (not targets of the intervention) [36]. As only member-purchases for a year-long period at the GFJ have been analyzed to date (plans for future analyses are described below), these results cannot show the full range of food purchases occurring in the store, nor what members purchased at other stores.

The food purchasing sales data was provided directly by the GFJ grocery store and was entered into a research database, then cleaned and categorized to allow for analysis. Sales data from the GFJ contains information on all food purchases made in the store, along with the membership database.

For our initial analyses, this resulted in information on 72,587 food purchases (by all users) during the period of interest of May 15, 2013, to April 30, 2014. During this period, 526 of the 1109 GFJ members in the data set did not make a purchase, leaving 583 members with 38,190 purchases available for analysis. Of the 583 members with purchase data, 361 (62%) lived in the "core" neighborhoods [36].

Food sales data from the store was categorized into 11 different categories using Stock Keeping Unit codes [37]. The categories were developed in reference to 2 Health Canada tools: Canada's Food Guide and the Canadian Nutrient File (a database containing information about nutrients in food in Canada) [38,39]. Five categories were considered healthy (eg, fruit, vegetables, meat and alternatives, dairy products, grains) and 6 categories were considered less healthy or nonfood (eg, sugar sweetened beverages, nonnutritive beverages, snack foods, prepared foods, flavoring, nonfood items) [39].

Longitudinal Food Access and Self-Reported Health Research with Shoppers

In order to answer the fourth and fifth research questions, a year-long 3-time point longitudinal study was conducted to record potential changes in perceived health status in people who made purchases at GFJ. Designed as a food access and health survey, the questions included perceptions of current health status, vegetable and fruit consumption, household food security, and perceptions of a sense of community in their neighborhood, all of which were taken from the Canadian Community Health Survey [40]. In addition, all participants were asked the questions covered in the cross-sectional food access and demographics survey described above.

The health and food access survey was conducted at 3 time points, with a cohort of 156 shoppers at the first time point. The intention was to have the survey administered 3 times with about 6 months between each administration (creating a year time frame of interviews conducted at months 0, 6, and 12). The first time point occurred between July and August 2013, the second was in February through April 2014, and the third administration occurred during July through November 2014.

Participants for this longitudinal study were recruited on-location at GFJ as they entered the store by the same trained interviewers who administered the cross-sectional door-to-door survey. Members of the research team were on-location for 2- to 3-hour periods during the initial recruitment phase. Team members alternated shifts between mornings and afternoons, in an effort to recruit as many shoppers as possible. In order to speed recruitment that was initially proceeding slowly, participants were also recruited through advertisement (predominantly poster and word-of-mouth) in the grocery store and nearby service agencies.

To participate, the respondent had to be over the age of 18, the primary shopper for their household, and was required to have shopped at GFJ at least 3 times in the previous 2 months. To prevent any possible overlap of households, participants were asked whether any other member of their household was already participating in the study. There were no stipulations for participants having to live within a certain geographic distance from the GFJ. It should be noted that residents who participated in the door-to-door survey described above were not recruited to participate in this part of the research.

Every effort was made with individual participants to leave a 6-month period between each iteration of survey administration. The surveys took an average 30 minutes to complete with administration always conducted with a trained interviewer. Due to the need for flexibility, a staff member from Station 20 West was trained to deliver the interview midway through the first iteration of data collection. This individual was well respected and known in the community and was available to participants who could not be accessed by the main interview team. This approach enabled the study to stay connected with participants who were highly transient or did not have phone numbers, and were therefore difficult to contact. Because they regularly attended Station 20 West to connect with resources available there, the staff member was able to ask them if they were willing to conduct follow-up interviews then and there. At each of the 3 data collection time points, participants were compensated for their time with a $25 GFJ gift card.

At the first data collection time point, 156 participants completed the survey. At the second administration of the survey, 129 participants from round 1 participated in the second survey (27 participants were lost to follow-up) but 24 new participants were added (recruitment was done in the same fashion as at the first time point), for a total of 153 participants completing the second round of data collection. In the third administration of the survey, 37 people were lost to follow-up and, therefore, 116 participants completed the survey. A total of 104 participants completed all 3 rounds of data collection and another 37 participants completed 2 rounds for a total of 141 participants with enough data to be included in the analysis.

Participants in this study were also offered a free lifetime membership (usual cost is $5) at the GFJ cooperative. This was done to provide the research team the possibility of analyzing their sales data in conjunction with their survey responses. It is not possible to determine whether being provided with a free membership influenced shopping habits, or whether this action incentivized usage of the store, but it is unlikely given that members do not receive any benefits beyond eligibility to participate in the annual general meeting.

Results

Data collection for this study is largely complete, but only a small fraction of it has been analyzed to date. Some data from the cross-sectional household food access survey and from sales at the Good Food Junction have been analyzed, but none of the longitudinal self-reported health and food access data from GFJ shoppers have been analyzed to date. The longitudinal research will likely be the largest contribution of this study to the literature, since very little longitudinal research on grocery store interventions in former food deserts has been published.

Two articles have been published to date: Cross-sectional analysis of a community-based cooperative grocery store intervention in Saskatoon, Canada [34], and Examining food purchasing patterns from sales data at a full-service grocery store intervention in a former food desert [36]. From analysis by Lotoski, Engler-Stringer, and Muhajarine of the door-to-door survey, it appears that residents are highly aware of the store (95% of residents were aware of the GFJ at the time of data collection) and most have shopped at the GFJ at least once [34]. Despite this, only 30 of the 251 (12.0%) households surveyed who had ever visited the GFJ used it as their primary grocery store.

Further analysis indicates that compared to residents who did not shop at the GFJ, residents who did shop at the GFJ had lower annual household incomes and were more likely to use local community-based food programs and services in comparison to non-users. This seems to indicate that the GFJ is serving households that are more likely to be facing food insecurity.

From the analysis by Fuller, Engler-Stringer, and Muhajarine [36], it appears that shoppers living in the core neighborhoods are making more healthy food purchases at the GFJ compared to shoppers who live outside of the core neighborhoods. For example, shoppers living in the core neighborhoods spend more on vegetables, and less on meat and alternatives and prepared foods, than shoppers who do not reside in those neighborhoods. This appears to be an indication that people will make healthy food purchases when healthy foods are accessible.

Discussion

Data analysis is on-going for this study. We will report on our data in several publications. The 3 time point, longitudinal self-reported health and food access research is currently in the early stages of analysis. There are 2 graduate students analyzing the longitudinal self-reported data on health and food access by GFJ shoppers; one focusing on the self-reported health, mental health, and sense of community of GFJ shoppers over time, and the other focusing on vegetable and fruit consumption and household food security of GFJ shoppers over time.

In terms of further analyses to be conducted on our door-to-door food access and demographics survey research, we intend to report on the distances traveled to the primary grocery store of choice and detail the use of community-based food programs of study participants. This will contribute to the literature examining food access practices by residents of low-income neighborhoods. In terms of GFJ sales data, we will also report on the temporality and seasonality of vegetable and fruit and other food purchasing in order to better understand (1) how these issues may impact the sustainability of food environment interventions and (2) how these types of interventions can better respond to the needs of users.

Finally, we are working on a publication that will discuss recruitment and retention challenges and lessons learned in conducting our study. We had to recruit and retain study participants from a marginalized population for this research, particularly very low-income and transient participants, and we found that we learned a great deal from this process, much of which we think will be relevant to others conducting similar research.

Conclusions

The Good Food Junction Grocery Store opened in 2012 due to a long-term concerted effort by Saskatoon core neighborhood residents and their supporters with the intended purpose of improving access to healthy food in a documented former food desert. Analyses in this study are on-going, but results to date show that shoppers are using the store for its intended purpose [34,36]. Our results show that residents of the neighborhoods directly adjacent to the store have very low household incomes and almost three-quarters of them use anywhere from 1 to 4 community-based food programs, including charitable programs (the food bank was the most widely reported) and numerous others, most of which focus on affordable access to vegetables and fruit. We have also found that the people who shop at GFJ have lower incomes and are more likely to be Aboriginal compared to those who do not. What is clear from our analysis to date is (1) the very low socioeconomic status of our study participants and (2) the importance of better understanding the needs of this population in order to support their access to healthy food.

To our knowledge this is the first large-scale study of a full-service grocery store intervention in a former food desert in Canada that has used multiple data sources, as well as longitudinal analyses, to examine its effects. The study's findings will contribute significantly to the knowledge base on food environment interventions.

Acknowledgments

The authors thank Paula Mowat for her help putting this article together. We also thank the GFJ, the Good Food Healthy Families research team, the Saskatchewan Population Health and Evaluation Research Unit staff, and, especially, Melissa Gan, Jacinda Sigurdson, Elsie Piché-Johnson, and Amanda Guthrie. Funding for this project was provided by the Canadian Institutes for Health Research (#127084).

Conflicts of Interest

None declared.

Multimedia Appendix 1

CIHR Peer-Review reports.

[PDF File (Adobe PDF File), 277KB - resprot_v5i2e52_app1.pdf]

References

1. Swinburn B, Egger G, Raza F. Dissecting obesogenic environments: the development and application of a framework for identifying and prioritizing environmental interventions for obesity. Prev Med 1999 Dec;29(6 Pt 1):563-570. [doi: 10.1006/pmed.1999.0585] [Medline: 10600438]
2. Cummins S, Macintyre S. Food environments and obesity--neighbourhood or nation? Int J Epidemiol 2006 Feb;35(1):100-104 [FREE Full text] [doi: 10.1093/ije/dyi276] [Medline: 16338945]
3. Lake A, Townshend T. Obesogenic environments: exploring the built and food environments. J R Soc Promot Health 2006 Nov;126(6):262-267. [Medline: 17152319]
4. Glanz K, Sallis JF, Saelens BE, Frank LD. Healthy nutrition environments: concepts and measures. Am J Health Promot 2005;19(5):330-3, ii. [Medline: 15895534]
5. Kirk S F L, Penney TL, McHugh TLF. Characterizing the obesogenic environment: the state of the evidence with directions for future research. Obes Rev 2010 Feb;11(2):109-117. [doi: 10.1111/j.1467-789X.2009.00611.x] [Medline: 19493302]
6. Townshend T, Lake AA. Obesogenic urban form: theory, policy and practice. Health Place 2009 Dec;15(4):909-916. [doi: 10.1016/j.healthplace.2008.12.002] [Medline: 19201641]
7. Larson N, Story MT, Nelson MC. Neighborhood environments: disparities in access to healthy foods in the U.S. Am J Prev Med 2009 Jan;36(1):74-81. [doi: 10.1016/j.amepre.2008.09.025] [Medline: 18977112]
8. Story M, Kaphingst KM, Robinson-O'Brien R, Glanz K. Creating healthy food and eating environments: policy and environmental approaches. Annu Rev Public Health 2008;29:253-272. [doi: 10.1146/annurev.publhealth.29.020907.090926] [Medline: 18031223]
9. Morland K, Diez Roux Ana V, Wing S. Supermarkets, other food stores, and obesity: the atherosclerosis risk in communities study. Am J Prev Med 2006 Apr;30(4):333-339. [doi: 10.1016/j.amepre.2005.11.003] [Medline: 16530621]
10. Sturm R, Datar A. Body mass index in elementary school children, metropolitan area food prices and food outlet density. Public Health 2005 Dec;119(12):1059-1068. [doi: 10.1016/j.puhe.2005.05.007] [Medline: 16140349]
11. Neff R, Palmer AM, McKenzie SE, Lawrence RS. Food systems and public health disparities. J Hunger Environ Nutr 2009 Jul;4(3-4):282-314 [FREE Full text] [doi: 10.1080/19320240903337041] [Medline: 23173027]
12. Auchincloss A, Diez Roux Ana V, Brown DG, Erdmann CA, Bertoni AG. Neighborhood resources for physical activity and healthy foods and their association with insulin resistance. Epidemiology 2008 Jan;19(1):146-157. [doi: 10.1097/EDE.0b013e31815c480] [Medline: 18091002]
13. Sharkey J. Measuring potential access to food stores and food-service places in rural areas in the U.S. Am J Prev Med 2009 Apr;36(4 Suppl):S151-S155. [doi: 10.1016/j.amepre.2009.01.004] [Medline: 19285206]
14. Horowitz C, Colson KA, Hebert PL, Lancaster K. Barriers to buying healthy foods for people with diabetes: evidence of environmental disparities. Am J Public Health 2004 Sep;94(9):1549-1554. [Medline: 15333313]
15. Caspi C, Sorensen G, Subramanian SV, Kawachi I. The local food environment and diet: a systematic review. Health Place 2012 Sep;18(5):1172-1187 [FREE Full text] [doi: 10.1016/j.healthplace.2012.05.006] [Medline: 22717379]
16. Gittelsohn J, Franceschini M, Rasooly I, Ries A, Ho L, Pavlovich W, et al. Understanding the food environment in a low-income urban setting: implications for food store interventions. J Hunger & Environ Nutr 2008 Apr 15;2(2-3):33-50. [doi: 10.1080/19320240801891438]
17. Gittelsohn J, Song HJ, Suratkar S, Kumar MB, Henry EG, Sharma S, et al. An urban food store intervention positively affects food-related psychosocial variables and food behaviors. Health Educ Behav 2010 Jun;37(3):390-402. [doi: 10.1177/1090198109343886] [Medline: 19887625]
18. IOM (Institute of Medicine)National Research Council (NRC). The public health effects of food deserts: Workshop summary; The National Academies Press: Washington, DC. : National Academies Press; 2009 Jun 02 Presented at: The Public Health Effects of Food Deserts; January 26-27, 2009; Washington, D.C.
19. Cummins S, Petticrew M, Higgins C, Findlay A, Sparks L. Large scale food retailing as an intervention for diet and health: quasi-experimental evaluation of a natural experiment. J Epidemiol Community Health 2005 Dec;59(12):1035-1040 [FREE Full text] [doi: 10.1136/jech.2004.029843] [Medline: 16286490]
20. Holmes A, Estabrooks PA, Davis GC, Serrano EL. Effect of a grocery store intervention on sales of nutritious foods to youth and their families. J Acad Nutr Diet 2012 Jun;112(6):897-901. [doi: 10.1016/j.jand.2012.01.012] [Medline: 22513119]
21. Morland KB. An evaluation of a neighborhood-level intervention to a local food environment. Am J Prev Med 2010 Dec;39(6):e31-e38. [doi: 10.1016/j.amepre.2010.08.006] [Medline: 21084065]

22. Cummins S, Flint E, Matthews SA. New neighborhood grocery store increased awareness of food access but did not alter dietary habits or obesity. Health Aff (Millwood) 2014 Feb;33(2):283-291 [FREE Full text] [doi: 10.1377/hlthaff.2013.0512] [Medline: 24493772]
23. Sadler R, Gilliland JA, Arku G. A food retail-based intervention on food security and consumption. Int J Environ Res Public Health 2013 Aug;10(8):3325-3346 [FREE Full text] [doi: 10.3390/ijerph10083325] [Medline: 23921626]
24. Wrigley N, Warm D, Margetts B. Deprivation, diet, and food retail access: findings from the Leeds 'food deserts' study. Environ Plan A 2003 Jan 01;35(1):151-188. [doi: 10.1068/a35150]
25. Cummins S, Findlay A, Higgins C, Petticrew M, Sparks L, Thomson H. Reducing inequalities in health and diet: findings from a study on the impact of a food retail development. Environ Plan A 2008 Feb 01;40(2):402-422. [doi: 10.1068/a38371]
26. Cummins S, Findlay A, Pettitcrew M, Sparks L. Healthy cities: The impact of food retail-led regeneration on food access, choice and retail structure. Built Environment 2005;31(4):288-301.
27. Cushon J, Creighton T, Kershaw T, Marko J, Markham T. Deprivation and food access and balance in Saskatoon, Saskatchewan. Chronic Dis Inj Can 2013 Jun;33(3):146-159 [FREE Full text] [Medline: 23735454]
28. Peters E, McCreary T. Poor neighbourhoods and the changing geography of food retailing in Saskatoon, Saskatchewan, 1994-2004. Canadian Journal of Urban Research 2008;17(1):78-106.
29. CommunityView Collaboration. CommunityView Collaboration. 2015. Saskatoon Community Profiles URL: http://www.communityview.ca/Catalogue/ResourceList/Browse/78 [accessed 2016-02-03] [WebCite Cache ID 6f1izFJ5k]
30. Statistics Canada. 2006 Census: Aboriginal Peoples in Canada in 2006: Inuit, Métis and First Nations, 2006 Census: Findings. Ottawa, Canada: Statistics Canada; 2006. Aboriginal peoples in canada in 2006: Inuit, Metis and First Nations URL: https://www12.statcan.gc.ca/census-recensement/2006/as-sa/97-558/index-eng.cfm [accessed 2016-02-03] [WebCite Cache ID 6f1j9oeFU]
31. Statistics Canada. NHS Aboriginal Population Profile, Saskatoon, CMA, Saskatchewan, 2011. Ottawa, Canada: Statistics Canada URL: http://www12.statcan.gc.ca/nhs-enm/2011/dp-pd/aprof/details/page.cfm?Lang=E&Geo1=CMA&Code1=725&Data=Count&SearchText=Saskatoon&SearchType=Begins&SearchPR=01&A1=All&B1=All&GeoLevel=PR&GeoCode=725&TABID=1
32. Good Food Junction. (June 22 2015), URL: http://goodfoodjunction.com/ [accessed 2016-02-03] [WebCite Cache ID 6f1hL1VwA]
33. Station 20 West. URL: http://www.station20west.org/ [accessed 2016-02-01] [WebCite Cache ID 6ezA7jn3D]
34. Lotoski L, Engler-Stringer R, Muhajarine N. Cross-sectional analysis of a community-based cooperative grocery store intervention in Saskatoon, Canada. Can J Public Health 2015;106(3):e147-e153. [Medline: 26125241]
35. Pampalon R, Hamel D, Gamache P, Raymond G. A deprivation index for health planning in Canada. Chronic Dis Can 2009;29(4):178-191 [FREE Full text] [Medline: 19804682]
36. Fuller D, Engler-Stringer R, Muhajarine N. Examining food purchasing patterns from sales data at a full-service grocery store intervention in a former food desert. Preventive Medicine Reports 2015;2:164-169. [doi: 10.1016/j.pmedr.2015.02.012]
37. Investopedia. (November 6,). 2015. Stock keeping unit - sku URL: http://www.investopedia.com/terms/s/stock-keeping-unit-sku.asp [accessed 2015-11-09] [WebCite Cache ID 6cumGzi3o]
38. Health Canada. 2011. Eating well with Canada's Food Guide; Ottawa, Ontario URL: http://www.hc-sc.gc.ca/fn-an/food-guide-aliment/index-eng.php [accessed 2016-02-03] [WebCite Cache ID 6f1hfF1NT]
39. Health Canada. 2010. The Canadian Nutrient File, version #160;2010 URL: http://www.hc-sc.gc.ca/fn-an/nutrition/fiche-nutri-data/cnf_aboutus-aproposdenous_fcen-eng.php [accessed 2016-02-03] [WebCite Cache ID 6f1ho5Iv4]
40. Health Canada. 2012. Canadian Community Health Survey URL: http://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&SDDS=5049

Abbreviations

GFJ: Good Food Junction Cooperative Store

Edited by G Eysenbach; submitted 09.11.15; this is a non–peer-reviewed article;accepted 10.12.15; published 14.04.16.

Please cite as:
Engler-Stringer R, Muhajarine N, Ridalls T, Abonyi S, Vatanparast H, Whiting S, Walker R
The Good Food Junction: a Community-Based Food Store Intervention to Address Nutritional Health Inequities
JMIR Res Protoc 2016;5(2):e52
URL: http://www.researchprotocols.org/2016/2/e52/
doi:10.2196/resprot.5303
PMID:27079140

Proposal

Development and Testing of a Computerized Decision Support System to Facilitate Brief Tobacco Cessation Treatment in the Pediatric Emergency Department: Proposal and Protocol

E. Melinda Mahabee-Gittens[1], MD, MS; Judith W Dexheimer[2], PhD; Jane C Khoury[3], PhD; Julie A Miller[1], PhD, APRN; Judith S Gordon[4], PhD

[1]Cincinnati Children's Hospital Medical Center, Division of Emergency Medicine, Cincinnati, OH, United States

[2]Cincinnati Children's Hospital Medical Center, Division of Emergency Medicine and Department of Biomedical Informatics, Cincinnati, OH, United States

[3]Cincinnati Children's Hospital Medical Center, Division of Biostatistics and Epidemiology, Cincinnati, OH, United States

[4]University of Arizona, Department of Family & Community Medicine, Tucson, AZ, United States

Corresponding Author:
E. Melinda Mahabee-Gittens, MD, MS
Cincinnati Children's Hospital Medical Center
Division of Emergency Medicine
3333 Burnet Avenue
Cincinnati, OH, 45229
United States
Phone: 1 5136367966
Fax: 1 5136367967
Email: melinda.mahabee-gittens@cchmc.org

Abstract

Background: Tobacco smoke exposure (TSE) is unequivocally harmful to children's health, yet up to 48% of children who visit the pediatric emergency department (PED) and urgent care setting are exposed to tobacco smoke. The incorporation of clinical decision support systems (CDSS) into the electronic health records (EHR) of PED patients may improve the rates of screening and brief TSE intervention of caregivers and result in decreased TSE in children.

Objective: We propose a study that will be the first to develop and evaluate the integration of a CDSS for Registered Nurses (RNs) into the EHR of pediatric patients to facilitate the identification of caregivers who smoke and the delivery of TSE interventions to caregivers in the urgent care setting.

Methods: We will conduct a two-phase project to develop, refine, and integrate an evidence-based CDSS into the pediatric urgent care setting. RNs will provide input on program content, function, and design. In Phase I, we will develop a CDSS with prompts to: (1) ASK about child TSE and caregiver smoking, (2) use a software program, Research Electronic Data Capture (REDCap), to ADVISE caregivers to reduce their child's TSE via total smoking home and car bans and quitting smoking, and (3) ASSESS their interest in quitting and ASSIST caregivers to quit by directly connecting them to their choice of free cessation resources (eg, Quitline, SmokefreeTXT, or SmokefreeGOV) during the urgent care visit. We will create reports to provide feedback to RNs on their TSE counseling behaviors. In Phase II, we will conduct a 3-month feasibility trial to test the results of implementing our CDSS on changes in RNs' TSE-related behaviors, and child and caregiver outcomes.

Results: This trial is currently underway with funding support from the National Institutes of Health/National Cancer Institute. We have completed Phase I. The CDSS has been developed with input from our advisory panel and RNs, and pilot tested. We are nearing completion of Phase II, in which we are conducting the feasibility trial, analyzing data, and disseminating results.

Conclusions: This project will develop, iteratively refine, integrate, and pilot test the use of an innovative CDSS to prompt RNs to provide TSE reduction and smoking cessation counseling to caregivers who smoke. If successful, this approach will create a sustainable and disseminable model for prompting pediatric practitioners to apply tobacco-related guideline recommendations. This systems-based approach has the potential to reach at least 12 million smokers a year and significantly reduce TSE-related pediatric illnesses and related costs.

(JMIR Res Protoc 2016;5(2):e64) doi:10.2196/resprot.4453

KEYWORDS

smoking; tobacco smoke; parent; secondhand smoke; medical informatics; clinical decision support; smoking cessation

Introduction

Background

Each year over 480,000 deaths in the United States are attributable to smoking, accounting for one in five deaths, and up to one-half of all smokers die prematurely [1]. In addition to the harmful consequences to the smoker, exposure of nonsmokers to tobacco smoke (TSE) is a serious health hazard. TSE is unequivocally harmful to children's health as evidenced by increased rates of asthma, bronchiolitis, and respiratory infections [2-4]. TSE-related illnesses result in increased Pediatric Emergency Department (PED) visits and hospitalizations [5-8]. In the United States, more than 25.5 million children are treated in PEDs each year [9] and our own research has found rates of smoking in caregivers as high as 48% (865/1809) [10-13]. Therefore, as many as 12 million children who visit the PED are exposed to tobacco smoke.

The American Academy of Pediatrics (AAP) considers tobacco use a "pediatric disease" given the pediatric morbidity caused by adult tobacco use and TSE [14]. The AAP and the *Clinical Practice Guidelines for Treating Tobacco Use and Dependence* (CPGs) [15,16] provide recommendations on the treatment of adult caregivers who smoke for pediatric practitioners, which includes three components: (1) use of electronic health records (EHR) to document or "ASK" about tobacco use and TSE at each clinical encounter, (2) use of clinical decision support systems (CDSS) to "ADVISE" and provide brief cessation counseling in the clinical setting, and (3) "ASSESS" readiness to change and "ASSIST" all smokers in their efforts to make their homes and cars smoke-free and quit smoking. This approach targets the benefits of quitting on reducing the child's TSE, and offers the potential to decrease tobacco-related morbidity in both the caregiver and child. This expanded use of the EHR to prompt nurses to treat tobacco dependence has been used in adult settings [15,17,18], and provides a means to standardize screening and counseling of tobacco users in the PED. However, despite these recommendations and evidence of effectiveness in adult settings, no standardized protocols currently exist in PEDs to guide practitioners in the treatment of adult smokers as recommended by the AAP or the CPGs. Our research has shown that tobacco interventions are feasible and effective in the PED setting [10,13].

This project will develop and test new approaches to increase nurse delivery of TSE and cessation interventions to caregivers who smoke who are not pediatric patients. Because past research has shown that PED nurses do not deliver TSE counseling in a systematic way due to barriers such as lack of training, time, and structured systems in intervening with adults [19-22], we plan to integrate CDSS prompts into the EHR to promote national treatment recommendations for caregivers in the PED in a time-efficient, simple way. We will implement a systems-based strategy that can be widely disseminated, and we will systematically assess tobacco use for all caregivers of PED patients.

For a CDSS to be successful, it must be integrated within the complex environment of the health care setting [23]. This technology must dynamically interact with practitioners, patients/parents, and existing health care systems [23-25]. One of the biggest challenges with implementation is clinical workflow integration because if the CDSS tools are too difficult or cumbersome to incorporate into the workflow, they will not be used [26-28]. Thus, it has been recommended that prior to integrating a CDSS into the health care setting, it is crucial to ensure that it first reflects the needs and preferences of the users (eg, nurses), and the organization systems (eg, PED) within which it is going to be implemented [25]. The CDSS should then only be introduced into clinical practice after an iterative formative evaluation, usability testing, and pilot field testing, designed to facilitate modifications to the CDSS based on user's needs and the clinical environment [25]. We will adopt this developmental approach and pilot testing strategy in the proposed project.

Framework and Design Objectives for the Clinical Decision Support System

We will adopt the Chronic Care Model as the framework for our proposed CDSS. This model is a widely disseminated paradigm for redesigning health care systems to be more proactive and focused on keeping people healthy rather than reactively treating preventable conditions [29-32]. Because we are addressing caregiver smoking in the PED setting during the child's (and not the caregiver's) acute care visit, this model is particularly appropriate and represents an innovative approach for developing our CDSS. Furthermore, because the elements of the model comprise all of the system approaches recommended for tobacco use, it provides a unifying approach for dealing with multiple behavioral risk factors [29,30]. Using this model as the guide, we will work to ensure positive caregiver-nurse interactions through the use of several systems that start during the PED visit.

The systems that we will use to provide a unifying approach that will facilitate caregiver-nurse interactions during the child's PED visit include: (1) clinical decision support: we will develop and integrate CDSS reminder prompts based on the CPGs [16] that will include "ASK," "ADVISE," "ASSESS," and "ASSIST" ("ARRANGE" and "ASSIST" behaviors will be consolidated under the "ASSIST" prompt) and the AAP recommendations (eg, home and car smoking bans), and provide training using the CPGs as a framework, (2) enhanced delivery: we will clearly define nurse roles and establish accountability for these roles by developing Feedback Reports to inform nurses about their TSE counseling behavior, (3) clinical information: we will create a caregiver registry within the EHR to identify smokers, keep track of who has been provided with TSE counseling, and capture caregiver/patient outcomes (using a convenience sample), (4) personalized cessation resources: we will facilitate a direct, "active" referral to the caregivers' choice of free, evidence-based cessation program/resources (eg, telephone Quitline (QL), SmokefreeTXT, SmokefreeGOV), and (5)

self-management support: we will ensure that caregivers are active participants in their care by providing information on cessation resources and written self-help and motivational materials.

The design objectives will be influenced by a team-oriented workflow of care in the PED and local adaptation of the CPGs and other cessation CDSS that have been integrated with the EHR in adult settings [15-18]. The design will include the following steps: identifying caregivers who smoke using easy-to-use screening prompts, providing an electronic link to the brief counseling advice that nurses should provide to caregivers, and evaluating nurse behavior in the ASK, ADVISE, ASSESS, and ASSIST steps. The CDSS prompts will facilitate screening and counseling reminder systems by integrating four different information systems that are part of the total PED system and clinical research infrastructure considered critical for successful implementation. These four systems are: (1) hospital-wide information systems: an enterprise EHR system, Epic, (2) PED clinical systems: the documentations screens used in the current workflow, (3) clinical research: the Research Electronic Data Capture (REDCap) [33] database, and (4) the CPGs for tobacco use: links will be provided to generate an active referral to cessation resources based on caregiver preference.

The CDSS will be built using a combination of the EHR and REDCap. The Epic EHR has approximately 11.6% of the total EHR market share in the United States [34,35]. It is used by approximately 835 customers in the United States, securely managing over 1.25 million patient health records per month. Approximately 40% of the US population has its medical information stored in an Epic EHR [36]. The emergency department information system allows the addition of modules to existing applications based on customer needs. We will display the child's TSE and the caregiver's smoking status within the child's EHR. However, because the counseling (ie, ADVISE, ASSESS, ASSIST) steps will solely relate to the caregivers, these steps will be completed outside of the child's EHR in REDCap. The use of REDCap is necessary in order to maintain separate records for the parents/caregivers, who are not patients, and for whom information cannot be stored in the child's health record. REDCap is a Web-based application for building and managing Internet surveys and longitudinal databases with a secure Web connection with authentication and data logging. It has the ability to create, share, and modify counseling prompt templates for use in any ED setting, can link to external webpages (eg, smokefreeTXT) and has automated, seamless export procedures for data downloads to statistical packages [33]. Each PED room contains an Internet-connected computer and access to the EHR. The EHR can provide a prompt to link to REDCap after the caregiver is identified as a current smoker so that the nurse will be able to collect data on caregivers, provide caregivers with cessation counseling messages based on the prompts, obtain QL fax referrals and/or TSE reduction tips, or provide "active" referrals by connecting to the SmokefreeTXT or SmokefreeGOV website [33]. REDCap can be accessed at any time so that counseling can be performed and recorded in the patient's room at the nurse's convenience. By using existing nursing workflow and automatic prompts, we will create a sustainable intervention requiring minimal additional data entry by nurses, and this will facilitate the clinical workflow between the PED nurse and physician.

Phase I: Development and Programming of the Decision Support System and Feedback Reports

We will conduct a two phase project with the following aims: Aim 1: convene an advisory panel of PED and EHR technical experts to develop the prototype CDSS with the ASK, ADVISE, ASSESS, and ASSIST prompts to facilitate caregiver tobacco screening and TSE counseling. The CDSS will use a software program (REDCap) that, due to being Web-based, has the capability to interface with an EHR system to trigger brief TSE counseling tips and direct links for registered nurses (RNs) to provide to caregivers. The CDSS template will contain all the necessary elements of text, graphics, and interactive features to ensure generalizability and disseminability. Aim 2: develop feedback reports from data extracted from the CDSS to show individual and overall RN compliance with the use of the tobacco screening and TSE counseling prompts. Aim 3: to refine CDSS functionality and improve feedback reports by conducting RN focus and user groups.

Phase II: Feasibility and Acceptability Trial of the Decision Support System

Finally, Aim 4: to conduct a feasibility and acceptability trial of the CDSS and feedback reports. We will: (1) obtain a baseline assessment of RNs' attitudes, barriers, and tobacco-related screening, advising, and assisting behaviors, (2) train RNs on the use of the CDSS and evidence-based TSE counseling strategies and resources for on-going tobacco cessation treatment, (3) assess changes in RNs' attitudes, perceived barriers, and behaviors 1- and 3-months after training and obtain RN's satisfaction with the CDSS, (4) assess the smoking behavior and child TSE of a convenience sample of caregivers and children who are current smokers. We will assess changes in TSE-related outcomes of total home/car smoking bans (validated via salivary cotinine) and caregiver smoking behavior (validated by expired CO in those caregivers who report abstinence) in a 10% subset of participants, and (5) conduct exit focused interviews of nurses at 3 months post-training to obtain recommendations for refining and sustaining the CDSS over time.

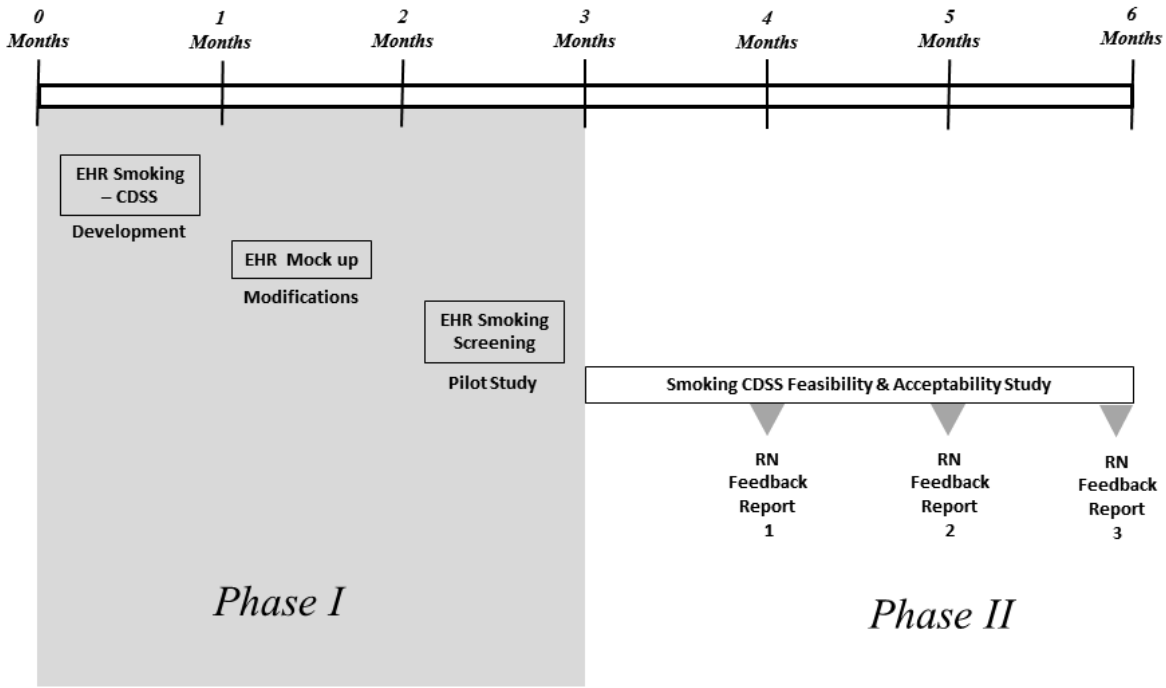
The following hypothesis will be explored during Phase I and Phase II. Hypothesis 1: at follow-up, there will be an increase in self-reported TSE counseling behaviors and attitudes and decreases in perceived barriers toward TSE counseling by trained RNs. Hypothesis 2: over the 3-month observation period, there will be an increase in CDSS verified TSE counseling behaviors by trained RNs receiving feedback reports. Hypothesis 3: over the 3-month period, there will be lower child TSE and caregivers will report decreases in cigarette use, increased motivation to quit, and increased use of cessation resources compared with baseline.

Methods

A Two-Phase Study

This study will be conducted in two phases. In Phase I, we will develop an alpha version of the CDSS with an advisory panel; the alpha version will be revised based on feedback from nurses in focused interviews and small focus groups; this refined version will be iteratively evaluated in a test environment. A portion of the alpha CDSS will be tested in the live environment prior to launching the beta (prototype) full CDSS version. Additionally, we will create nurse feedback reports to encourage the use of the CDSS prompts. The feedback reports will be designed to illustrate how frequently the nurses perform the different tasks within the CDSS compared with other study nurses. In Phase II, we will test the feasibility and acceptability of the CDSS and the feedback reports with RNs working in the Urgent Care portion of the Cincinnati Children's Hospital Medical Center (CCHMC) PED. Please see Figure 1. Descriptions of each phase are listed below.

Figure 1. Steps in the development and testing of the smoking Clinical Decision Support System.



Phase I: Definition Phase and Iterative Usability and Validity Testing

This phase will be devoted to the development, programming, and integration of the CDSS prompts into the EHR and creation of nurse feedback reports. The prompts will facilitate nurse documentation and administration of the screening and TSE counseling components. After developing the CDSS and feedback reports based on input from a multidisciplinary advisory panel, we will conduct nurse-focused interviews, small focus groups, and small user groups to refine the CDSS and feedback report content and interface.

Setting

CCHMC is the primary provider of inpatient, subspecialty, and emergency care in Greater Cincinnati and the surrounding counties serving over 2 million people. CCHMC is a 628-bed, freestanding, academic, pediatric medical center with more than 1.2 million patient encounters annually and over 800 faculty members and 15,000 employees. It has over 30,000 admissions, 33,000 surgeries, 900,000 ambulatory encounters, and 125,000 emergency department visits per year. This study will occur in the Urgent Care portion of the PED at CCHMC. The PED is a 24/7 facility with five separate Urgent Care sites. The Urgent Care sites are open 7 days a week with varying hours that range from 3 PM to midnight during weekdays and 9 AM to midnight on the weekends. CCHMC uses an enterprise EHR system from Epic. The EHR has been in use since 2009.

Participants

The participants will consist of an advisory panel and focused interviews and user groups**.** The advisory panel will include a multidisciplinary panel consisting of experts in tobacco cessation, biomedical informatics, PED nurse managers, clinical

PED nurses, PED physicians, EHR analysts, and PED flow experts. The focused interviews and user groups will include nurses who work at least once a month in the urgent care will be recruited and verbally consented. These RNs care for 10 to 40 patients during a 12-hour shift. We will obtain institutional review board approval for all study-related activities and consent procedures.

Procedures for Data Collection and Analysis

The advisory panel will evaluate the current PED workflow and EHR. They will evaluate which providers input information and how data from past records are incorporated into new PED visits. This group will then develop the "ASK, ADVISE, ASSESS, and ASSIST prompts that will be used to identify and counsel smokers and the group will assess how these prompts will affect patient flow and health care delivery to avoid any interruptions in care of the pediatric patient. The CDSS will use REDCap to trigger brief TSE counseling tips and direct links for RNs to provide to caregivers. The counseling steps will not be part of the child's EHR.

We will conduct focused interviews and small focus groups with PED nurses. During the focus interviews/groups, nurses will be presented with paper copies of mock-ups of each of the prompts in the CDSS and they will provide input on each of the prompts and on the interface with the CDSS in the EHR and with REDCap. They will provide input to make iterative changes. Nurses will be asked structured questions on the content, appearance, design, and format of the prompts and feedback reports and will provide input on the functionality, use, and adaptation of the prompts into their clinical workflow.

After iterative changes have been made based on the feedback provided by the nurses in the focused interviews/groups, we will user-test the CDSS in a test environment to allow nurses to access the CDSS to assess usability. Staff will perform usability testing of the additions to the EHR using observational and "think-aloud" procedures. Nurses will be observed interacting with the CDSS and will be asked to complete a brief survey upon completion of the suggested tasks; any problems will be noted. Notes will be reviewed and the survey will be completed by nurses to determine which independent thematic aspects will be organized around the CDSS and prompts to assess the following: functionality, content, number of "clicks," length, appearance, format, and type, ease of use, time to use, linkage from Epic to REDCap, linkage to cessation materials, linkage to the SmokefreeGOV website, SmokefreeTXT, integration with regular PED and Urgent Care workflow, technical support and training required, perception of maintenance of use and sustainability, and acceptability of feedback reports. This data will be used to iteratively refine the CDSS and feedback reports for use in Phase II. We will perform an iterative design process. All data will be analyzed, integrated, and used to refine the prompts with components from the CPGs and prior efficacious TSE and cessation interventions [10,13,16,37-39]. Following these analyses, we will develop a list of design changes that will be incorporated into the revised CDSS by the Epic team and used in the next round of usability testing.

Programming of the CDSS and Creation of Feedback Reports

Electronic Health Record Design

The EHR data collection section will fit into the current nursing workflow. The smoking cessation parent and caregiver screening and counseling will be integrated into the existing EHR. This integration will include coding within the EHR and adherence to the existing workflow. This integration will require a link to an external system (REDCap) to complete screening. We will include an external database to collect data because the cessation screening data is directly related to the parents and caregivers (who are not our patients), and therefore is not appropriate to be stored in the child's EHR. All code is contained and adheres to the CCHMC customization of the Epic EHR.

Adhering to constraints of the EHR, we will integrate cessation screening questions with branching logic to streamline the collection of demographic smoking status data for caregivers. If any caregiver screens positive for smoking, we will launch an alert requesting the nurse provide cessation counseling. The nurse will be able to close the alert and select an appropriate refusal reason if necessary, click a link that goes directly to a REDCap survey, or create a nursing order as a reminder to perform cessation screening at a time that is more convenient. This order will include a link to the REDCap database.

Research Electronic Data Capture Design

The REDCap database will be developed based on advisory panel recommendations for the ASK, ADVISE, ASSESS, and ASSIST steps. Patient medical record number will be used to link parent responses with the patient chart. We will use branching logic to display a minimum survey if the caregivers answer "No" to cessation information. The survey results will be used to drive the nursing feedback reports.

Feedback Report Design

The nursing feedback reports will be based on the proportion of patients seen during the prior month's shifts to account for differences in nursing workloads. Feedback reports will display the number of patient caregivers screened (EHR documentation complete in the "ASK" step) compared with the number of patients that the nurse treated that month. For the caregivers screened as positive, REDCap data will be aligned to calculate the proportion of patients who had the ADVISE, ASSESS, and ASSIST steps completed. These data will be presented graphically to the participating nursing staff monthly through a study email account. Nurses will only have their specific results compared with an aggregate average.

CDSS Screening and Counseling Prompts and Feedback Reports

Screening, or ASK Prompt

The caregiver's current smoking status will be assessed within the EHR, as screening will be integrated into the existing PED workflow during the routine medical intake process by the nurse. The new field will read "Do any of the primary caregivers smoke inside or outside of the home?" If the caregiver answers "Yes," then a series of question will assess the number of caregivers

who smoke, the relationship of the caregivers to the patient, and then finally, if that caregiver smokes "every day" or "some days". The appropriate smoking status will be selected and recorded within the EHR. If more than one caregiver is present and verified as primary caregivers, both will be screened. If a caregiver has a repeat visit, the prior screening information will be available from the last visit. Completion of the screening prompt will be optional but strongly encouraged for the nurse to proceed further in the patient's EHR documentation.

Once these questions are completed and one or more caregivers are identified as current smokers, a Best Practice Advisory, pop-up alert window opens up that recommends that smoking cessation counseling be given and asks if the nurse would like to provide counseling. Nurses may select check boxes to counsel now, counsel later (in which case orders will be generated), or to decline counseling for reasons such as patient acuity, time constraints, non-English speaking caregivers, and so on. The completion of the counseling prompts will not be mandatory so that the nurse can use their clinical judgment to opt out as necessary.

Counseling Prompts – Overview

When a caregiver(s) is identified as being a current smoker, the coded results from this electronic question will be used to generate counseling prompts and reminders of the stepwise series of the CPGs. To make these prompts and reminders appear less burdensome, we will consolidate the key counseling elements of the CPGs into three steps: ADVISE to quit, ASSESS readiness to quit, and ASSIST in cessation attempt. Our approach is similar to "Ask, Advise, Refer," which has been used successfully in other settings [40].

ADVISE Prompt

The ADVISE prompt will assist nurses to provide information on how quitting will benefit their child. Nurses will be given training on additional advice that they can give such as: implementing complete home/car smoking bans and quitting smoking; asking caregivers about the perceived impact of smoking on their childÃ¢â‚¬â„¢s health, barriers to implementing smoking bans and/or quitting, and perceived health/lifestyle benefits associated with bans/quitting for their child and themselves; and setting goals for reducing TSE/quitting [41,42].

ASSESS Prompt

The ASSESS prompt will cue the nurse to ask if the caregiver is ready to quit smoking in the next 30 days. Caregivers who respond that they are not ready will be told "I understand that you're not ready to quit now" and offered an information packet for when they are ready to quit. Those who respond that they are ready or may be ready to quit will be offered assistance by the nurse.

ASSIST Prompt

When the ASSIST prompt is selected, a set of options with branched logic will appear. Nurses will be cued to ask "May I tell you about three options?" The nurses will then be prompted to provide information about one or more of the following options: the QL: Nurses will give information about the services that the QL provides and offered a fax referral to the QL [43]; SmokefreeGOV website: nurses will give information about the services that SmokefreeGOV provides and they may log directly onto SmokefreeGOV from REDCap using the computer in the patient's PED room; smokefreeTXT: nurses will give information about the services that SmokefreeTXT provides and they may log directly onto the SmokefreeTXT site from REDCap where they can fill in the caregiver's information to sign him/her up for text messages. Finally, caregivers will be offered a packet of written materials [40,44], with information about the effects of smoke exposure on children, the benefits of quitting on their child's health, how to implement smokefree bans, information on quitting, and information on the QL, the SmokefreeGOV website, and SmokefreeTXT.

Feedback Reports

The use of the CDSS prompts will be further encouraged via feedback reports. Confidential, individualized reports will be provided monthly to each study nurse, similar to the work by Bentz et al [17]. For each nurse, we will compute adherence to each of the intervention behaviors (eg, ADVISE, ASSESS, ASSIST) and present these monthly in a feedback report. Each nurse's feedback report will include a comparison of individual performance to the overall performance average of all of the study RNs [17,45]. Only the study team will have access to the reports, and each nurse will have access only to their report. The study team will introduce the nurses to their first feedback report. Subsequent reports will be delivered monthly (3 total) to each nurse via their personal email; feedback reports will not be used to judge clinical performance.

Screening Pilot Phase

We will conduct a pilot phase for a period of 2 months in which the nurses will use only the screening questions in the EHR. These will include some or all of the items that ask if any of the primary caregivers smoke, the number of caregivers that smoke, the relationship of the caregivers who smoke to the patient (eg, mother, father, grandmother), and whether those caregivers smoke every day or some days. We will assess the use of these prompts (eg, how often the prompt is used, how many caregivers who smoke are identified) by nurses, and we will email and ask nurses if they experienced any issues or problems while using the screening prompts and/or have any questions.

Phase II: Feasibility and Acceptability Trial of the Decision Support System

In Phase II, we will conduct a feasibility trial of the CDSS. They will be assessed at baseline, 1 and 3 months after training. The baseline assessment will consist of self-report assessments of TSE counseling behaviors, attitudes, and perceived barriers. In addition, we will enroll a convenience sample of caregivers and their children and assess caregiversÃ¢â‚¬â„¢ smoking behavior and child TSE. We will conduct exit focused interviews with nurses to obtain recommendations on improving the CDSS and perceived barriers to sustainability.

Setting

Nurses, Caregivers, and Children

Nurses who work at least once a month in the Urgent Care will be recruited and written informed consent will be obtained for

participation in the feasibility trial. The clinical research coordinator (CRC) will recruit a convenience sample of 150 caregivers who present to the Urgent Care, are screened, and identified as a smoker who smokes "everyday" or "some days." The CRC will approach them to obtain informed consent to the collection of baseline and follow-up data about their smoking behavior and their child's TSE. We will validate child TSE on a racial/ethnically representative sample of children under age 6 at baseline and 3 months, as these children are more likely to be exposed to smoke [1-4].

Procedures for Feasibility Trial

We will conduct a feasibility and acceptability trial of the CDSS and feedback reports. We will (1) obtain a baseline assessment of nurses' attitudes, barriers, and tobacco-related screening, advising, and assisting behaviors, (2) train nurses on the use of the CDSS and evidence-based TSE counseling strategies and resources for on-going tobacco cessation treatment, (3) assess changes in attitudes, perceived barriers, and behaviors 1 and 3 months after training and obtain nurses' satisfaction with the CDSS, (4) assess the smoking behavior and child TSE of a convenience sample of caregivers and children who are current smokers. We will assess changes in TSE-related outcomes of total home/car smoking bans (validated via salivary cotinine) and caregiver smoking behavior (validated by expired CO in those caregivers who report abstinence) in a 10% subset of participants, and (5) conduct exit focused interviews of nurses at 3 months post-training to obtain recommendations for refining and sustaining the CDSS over time.

Our hypotheses are that at 3-month follow-up, there will be an increase in self-reported TSE counseling behaviors and attitudes and decreases in perceived barriers toward TSE counseling by trained RNs and that over the 3-month observation period, there will be an increase in CDSS verified TSE counseling behaviors by trained nurses receiving feedback reports. We also hypothesize that over the 3-month period, there will be lower child TSE and caregivers will report decreases in cigarette use, increased motivation to quit, and increased use of cessation resources compared with baseline.

Training for Participating Nurses

Prior to the launch of the CDSS in Epic and the start of the feasibility trial, nurses must complete a 20-minute Web-based audiovisual training created by the study investigators. The training will provide an introduction on the importance and effectiveness of TSE counseling and tobacco dependence treatment, and instruction in the use of the CDSS, including: completion of the prompts, delivery of brief TSE and smoking cessation counseling, and how to provide connection with the QL, the SmokefreeGOV website, or SmokefreeTXT during the PED visit [46,47]. During and after the training period, study staff will be available to answer any questions and provide help as needed.

Baseline Assessments

Nurses

Prior to training, nurses will complete a baseline self-reported assessment to determine their TSE behaviors and attitudes, perception of barriers that inhibit regular intervention with caregivers, and their self-efficacy in intervening with caregivers who smoke. Using principal components analysis, we have developed scales to measure barriers, confidence, and self-efficacy in providing the ASK, ADVISE, ASSESS, and ASSIST behaviors [48,49]. The CRC will conduct an EHR review on a random sample of patients cared for by the Phase II study nurses over the 1-month period prior to training to assess the TSE-reduction behaviors of nurses.

Caregivers and Their Children

We will assess and define the smoking status of all caregivers (eg, current every day smoker, current some day smoker) using the CDSS prompts. The data from the nurses' counseling prompts (eg, ADVISE and ASSIST) will be summarized.

We will collect detailed in-person smoking behavior data (eg, nicotine dependence, number of cigarettes smoked daily, motivation to quit) on a convenience sample of 150 caregivers and detailed TSE data (eg, number of smokers in the home; presence of smoking bans in the home or car) on their children. We will conduct cotinine analyses of child saliva samples collected on a sample of children at baseline to validate child TSE [2-4].

Follow-up Assessments

Self-Report by Nurses

Nurses will be reassessed by self-report at 1 and 3 months after training to evaluate change in practice behaviors, attitudes, barriers, and self-efficacy in intervening with caregivers and providing screening and TSE counseling, and maintenance of the intervention components. We will use the same scales as used at baseline to measure their intervention-related barriers, confidence, and self-efficacy.

Exit Focused Interviews

After the 3-month assessment, the study team will conduct exit focused interviews in which nurses will be asked for suggestions on how to improve the CDSS and they will be asked to identify factors and barriers that they perceive will be associated with the sustainability of the CDSS components into real-world practice. Data will be analyzed and results and recommendations incorporated into the design of a future, large R01 trial.

EHR Review of Patients

During the entire 3-month period of the pilot trial, the CRC will conduct daily EHR reviews for each patient cared for by the nurses whose caregiver screened positive for current smoking. The review will assess sociodemographics, chief complaint, and discharge diagnosis. The CRC will assess the nurses' compliance with the TSE components: Ask about smoking, Advise to quit, Assess readiness to quit, Assist in quitting, and delivery of written materials.

Caregiver Cessation and Child TSE

Smoking behavior and cessation outcomes will be assessed by self-report at 3-months on the convenience sample of 150 caregivers that were assessed at baseline; child TSE will be validated with salivary cotinine on the 10% subsample via in-person visits at 3-months. Outcomes will include nicotine dependence; readiness to change; quit attempts ≥24 hours;

nicotine replacement therapy or use of cessation resources, abstinence; and child TSE. Abstinence in caregivers will be verified via expired carbon monoxide testing during in-person visits.

Analytic Plan

Preliminary Data Analyses

Prior to the primary analyses, we will generate descriptive statistics for all variables (eg, means, medians, standard deviations, ranges, skewness) and we will examine potential outliers and patterns of missing data. To assess potential enrollment bias of nurses and/or caregivers, we will compare demographics of those enrolled versus those not enrolled; differences will be assessed according to variable type, chi-square test/Fisher's exact test for categorical variables or *t*-tests/Wilcoxon-Mann Whitney tests for continuous variables. Attrition analyses will be done to assess if those nurses without complete follow-up differ from those retained. If key independent variables significantly predict attrition, we will conduct the analysis with and without drop-outs. Primary outcomes will be compared using complete case analysis and intention to treat, assuming drop-outs are like those who do not comply with the TSE counseling behaviors.

Analysis of Focused Interview and User Group Data in Phase I

We will develop and integrate the CDSS into the EHR using qualitative data from the advisory panel and focused interview and user group data. We will present the prototype CDSS with the ASK, ADVISE, and ASSIST prompts to the advisory panel and ask for their views on use of the CDSS interface with the child's EHR. This CDSS will be iteratively edited based on expert advice. We will create the feedback reports and nurse recommendations, which will be based on user group input. Detailed notes will be obtained, typed, and evaluated to determine which independent thematic aspects will be organized around the CDSS and prompts to assess: functionality, content, number of clicks, length, appearance, format, and type, ease of use, time to use, linkage from the EHR to REDCap, linkage to cessation materials, linkage to the SmokefreeGOV website, linkage to SmokefreeTXT, integration with regular PED and Urgent Care workflows, technical support and training required, perception of maintenance of use and sustainability, and acceptability of feedback reports. This data will be used to iteratively refine the CDSS and reports for use in Phase II. Additionally, exit focused interviews at 3 months will be used to obtain nursesÃ¢â‚¬â„¢ views on the factors, barriers, suggestions, and recommendations on improving the CDSS. Data will be synthesized and used in future trials.

Analysis of Data from Feasibility Trial

To assess if there are increased self-reported TSE counseling behaviors (primary outcomes), improved attitudes and decreased barriers toward counseling (secondary outcomes) by study nurses, we will use the self-assessment at baseline, 1, and 3 months and examine changes in reported and EHR-verified behaviors, and changes in attitudes and barriers at baseline and each follow-up point. The first approach will be the intention to treat analysis; a generalized linear mixed-model will be used to allow use of the appropriate link function and examination of change over time. Second, incorporation of generalized estimating equations will allow for missing data, and then addition of any potential covariates.

To assess if there are increased CDSS-based TSE counseling behaviors by nurses receiving feedback reports, we will conduct an EHR review of 100% of the patients cared for by study nurses during the 3 months of the feasibility trial. We will compute descriptive statistics of compliance with the prompts. Options selected under these prompts will include: Ask about smoking, Advise to quit, Assess readiness to quit, and Assist in TSE reduction and quit attempt advice (QL fax, SmokefreeGOV website, SmokefreeTXT, and delivery of written materials). For each nurse, we will compute the percentage of the tobacco cessation intervention behaviors addressed (eg, Advise, Assess, Assist) and obtain descriptive statistics. We will assess if there are trends in the association of nurse protocol to child sociodemographics, chief complaint, or discharge diagnosis. As above, we will employ the generalized linear mixed-modeling to account for the nesting of caregivers within nurses and look at changes over time, adding the potential time-dependent covariates into the model.

Finally, we will assess if there is lower TSE in children and if caregivers will report decreased cigarette use, increased motivation to quit, and increased use of cessation resources at 3 months compared with baseline. Participant characteristics at baseline and 3 months will be summarized using descriptive statistics. Pairwise (within subjects) *t*-tests or McNemar's test or Cochran's Q test, as appropriate, will be conducted to examine differences in child TSE and caregiver smoking behavior and motivation to quit at baseline compared with 3 months.

Results

This study is ongoing. We are currently in the data collection and analysis stage of Phase II. This study may inform future research among pediatric urgent care or emergency department nurses and other providers working with adult caregivers who use tobacco. The results will provide evidence as to whether brief tobacco screening and tobacco cessation counseling prompts are feasible, acceptable, and easily incorporated into the workflow of urgent care nurses.

Discussion

This is the first study to develop a CDSS, integrate it with a widely-used EHR (Epic), and test its use to facilitate tobacco screening and TSE counseling of adult smokers in the PED setting. The CDSS will use a system of prompts and templates that can be implemented in all emergency settings regardless of the EHR type. We will ensure that the CDSS is reproducible, generalizable, and disseminable by carefully choosing an EHR platform and research template which allows for the creation, sharing and modification of prompt templates regardless of setting (pediatric or adult). Thus, if effective, this type of CDSS and systems-based strategy can be widely disseminated and incorporated into other emergency settings.

By incorporating tobacco screening and treatment into an existing clinical EHR system and providing prompts and feedback on the delivery of TSE and tobacco treatment, we will maximize the probability of creating a sustainable, disseminable model for use in the PED setting. If successful, this research has a high likelihood of translation into other emergency settings and sustainability over time. This proposed approach has the potential to reach over 12 million smokers a year and significantly reduce TSE-related pediatric illness and related costs.

Acknowledgments

Funding Source: National Cancer Institute/National Institutes of Health 1R21CA184337 (Dr. Mahabee-Gittens and Dr. Gordon).

Conflicts of Interest

None declared.

Multimedia Appendix 1

NIH study section reviews of this funded project.

[PDF File (Adobe PDF File), 202KB - resprot_v5i2e64_app1.PDF]

References

1. U.S. Department of Health and Human Services. The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014. URL: http://www.surgeongeneral.gov/library/reports/50-years-of-progress/full-report.pdf [WebCite Cache ID 6avq8wfKe]
2. Jones LL, Hashim A, McKeever T, Cook DG, Britton J, Leonardi-Bee J. Parental and household smoking and the increased risk of bronchitis, bronchiolitis and other lower respiratory infections in infancy: systematic review and meta-analysis. Respir Res 2011;12:5 [FREE Full text] [doi: 10.1186/1465-9921-12-5] [Medline: 21219618]
3. Jones LL, Hassanien A, Cook DG, Britton J, Leonardi-Bee J. Parental smoking and the risk of middle ear disease in children: a systematic review and meta-analysis. Arch Pediatr Adolesc Med 2012;166:18-27. [doi: 10.1001/archpediatrics.2011.158] [Medline: 21893640]
4. Leonardi-Bee J, Britton J, Venn A. Secondhand smoke and adverse fetal outcomes in nonsmoking pregnant women: a meta-analysis. Pediatrics 2011;127:734-741 [FREE Full text] [doi: 10.1542/peds.2010-3041] [Medline: 21382949]
5. Andrews AL, Shirley N, Ojukwu E, Robinson M, Torok M, Wilson KM. Is secondhand smoke exposure associated with increased exacerbation severity among children hospitalized for asthma? Hosp Pediatr 2015;5:249-255. [doi: 10.1542/hpeds.2014-0128] [Medline: 25934808]
6. Tutka P, Wielosz M, ZatoÃƒÆ'Ã¢â‚¬Â¦ÃƒÂ¢Ã¢â€šÂ¬Ã…Â¾ski W. Exposure to environmental tobacco smoke and children health. Int J Occup Med Environ Health 2002;15:325-335. [Medline: 12608620]
7. Mahabee-Gittens E, Gordon J. Review of adult smoking cessation interventions conducted in the emergency department and application to the pediatric emergency department setting. US Resp Dis 2008;4:125-128.
8. Ahn A, Edwards KM, Grijalva CG, Self WH, Zhu Y, Chappell JD, et al. Secondhand Smoke Exposure and Illness Severity among Children Hospitalized with Pneumonia. J Pediatr 2015. [doi: 10.1016/j.jpeds.2015.06.049] [Medline: 26231828]
9. Centers for Disease Control and Prevention, National Center for Health Statistics. National Hospital Ambulatory Medical Care Survey: 2010 Emergency Department Summary Tables. 2010. URL: http://www.cdc.gov/nchs/data/ahcd/nhamcs_emergency/2010_ed_web_tables.pdf [accessed 2015-08-24] [WebCite Cache ID 6b1revjzp]
10. Mahabee-Gittens EM, Gordon JS, Krugh ME, Henry B, Leonard AC. A smoking cessation intervention plus proactive quitline referral in the pediatric emergency department: a pilot study. Nicotine Tob Res 2008;10:1745-1751 [FREE Full text] [doi: 10.1080/14622200802443494] [Medline: 19023825]
11. Mahabee-Gittens EM, Stone L, Gordon JS. Pediatric emergency department is a promising venue for adult tobacco cessation interventions. Nicotine Tob Res 2013;15:1792-1793 [FREE Full text] [doi: 10.1093/ntr/ntt069] [Medline: 23709612]
12. Mahabee-Gittens M. Smoking in parents of children with asthma and bronchiolitis in a pediatric emergency department. Pediatr Emerg Care 2002;18:4-7. [Medline: 11862128]
13. Mahabee-Gittens EM, Khoury JC, Ho M, Stone L, Gordon JS. A smoking cessation intervention for low-income smokers in the ED. Am J Emerg Med 2015;33:1056-1061. [doi: 10.1016/j.ajem.2015.04.058] [Medline: 25976268]
14. Committee on Environmental HealthHealth, Committee on Substance Abuse, Committee OA, Committee on Native American Child. From the American Academy of Pediatrics: Policy statement--Tobacco use: a pediatric disease. Pediatrics 2009;124:1474-1487. [doi: 10.1542/peds.2009-2114] [Medline: 19841108]
15. Boyle RG, Solberg LI, Fiore MC. Electronic medical records to increase the clinical treatment of tobacco dependence: a systematic review. Am J Prev Med 2010;39(6 Suppl 1):S77-S82. [doi: 10.1016/j.amepre.2010.08.014] [Medline: 21074681]

16. Fiore MC, Jaen CR, Baker TB, Bailey WC, Benowitz NL, Curry SJ, et al. Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline. Rockville: U.S. Department of Health and Human Services; 2008. URL: http://www.ncbi.nlm.nih.gov/books/NBK63952/ [accessed 2016-04-05] [WebCite Cache ID 6gXmtsetr]
17. Bentz CJ, Bayley KB, Bonin KE, Fleming L, Hollis JF, Hunt JS, et al. Provider feedback to improve 5A's tobacco cessation in primary care: a cluster randomized clinical trial. Nicotine Tob Res 2007;9:341-349. [doi: 10.1080/14622200701188828] [Medline: 17365766]
18. Linder JA, Rigotti NA, Schneider LI, Kelley Jennifer H K, Brawarsky P, Haas JS. An electronic health record-based intervention to improve tobacco treatment in primary care: a cluster-randomized controlled trial. Arch Intern Med 2009;169:781-787 [FREE Full text] [doi: 10.1001/archinternmed.2009.53] [Medline: 19398690]
19. Deckter L, Mahabee-Gittens EM, Gordon JS. Are pediatric ED nurses delivering tobacco cessation advice to parents? J Emerg Nurs 2009;35:402-405 [FREE Full text] [doi: 10.1016/j.jen.2007.10.018] [Medline: 19748018]
20. Geller AC, Brooks DR, Woodring B, Oppenheimer S, McCabe M, Rogers J, et al. Smoking cessation counseling for parents during child hospitalization: a national survey of pediatric nurses. Public Health Nurs 2011;28:475-484. [doi: 10.1111/j.1525-1446.2011.00954.x] [Medline: 22092457]
21. Mahabee-Gittens EM, Dixon CA, Vaughn LM, Duma EM, Gordon JS. Parental tobacco screening and counseling in the pediatric emergency department: practitioners' attitudes, perceived barriers, and suggestions for implementation and maintenance. J Emerg Nurs 2014;40:336-345 [FREE Full text] [doi: 10.1016/j.jen.2013.06.001] [Medline: 24029045]
22. Stephenson KR, Allen PJ. The role of pediatric primary care providers in parental smoking cessation: assessing and motivating parents to quit. Pediatr Nurs 2007;33:434-441. [Medline: 18041334]
23. Marcy TW, Kaplan B, Connolly SW, Michel G, Shiffman RN, Flynn BS. Developing a decision support system for tobacco use counselling using primary care physicians. Inform Prim Care 2008;16:101-109 [FREE Full text] [Medline: 18713526]
24. Wears RL, Berg M. Computer technology and clinical work: still waiting for Godot. JAMA 2005;293:1261-1263. [doi: 10.1001/jama.293.10.1261] [Medline: 15755949]
25. Hesse BW, Shneiderman B. eHealth research from the user's perspective. Am J Prev Med 2007;32(5 Suppl):S97-S103 [FREE Full text] [doi: 10.1016/j.amepre.2007.01.019] [Medline: 17466825]
26. Lee J, Cain C, Young S, Chockley N, Burstin H. The adoption gap: health information technology in small physician practices. Understanding office workflow can help realize the promise of technology. Health Aff (Millwood) 2005;24:1364-1366 [FREE Full text] [doi: 10.1377/hlthaff.24.5.1364] [Medline: 16162585]
27. Wachter RM. Expected and unanticipated consequences of the quality and information technology revolutions. JAMA 2006;295:2780-2783. [doi: 10.1001/jama.295.23.2780] [Medline: 16788133]
28. Elson RB. Clinical Practice Guidelines. Disease Management & Health Outcomes 1997;1:63-74. [doi: 10.2165/00115677-199701020-00001]
29. Hung DY, Glasgow RE, Dickinson LM, Froshaug DB, Fernald DH, Balasubramanian BA, et al. The chronic care model and relationships to patient health status and health-related quality of life. Am J Prev Med 2008;35(5 Suppl):S398-S406. [doi: 10.1016/j.amepre.2008.08.009] [Medline: 18929987]
30. Hung DY, Shelley DR. Multilevel analysis of the chronic care model and 5A services for treating tobacco use in urban primary care clinics. Health Serv Res 2009;44:103-127 [FREE Full text] [doi: 10.1111/j.1475-6773.2008.00896.x] [Medline: 18783454]
31. Rigotti NA. Integrating comprehensive tobacco treatment into the evolving US health care system: it's time to act: comment on "A randomized trial of Internet and telephone treatment for smoking cessation". Arch Intern Med 2011;171:53-55. [doi: 10.1001/archinternmed.2010.491] [Medline: 21220661]
32. Wagner EH, Austin BT, Davis C, Hindmarsh M, Schaefer J, Bonomi A. Improving chronic illness care: translating evidence into action. Health Aff (Millwood) 2001;20(6):64-78 [FREE Full text] [Medline: 11816692]
33. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377-381 [FREE Full text] [doi: 10.1016/j.jbi.2008.08.010] [Medline: 18929686]
34. Jayanthi A. Top 10 EHR vendors by overall market share.: Becker's Health IT & CIO Review; 2015 Feb 13. URL: http://www.beckershospitalreview.com/healthcare-information-technology/top-10-ehr-vendors-by-overall-market-share.html [accessed 2016-04-05] [WebCite Cache ID 6gXoUn55K]
35. Office of the National Coordinator for Health Information Technology. Electronic health record vendors reported by hospitals participating in the CMS EHR incentive programs. Health IT Quick-Stat #29.: HealthIT.gov Dashboard; 2015 Mar. URL: http://dashboard.healthit.gov/quickstats/pages/FIG-Vendors-of-EHRs-to-Participating-Hospitals.php [accessed 2015-08-20] [WebCite Cache ID 6avqh6DOt]
36. Glenn B. Why Epic's market dominance could stifle AEHR and health IT innovation.: Medical Economics; 2013 Apr 25. URL: http://medicaleconomics.modernmedicine.com/medical-economics/content/tags/electronic-health-records/why-epics-market-dominance-could-stifle-ehr [accessed 2015-08-20] [WebCite Cache ID 6avpXEbpj]
37. Winickoff JP, Nabi-Burza E, Chang Y, Finch S, Regan S, Wasserman R, et al. Implementation of a parental tobacco control intervention in pediatric practice. Pediatrics 2013;132:109-117 [FREE Full text] [doi: 10.1542/peds.2012-3901] [Medline: 23796741]

38. Rosen LJ, Noach MB, Winickoff JP, Hovell MF. Parental smoking cessation to protect young children: a systematic review and meta-analysis. Pediatrics 2012;129:141-152 [FREE Full text] [doi: 10.1542/peds.2010-3209] [Medline: 22201152]
39. Winickoff JP, Healey EA, Regan S, Park ER, Cole C, Friebely J, et al. Using the postpartum hospital stay to address mothers' and fathers' smoking: the NEWS study. Pediatrics 2010;125:518-525. [doi: 10.1542/peds.2009-0356] [Medline: 20123776]
40. Gordon JS, Andrews JA, Crews KM, Payne TJ, Severson HH, Lichtenstein E. Do faxed quitline referrals add value to dental office-based tobacco-use cessation interventions? J Am Dent Assoc 2010;141:1000-1007 [FREE Full text] [Medline: 20675426]
41. Emmons KM, Hammond SK, Fava JL, Velicer WF, Evans JL, Monroe AD. A randomized trial to reduce passive smoke exposure in low-income households with young children. Pediatrics 2001;108:18-24. [Medline: 11433049]
42. Hovell MF, Zakarian JM, Matt GE, Liles S, Jones JA, Hofstetter CR, et al. Counseling to reduce children's secondhand smoke exposure and help parents quit smoking: a controlled trial. Nicotine Tob Res 2009;11:1383-1394 [FREE Full text] [doi: 10.1093/ntr/ntp148] [Medline: 19875762]
43. Lichtenstein E, Zhu S, Tedeschi GJ. Smoking cessation quitlines: an underrecognized intervention success story. Am Psychol 2010;65:252-261 [FREE Full text] [doi: 10.1037/a0018598] [Medline: 20455619]
44. Winickoff JP, Park ER, Hipple BJ, Berkowitz A, Vieira C, Friebely J, et al. Clinical effort against secondhand smoke exposure: development of framework and intervention. Pediatrics 2008;122:e363-e375 [FREE Full text] [doi: 10.1542/peds.2008-0478] [Medline: 18676523]
45. Kiefe CI, Allison JJ, Williams OD, Person SD, Weaver MT, Weissman NW. Improving quality improvement using achievable benchmarks for physician feedback: a randomized controlled trial. JAMA 2001;285:2871-2879. [Medline: 11401608]
46. Gordon J, Andrews J, Albert D, Crews K, Payne T, Severson H. Tobacco cessation via public dental clinics: results of a randomized trial. Am J Public Health 2010;100:1307-1312. [doi: 10.2105/AJPH.2009.181214] [Medline: 20466951]
47. Severson HH, Andrews JA, Lichtenstein E, Gordon JS, Barckley MF. Using the hygiene visit to deliver a tobacco cessation program: results of a randomized clinical trial. J Am Dent Assoc 1998;129:993-999. [Medline: 9685764]
48. Gordon JS, Andrews JA, Lichtenstein E, Severson HH. The impact of a brief tobacco-use cessation intervention in public health dental clinics. J Am Dent Assoc 2005;136:179-86; quiz 230. [Medline: 15782521]
49. Gordon JS, Andrews JA, Lichtenstein E, Severson HH, Akers L. Disseminating a smokeless tobacco cessation intervention model to dental hygienists: a randomized comparison of personalized instruction and self-study methods. Health Psychol 2005;24:447-455. [doi: 10.1037/0278-6133.24.5.447] [Medline: 16162038]

Abbreviations

AAP: American Academy of Pediatrics
CCHMC: Cincinnati Children’s Hospital Medical Center
CDSS: clinical decision support systems
CPGs: clinical practice guidelines
CRC: clinical research coordinator
EHR: electronic health records
PED: pediatric emergency department
REDCap: Research Electronic Data Capture
RNs: registered nurses
QL: Quitline
TSE: tobacco smoke exposure

Edited by P Bamidis; submitted 09.09.15; peer-reviewed by A Billis, S Regan, S Hors-Fraile; comments to author 07.10.15; revised version received 21.10.15; accepted 04.02.16; published 20.04.16.

Please cite as:
Mahabee-Gittens EM, Dexheimer JW, Khoury JC, Miller JA, Gordon JS
Development and Testing of a Computerized Decision Support System to Facilitate Brief Tobacco Cessation Treatment in the Pediatric Emergency Department: Proposal and Protocol
JMIR Res Protoc 2016;5(2):e64
URL: http://www.researchprotocols.org/2016/2/e64/
doi:10.2196/resprot.4453
PMID:27098215

Protocol

Reducing Physical Risk Factors in Construction Work Through a Participatory Intervention: Protocol for a Mixed-Methods Process Evaluation

Jeppe Ajslev[1], MSS, PhD; Mikkel Brandt[1,2], MSc; Jeppe Lykke Møller[3], MSS; Sebastian Skals[1], MSc; Jonas Vinstrup[1,2], MSc; Markus Due Jakobsen[1], MSc, PhD; Emil Sundstrup[1], MSc, PhD; Pascal Madeleine[2], PhD, DSc; Lars Louis Andersen[1,2], PhD

[1]National Research Centre for the Working Environment, Copenhagen, Denmark

[2]Physical Activity and Human Performance group - SMI, Dept. of Health Science and Technology, Aalborg University, Aalborg, Denmark

[3]Centre for Working Life Research, Roskilde University, Roskilde, Denmark

Corresponding Author:
Jeppe Ajslev, MSS, PhD
National Research Centre for the Working Environment
Lersø Parkallé 105
Copenhagen, 2100
Denmark
Phone: 45 61304754
Fax: 45 39 16 52 01
Email: ajslev@gmail.com

Abstract

Background: Previous research has shown that reducing physical workload among workers in the construction industry is complicated. In order to address this issue, we developed a process evaluation in a formative mixed-methods design, drawing on existing knowledge of the potential barriers for implementation.

Objective: We present the design of a mixed-methods process evaluation of the organizational, social, and subjective practices that play roles in the intervention study, integrating technical measurements to detect excessive physical exertion measured with electromyography and accelerometers, video documentation of working tasks, and a 3-phased workshop program.

Methods: The evaluation is designed in an adapted process evaluation framework, addressing *recruitment*, *reach*, *fidelity*, *satisfaction*, *intervention delivery*, *intervention received*, and *context* of the intervention companies. Observational studies, interviews, and questionnaires among 80 construction workers organized in 20 work gangs, as well as health and safety staff, contribute to the creation of knowledge about these phenomena.

Results: At the time of publication, the process of participant recruitment is underway.

Conclusions: Intervention studies are challenging to conduct and evaluate in the construction industry, often because of narrow time frames and ever-changing contexts. The mixed-methods design presents opportunities for obtaining detailed knowledge of the practices intra-acting with the intervention, while offering the opportunity to customize parts of the intervention.

(JMIR Res Protoc 2016;5(2):e89) doi:10.2196/resprot.5648

KEYWORDS

musculoskeletal disorders; process evaluation; intervention study; mixed-methods study; social science; physical exposure; masculinity; construction work

Introduction

Musculoskeletal disorders are a major economic, social, and health challenge in the construction industry, as well as in other occupations characterized by high levels of physical exertion at work [1,2]. Physical exertion and strenuous work tasks such as heavy lifting, pushing, dragging, and working in awkward positions are known to increase the risk of developing musculoskeletal pain [3]. Considering that most of these risk factors are a natural part of the everyday practices in construction work, it is surprising that only a few interventions are aimed at reducing the physical exposure associated with

construction work. Furthermore, studies of these interventions have reported very low degrees of measurable success [4,5]. In general, interventions targeting the prevention of musculoskeletal disorders have shown very limited effect, or the evidence has been characterized as being of low quality [6-8], except for a few studies focusing on increasing individual workers' physical capacity and thereby their resilience against physical exposure at work [6,9-11].

As a consequence of this limited success in preventing musculoskeletal disorders in the working population in general, and for construction workers in particular, evaluators and researchers have called for more multidisciplinary-anchored interventions [4,6,8]. Furthermore, to achieve a successful intervention and for sustaining organizational change and engagement, several sources point out that the inclusion of relevant parties (ie, health and safety professionals, workers, and management) is pivotal [12-15].

In response to this, we have tailored an intervention that engages workers and management, and integrates the use of technical quantitative measurements of excessive physical workload measured with electromyography and accelerometers, video documentation of working tasks, and a 3-phased workshop program. Whereas Brandt et al [16] described the protocol for the technical physical measurements and quantitative survey on physical exertion and pain, this study protocol describes the mixed-methods process evaluation of social, subjective, and organizational processes that play important roles in the outcome of the intervention project.

Research shows that reducing physical exertion in construction work is a complex issue [15,17]. As Nielsen et al [18] emphasized, evaluations of organizational research must be contextually grounded. To ensure that we obtain the best possible knowledge from our intervention, we must carefully tailor the process evaluation to identify the agential roles of the various agencies intra-acting with rationalities at work—with, in, and between workers, in the physical characteristics of construction workers and work, and in the organizational practices of companies where the interventions are implemented.

Construction work is a broad category that encompasses many different trades composed of different tasks, skillsets, and cultural norms. However, physically exerting work is a common denominator. Across carpentry, bricklaying, concrete work, scaffolding, plumbing, etc, the entangled body and subjectivity of the worker is a main resource of production, a point that takes a line of arguments to unfold. However, it is highly important for understanding the social framing of the intervention context.

The necessity of undertaking tasks in a physically exerting manner is embedded in the organization of work, where planned availability and usage of technical assistive devices play important roles. Technical assistive devices have the potential to substantially decrease physical exertion at work, but numerous political, organizational, and subjective agencies challenge the development, proliferation, and usage of such technical assistive devices [19-21]. Thus, interventions addressing the increased use of assistive devices should carefully consider this context in the process evaluation.

One of these agencies lies in the material and organizational orchestration of work that takes place at geographically delimited sites for a certain amount of time, after which, on project completion, the whole organization breaks up to be reconfigured at new worksites. Here the tasks involve many of the same skills but are usually still markedly different, and pose new and different flows of processes, still containing physically exerting work tasks. For this reason, planning of construction sites is a complicated matter, in which the usage of technical assistive devices is sometimes not thoroughly considered. This means that adequate measures for reducing physical exertion may not always be present in the construction process. Without a rigorous process evaluation, important opportunities and barriers in this regard could easily be missed.

At a political and societal level, the competition among entrepreneurs to secure projects has been described as a barrier for implementing initiatives prioritizing health and safety [20,22]. In previous studies, entrepreneurs described how health and safety measures are often the target of budget cuts. When bids are produced, time pressure as a result of tight planning schedules is also very likely to affect all phases of production, leading to a faster work pace among workers [22]. This may also reduce the incentive for investment in technical assistive devices, particularly in companies where profit margins are relatively narrow. Consequently, process evaluations of interventions should also consider time pressure and budget constraints.

Furthermore, many construction projects are completed on some form of performance-based payment (eg, piece rate), which provides the worker with an economic incentive for working faster with less variation, and not using technical assistive devices unless they directly increase production [22-24]. This can play an important role in relation to the effectiveness of our intervention. Part of the process evaluation should therefore also evaluate incentives for increased bodily strain in the above-mentioned forms. The options for working for performance-based wages are guaranteed in agreements between unions and employers' associations, and are therefore tied to political decision-making processes.

In previous studies, communication between the managerial staff and workers has been suggested as a potential barrier to improving health and safety at the workplace [12,25]. Even though there is a dedicated health and safety organization at every major Danish construction site, the workers' representatives report being ignored by management, and the management report that workers display a lack of interest in both health and safety, and the organizational need for cooperation to obtain smooth production [26]. This may potentially affect experiences of physical exertion and pain among workers, as higher levels of worker influence on health and safety has been linked to lower levels of exertion and pain [27]. This, at times, negative relationship may obstruct implementing and anchoring the intervention within the organization, and is an issue that demands special attention from researchers conducting the intervention to avoid being seen as either employees' or management's allies. Thus, evaluation of communication at the workplace is also an important part of the process evaluation.

In addition, many construction workers embody and socially transmit traditional masculine working-class qualities [28,29], such as endurance, strength, self-reliance, pain habituation, and breadwinning, as positive identity characteristics [20]. Being able to display and participate in discursive-material practices, reconfiguring the worker in accordance with these qualities, in many cases functions as a parameter for maintaining social position in the work gang and a job within the company. Not participating in these traditional masculine working-class practices may be costly to the worker, as sickness absence is frowned upon and employment can be terminated with only 1 day's notice unless the worker has been employed by the company for more than 1 year [22]. As such, the need to participate in these practices can increase physical exertion and may, furthermore, complicate intervention, as taking care of the individual worker's body is likely a low priority for both colleagues and the company. Thus, the process evaluation should also evaluate how worker identity plays into the intervention.

In our evaluation, all these agencies and their entangled roles are points of attention, as we aim to understand the facilitators and barriers to reducing physical exertion. The purpose of the process evaluation is to investigate how the intervention intra-acts with both the worker's body and subjectivity, as well as social and organizational relations acting as facilitators and barriers to reducing physical exertion. An additional aim is to perform analyses using the mixed-methods design to evaluate potential consequences of the intervention in terms of productivity, sickness absence, and time frames.

Methods

The Intervention

The intervention is taking place in a design containing several phases as thoroughly described by Brandt et al [16].

In the first phase of the intervention, 20 construction gangs (N=80 workers) will be randomly assigned at a cluster level to a participatory intervention group or a control group. We will record in situ physical workload during a working day using technical measurements (electromyography, accelerometers, and video recordings) before and after the intervention. Based on these measurements, a physical load matrix for each worker will be developed. This matrix is based on outcomes obtained from the analyses of the simultaneously recorded electromyograms and accelerometer data.

The second phase is designed as a participatory process consisting of 3 workshops: 1) workshop I at baseline, involving presentation of video clips of the work tasks with excessive physical load customized for each gang, followed by a participatory development of solutions on how to reduce excessive workloads, leading to the development of an action plan on how to implement these solutions at the workplace, 2) workshop II, where the implemented solutions will be further developed and qualitatively evaluated during group discussion, 3) workshop III at follow-up to enhance long-term organizational sustainability of the implemented solutions. All workshops will aim to include researchers, workers, occupational health and safety (OHS) staff at the companies, and a management representative as participants. We will facilitate the elaboration of solutions aimed at lowering the physical exertion related to the participants' suggestions. The control groups are not targeted in the evaluation study and are therefore not addressed in this protocol.

Evaluation Design

The evaluation is designed in a mixed-methods framework to address different aspects of the intervention, which has been recommended by several sources on evaluation research [30,31]. To assure that our evaluation addresses key pieces of information about the interventions, we draw upon an adapted version of the framework presented by Saunders et al for process evaluation in public health interventions [32-34]. More specifically, using this framework means addressing *recruitment*, *reach*, *fidelity*, *satisfaction*, *intervention delivery*, *intervention received*, and *context* [34]. Because previous studies have used these terms differently, we define their specific use in the present study below. Figure 1 shows the timeline for the intervention project and process evaluation. Textbox 1 shows the description of evaluation components.

Textbox 1. Process evaluation components and description of their elements.

Recruitment

- Number of companies asked to participate
- Number of companies agreeing to participate
- Number of gangs participating (intervention and control groups)
- Number of workers participating (intervention and control groups)
- Number of workers responding to questionnaires
- Number of workers asked to participate in interviews
- Number of workers participating in interviews
- Number of occupational health and safety (OHS) staff asked to participate in interviews
- Number of OHS staff participating in interviews

Reach

- Number of technical measurements completed
- Number of workshops completed

Fidelity

- The extent to which the workshop program was completed in accordance with intentions

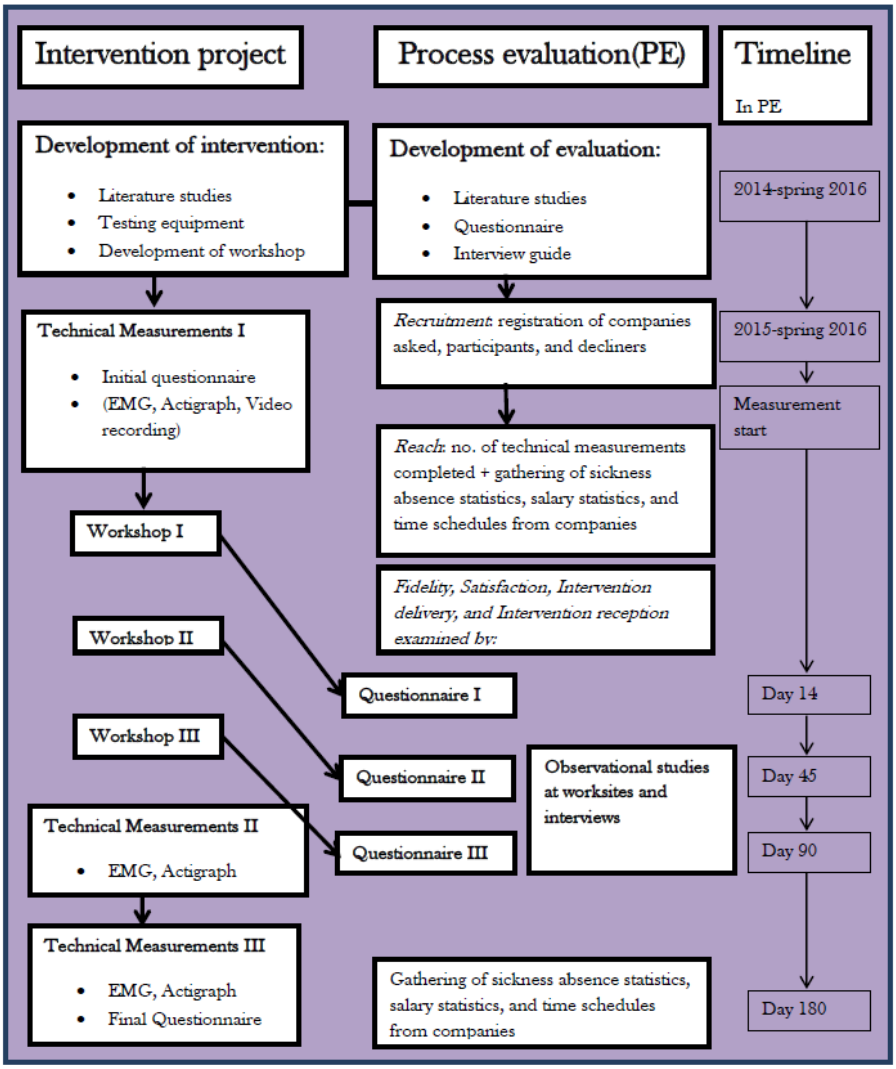
Satisfaction

- Workers' and OHS staff's satisfaction with prioritized risk factors, the competencies of workshop facilitators, and the time for workshops
- Workers' and OHS staff's satisfaction with the method of the workshops
- Workers' and OHS staff's satisfaction with the implementation of measures for improving ergonomic work environment

Intervention delivery

- Perceived intervention implementation according to researchers
- Intervention reception
- Perceived intervention implementation according to workers and OHS staff

Figure 1. Process evaluation activities and timeline for a participatory intervention to reduce physical risk factors in construction work. EMG: electromyography.



Recruitment

In our evaluation, recruitment is defined by several parameters: 1) the number of companies asked to participate, and 2) the number of companies agreeing to participate. We will also record 3) the number of work gangs randomly assigned to the intervention and control groups, as well as how many of these completed the study, 4) the number of workers and OHS staff asked to participate in the intervention at each participating company, to answer questionnaires and to participate in interviews, and 5) the number of workers and OHS staff agreeing to participate in the study, to answer questionnaires and to participate in interviews.

Reach

Reach can be defined as the proportion of the intended recruited participants who actually received the intervention, as defined by Saunders et al [34]. In our study, the reach of the intervention is defined as the number of technical measurements and workshops completed in each gang of the project in total. We will list the number of workshops that we deliver and will note the reasons for cancellation. We will also list the number of participants volunteering to take part in technical quantitative measurements and workshops, will note the reasons for individual absence.

Fidelity and Satisfaction

After each workshop, we will ask all participants to complete a questionnaire addressing workers' and OHS staff's perceptions of the workshop. Fidelity will be addressed in 2 ways. First, we will ask workers to rate each workshop phase on a 5-point scale (very bad, bad, neutral, good, very good). Second, we will record all activities of the workshops to assess whether they were completed in accordance with the planned activities.

Likewise, we will assess satisfaction based on the workers' and OHS staff's satisfaction with 1) prioritized risk factors, 2) the competencies of workshop facilitators, 3) the time frames for the workshops, 4) the structure of the workshops, and 5) the implementation of solutions for lowering physical exertion and improving the work environment. All of these parameters will be rated on 5-point scales (very unsatisfied, unsatisfied, neutral, satisfied, very satisfied). Through qualitative interviews in selected cases, we will gain further knowledge of workers' and OHS staff's satisfaction with and knowledge of particularly well-functioning or dysfunctional elements of the intervention. This will allow us to use the evaluation in a formative manner,

adjusting the intervention for better implementation, as previously suggested [35,36].

Intervention Delivery

What we term *intervention*, *delivery*, and *reception* is based on the definition by Saunders et al [34], originally termed *dose delivered*. Referring to a complex organizational and ergonomic intervention as a dose does, however, in our opinion, risk confusing the intervention with a medical injection, which would be misleading because the intervention is a framework for developing preventive solutions that intra-acts *with* other agencies in work and organizations. The intervention should not be seen as something we inject into the organization with determinate effects.

Immediately after completing each day of technical measurements and each workshop, the facilitating researchers will have an evaluative meeting. Minutes of the meeting will be produced to evaluate the success of the activities. Furthermore, we will conduct observational studies at the worksites during 2–5 workdays between workshops I and III in order to assess whether solutions on how to reduce excessive workloads were actually used during work. We also record the number of visits and observations during these visits.

Intervention Received

After each workshop, we will evaluate the intervention received by using questionnaires. We will ask each of the workers and OHS staff to assess whether the decided measures have been implemented and integrated as part of work. This will be answered on a 5-point scale (very low degree, low degree, moderate degree, high degree, very high degree). More precise descriptions of the measures that were actually implemented will be explored through interviews with participants.

Context

We will investigate the intervention context through interviews with workers and OHS staff to explore their positioning in relation to different agencies intra-acting with the intervention. To address the subjective, social, and organizational practices intra-acting with the implementation of the project, we have designed an in-depth qualitative study consisting of observations, interviews, and document analysis. The qualitative design focused on a limited number of intervention cases offering insights on productivity, sickness absence, and time frames, as well as how the intervention intra-acts with worker identity and meaning in work as initially described.

For the qualitative study we will select 4 work gangs based on a *critical case* argumentation for validity and generalization from case study research. Our aim is to select 2 cases (gangs) in which the implementation seems to be particularly successful, and 2 cases in which the intervention seems to meet resistance or other barriers. By selecting “best” and “worst” cases, we have the opportunity of making generalizations of the type “if the implementation meets X as a barrier/facilitator in this case, it will be likely/unlikely to work better/worse in other cases’ [37].

Initial and Final Questionnaires

We will distribute the survey questionnaires to the workers of both the intervention and control groups at the time of the initial technical measurements and again after the intervention period. The questionnaire will contain questions addressing the physical work environment and several risk factors of particular relevance to work in the construction industry drawn from previous research [3,22,38]. Of particular interest are questions related to the worker’s capacity for taking care of the body in work, their physical exertion, managerial support for improving health and safety at work, the worker’s influence on health and safety, and the availability and usage of technical assistive devices.

Questionnaires I, II, and III

These questionnaires will be handed out to participants of the intervention group directly after each workshop and will address fidelity, satisfaction, and the intervention delivered.

Interviews

We will conduct interviews with the intervention group and address the workers’ and OHS staff’s satisfaction and context. As described for *context* above, we will select cases for interviews through a critical case definition, as discussed by Flyvbjerg [37]. Based on this, we will select cases in which the intervention seems to be working particularly well, and cases where the intervention meets particular complications (best and worst cases). From this selection strategy, we will be able to make generalizations of the sort “if this is (not) valid for this case, then it applies to all (no) cases” (p. 230 in [37]). The interviews are aimed at producing knowledge about how the participants make sense of the intervention. To gain in-depth insight into the practices taking place in relation to the implementation, we will interview workers, health and safety professionals, and managers engaged with the project in each of the 4 cases. We will design and conduct the interviews in a semistructured interview format, where most questions will be posed rather openly and important themes will be explored through follow-up questions, asking the participants to discuss and elaborate their answers. To facilitate discussion and positioning statements among workers, we chose to implement a focus group interview structure, because group negotiations of what is going on at the workplace are an important source of information in the analysis of the scope for changing or developing the working environment. This can be challenging with regard to managers and OHS staff, as these groups are often singularly represented on site, but we will carry out focus groups where possible. If this proves impossible, we will conduct interviews with managers and OHS staff individually.

We will conduct the interviews between workshops II and III to ensure that the participants have the intervention fresh in their memories, while also having some experience of the action taking place during the intervention.

All interviews will be transcribed and imported to NVivo (QSR International Pty Ltd) for coding and to facilitate the analysis. The interview analysis will draw on a view of lingual productions as positioning in discursive-material practice in an analytical framework composed on the thoughts of Davies and Harré [39] and Barad [40]. Positioning theory in an agential

realist framework is a theory conceptualizing the ways in which people (re)configure subjectivities through lingual and physical engagement with other people and the materialities of the world, including work. This approach will allow us to analyze how participants draw on elements of work and the body, as well as social and organizational practices, to describe and rationalize their experiences of the intervention.

Observations

Observations will be conducted in 2 forms and particularly address the delivery of the intervention as well as the context. First, we will video record all workshops in the project to permit analysis of the processes taking place during the workshops. This analysis will illustrate the communication concerning lowering physical exertion through the intervention. In particular, we are interested in how participants use the technology and what solutions are reachable in the interplay between workers, health and safety professionals, and management. We will also analyze this observational material through positioning theory [39] in a modified agential realist framework drawing on Barad [40], allowing a focus on positioning of both physical and subjective characteristics of work and the intervention.

Second, a researcher will follow the work at the intervention sites during the intervention period in order to gain insight into the practices in the organization during the time of implementation. These observations will be drawing on observational methodology and analysis by Czarniawska, who suggests observing particular practices, objects, or people [41]. From these suggestions, we intend to follow practices and objects of particular relevance to the solutions on how to reduce excessive workloads developed in the intervention. During these observations, we will record field notes for analysis. These notes will be taken immediately after each day of observation elaborated by the conducting researcher and used for analysis of practices in the organizations and worksites where the interventions are conducted.

Document Analysis

In the participating companies, we will obtain documentation of sickness absence, time frames, and economic measurements (performance-based salary levels or budget numbers). Through analysis of these documents, we will attempt to gain insight into some of the measures of how the intervention affects productivity, which is very important to estimating the potential costs of this type of intervention.

Mixed-Methods Analysis

We will analyze the different empirical elements of the study in relation to each other. We will focus on combining triangulation and a complementary approach to the mixed-methods design rather than on quantifying qualitative material or other approaches to mixed methods [42]. In practice, our mixed-methods analyses will be focused on discovering consistencies and inconsistencies in the physical measurements, questionnaires, qualitative data, and document. Further, we will use our qualitative data to elaborate on the physical measurements, which are of limited character. By pursuing this approach, we can analyze in a detailed manner how the intervention functioned in the different settings, in line with Bamberger et al [30]. Table 1 summarizes the tools used for each evaluation component.

Table 1. Tools used for each component.

Component	Methodological tool
Recruitment	Checklist, questionnaires, interviews
Reach	Checklist
Fidelity	Summary of researchers' evaluation discussion
Satisfaction	Questionnaires I, II and III, and interviews
Program delivery	Summary of researchers' evaluation discussion, observational studies
Program reception	Questionnaires I, II and III, and interviews

Results

At the time of submitting this paper (February 2016), we have made initial contact with cases for the intervention and evaluation, and 40 workers have agreed to participate so far. We have completed evaluation design and have prepared interview guides and the observational methodology. The intervention and evaluation are designed to run over the course of winter 2015 to winter 2016, after which time we will undertake the analysis.

Discussion

One practical issue when conducting research, interventions in particular, in the construction industry can be that time frames are often very narrow, which is why workers often do not have the time to participate in interventions. One particular challenge will be to engage workers, OHS staff, and managers to cooperate in developing and implementing solutions for reducing physical exertion in work, as these groups are usually not engaged in such activities. These challenges can complicate our aim to complete the workshops and group interviews. We will, however, attempt to follow through.

A particular strength of the evaluation design is the mixed-methods framework. Through using lingual communications, observed practices, and quantified assessments, we have configured an analytical apparatus capable of describing how the intervention intra-acts with the workplaces in which it is implemented. We get the opportunity to identify mutually supportive configurations of these relationships, as well as the

ability to identify differences occurring through only one or two methodological approaches.

Also, the formative evaluation design allows us to use the insights produced through the evaluation to customize parts of the intervention to better address the context's or participants' requirements for a fruitful implementation.

However, we do expect that completing the mixed-methods analysis of the various sources of data and measurements will pose significant challenges. For instance, weighing the different approaches in relation to each other will demand attention and carefulness in the research group working with the study. For these reasons, we expect to be able to illustrate how agencies in construction work intra-act in relation with the ergonomic intervention and to reconfigure the boundaries of material work, organization of physically exerting work tasks, and worker subjectivity. These insights will provide pointers for future action and interventions targeting physical exposure in construction work.

Acknowledgments

LLA obtained a grant from the Danish Working Environment Research Fund for this study (grant number 51-2014-03).

In accordance with the Helsinki Declaration, we will collect informed consent to participate in the intervention study from all participants. This will take place only after participants have been informed about the objective and content of the study. This information will be given to a researcher. The intervention study is approved by The Danish National Committee on Biomedical Research Ethics (local ethical committee of Frederiksberg and Copenhagen, H-3-2010-062), and registered at the Danish data Protection agency (215-57-0074) and on ClinicalTrials.gov (NCT02498197).

Authors' Contributions

JZNA, MB, JM, PM, and LLA designed the study; JZNA, MB, LLA, SS, JØV, ES, and MDJ designed the questionnaires. JZNA and JM designed interview guides and observational methodology. JZNA drafted the manuscript, and all authors read, critically reviewed, and approved the final version.

Conflicts of Interest

None declared.

References

1. Arndt V, Rothenbacher D, Daniel U, Zschenderlein B, Schuberth S, Brenner H. Construction work and risk of occupational disability: a ten year follow up of 14 474 male workers. Occup. Environ. Med 2005;62(8):559-566.
2. Schneider E, Irastorza X, European Agency for Safety and Health at Work. OSH in Figures: Work-Related Musculoskeletal Disorders in the EU - Facts and Figures. Luxembourg: Publications Office of the European Union; 2010. URL: https://osha.europa.eu/en/tools-and-publications/publications/reports/TERO09009ENC [accessed 2016-05-05] [WebCite Cache ID 6hHMb6XLL]
3. Andersen J, Haahr J, Frost P. Risk factors for more severe regional musculoskeletal symptoms: A two-year prospective study of a general working population. Arthritis Rheum 2007;56(4):1355-1364.
4. de Boer AGEM, Burdorf A, van Duivenbooden C, Frings-Dresen M. The effect of individual counselling and education on work ability and disability pension: a prospective intervention study in the construction industry. Occup Environ Med 2007 ;64(12):792-797.
5. Oude Hengel KM, Blatter B, van der Molen HF, Bongers P, van der Beek AJ. The effectiveness of a construction worksite prevention program on work ability, health,sick leave: results from a cluster randomized controlled trial. Scand J Work Environ Health 2013 ;39(5):456-467.
6. Burton A, Balagué F, Cardon G, Eriksen HR, Henrotin Y, Lahad A, et al. Chapter 2 European guidelines for prevention in low back pain: November 2004. Eur Spine J 2006 ;15(2):136-168.
7. Steffens D, Maher C, Pereira LS, Stevens ML, Oliveira VC, Chapple M, et al. Prevention of low back pain: a systematic review and meta-analysis. JAMA Intern Med 2016 Feb 1;176(2):199-208. [doi: 10.1001/jamainternmed.2015.7431] [Medline: 26752509]
8. Westgaard R, Winkel J. Ergonomic intervention research for improved musculoskeletal health: a critical review. Int J Ind Ergonomics 1997;20(6):463-500.
9. Andersen L, Christensen K, Holtermann A, Poulsen O, Sjøgaard G, Pedersen M, et al. Effect of physical exercise interventions on musculoskeletal pain in all body regions among office workers: A one-year randomized controlled trial. Manual Ther 2010 ;15(1):100-104.
10. Jakobsen M, Sundstrup E, Brandt M, Jay K, Aagaard P, Andersen L. Effect of workplace- versus home-based physical exercise on musculoskeletal pain among healthcare workers: a cluster randomized controlled trial. Scand J Work Environ Health 2015 ;41(2):153-163.

11. Sundstrup E, Jakobsen M, Andersen C, Jay K, Persson R, Aagaard P, et al. Effect of two contrasting interventions on upper limb chronic pain and disability: a randomized controlled trial. Pain Physician 2014 ;17(2):145-154.
12. Choudhry R, Fang D, Mohamed S. The nature of safety culture: a survey of the state-of-the-art. Safety Sci 2007 ;45(10):993-1012.
13. Gilmore B, Vallières F, McAuliffe E, Tumwesigye NM, Muyambi G. The last one heard: the importance of an early-stage participatory evaluation for programme implementation. Implement Sci 2014;9:137 [FREE Full text] [doi: 10.1186/s13012-014-0137-5] [Medline: 25253191]
14. Sannerud R. Methods for developing the construction site as a learning space. In: Aagaard Nielsen K, Svensson L, editors. Action Research and Interactive Research. Maastricht, Netherlands: Shaker Publishing; 2006.
15. Vink P, Koningsveld E, Molenbroek J. Positive outcomes of participatory ergonomics in terms of greater comfort and higher productivity. Appl Ergonomics 2006 ;37(4):537-546.
16. Brandt M, Madeleine P, Ajslev JZN, Jakobsen MD, Samani A, Sundstrup E, et al. Participatory intervention with objectively measured physical risk factors for musculoskeletal disorders in the construction industry: study protocol for a cluster randomized controlled trial. BMC Musculoskelet Disord 2015;16:302 [FREE Full text] [doi: 10.1186/s12891-015-0758-0] [Medline: 26474867]
17. van der Molen HF, Sluiter J, Hulshof C, Vink P, Frings-Dresen M. Effectiveness of measures and implementation strategies in reducing physical work demands due to manual handling at work. Scand J Work Environ Health 2005;31(2):75-87.
18. Nielsen K, Abildgaard J, Daniels K. Putting context into organizational intervention design: Using tailored questionnaires to measure initiatives for worker well-being. Hum Relations 2014 ;67(12):1537-1560.
19. Ajslev JZN. Smerte Som Kollektiv Vane: Om Bygningsarbejdere og Smerte i en Agentiel Realistisk Ramme for en Biopsykosocial Model. Roskilde, Denmark: Roskilde University; 2015.
20. Paap K. Working Construction: Why White Working-Class Men Put Themselves - and the Labor Movement - in Harms Way. Ithaca, NY: Cornell University Press; 2006.
21. Thiel D. Builders: Class, Gender and Ethnicity in the Construction Industry. London, UK: Routledge; 2012.
22. Ajslev JZN, Lund HL, Møller JL, Persson R, Andersen LL. Habituating pain: questioning painphysical strain as inextricable conditions in the construction industry. Nordic J Working Life Stud 2013;3(3):195-218.
23. Ajslev JZN, Persson R, Andersen LL. Associations between wage system and risk factors for musculoskeletal disorders among construction workers. Pain Res Treat 2015;2015:513903 [FREE Full text] [doi: 10.1155/2015/513903] [Medline: 26605083]
24. Westgaard RH, Winkel J. Occupational musculoskeletal and mental health: significance of rationalization and opportunities to create sustainable production systems - A systematic review. Appl Ergonomics 2011;42(2):261-296.
25. Guldenmund RW. The nature of safety culture: a review of theory and research. Safety Sci 2000;34(1):215-257.
26. Ajslev JZN. Fordelingen af arbejdet i byggesjakket og muskel-og skeletbesvaer.: Skriftserie for Center for Arbejdslivsstudier; 2014. URL: http://rossy.ruc.dk/ojs/index.php/caf [accessed 2016-05-04] [WebCite Cache ID 6hGFTs2w2]
27. Ajslev JZN. Muskel-og skeletbesvaer i byggebranchen kortlaegning af organisationsfaktorer samt individuelle holdninger og forstaaelser. 2014. URL: http://rossy.ruc.dk/ojs/index.php/caf [accessed 2016-05-04] [WebCite Cache ID 6hGFaUknU]
28. Connell RW. The big picture: masculinities in recent world history. Soc Theory 1993 ;22(5):597-623.
29. Reinicke K. Arbejdsliv, maskulinitet og karrieredilemmaer. Tidsskrift Arbejdsliv 2010;12(2):36-53.
30. Bamberger M, Rao V, Woolcock J. Using mixed methods in monitoring and evaluationxperiences from international development. In: Tashakkori A, Teddlie C, editors. Sage Handbook of Mixed Methods in Social and Behavioral Sciences. 2nd edition. Thousand Oaks, CA: SAGE Publications, Inc; 2010.
31. Pawson R, Tilley N. Realistic Evaluation. 1st edition. Thousand Oaks, CA: SAGE Publications, Ltd; 1997.
32. Andersen LL, Zebis MK. Process evaluation of workplace interventions with physical exercise to reduce musculoskeletal disorders. Int J Rheumatol 2014:1-11.
33. Driessen MT, Proper KI, Anema JR, Bongers PM, van der Beek AJ. Process evaluation of a participatory ergonomics programme to prevent low back pain and neck pain among workers. Implementation Sci 2010;5 [FREE Full text] [doi: 10.1186/1748-5908-5-65] [Medline: 20735823]
34. Saunders RP, Evans MH, Joshi P. Developing a process-evaluation plan for assessing health promotion program implementation: a how-to guide. Health Promot Pract 2005;6(2):134-147.
35. Devaney B, Rossi P. Thinking through evaluation design options. Children Youth Serv Rev 1997;19(7):587-606.
36. Helitzer D, Yoon S, Wallerstein N, Dow y Garcia-Velarde L. The role of process evaluation in the training of facilitators for an adolescent health education program. J Sch Health 2000;70(4):141-147.
37. Flyvbjerg B. Five misunderstandings about case-study research. Qualitative Inquiry 2006 ;12(2):219-245.
38. Kines P, Andersen LPS, Spangenberg S, Mikkelsen KL, Dyreborg J, Zohar D. Improving construction site safety through leader-based verbal safety communication. J Safety Res 2010 ;41(5):399-406.
39. Davies B, Harré R. Positioning and personhood. In: Harré R, van Langenhove L, editors. Positioning Theory. London, UK: Blackwell Publishers; 1999:32-52.
40. Barad K. Meeting the Universe Halfway: Quantum Physics and the Entanglement of Matter and Meaning. Durham, NC: Duke University Press; 2007.

41. Czarniawska B. Shadowing: And Other Techniques for Doing Fieldwork in Modern Societies. Copenhagen, Denmark: Copenhagen Business School Press; 2007.
42. Palinkas LA, Aarons GA, Horwitz S, Chamberlain P, Hurlburt M, Landsverk J. Mixed method designs in implementation research. Adm Policy Ment Health 2011 ;38(1):44-53.

Abbreviations

OHS: occupational health and safety

Edited by G Eysenbach; submitted 15.02.16; peer-reviewed by F Drozd, AM Dale; comments to author 28.03.16; accepted 11.04.16; published 26.05.16.

Please cite as:
Ajslev J, Brandt M, Møller JL, Skals S, Vinstrup J, Jakobsen MD, Sundstrup E, Madeleine P, Andersen LL
Reducing Physical Risk Factors in Construction Work Through a Participatory Intervention: Protocol for a Mixed-Methods Process Evaluation
JMIR Res Protoc 2016;5(2):e89
URL: http://www.researchprotocols.org/2016/2/e89/
doi:10.2196/resprot.5648
PMID:27230696

Protocol

Perspectives of People Living with HIV on Access to Health Care: Protocol for a Scoping Review

Shabnam Asghari[1], MD, MPH, PhD; Allison Maybank[1], BSc; Oliver Hurley[1], MSc; Hilary Modir[2]; Alison Farrell[3], MLIS; Zack Marshall[4], MSW; Claire Kendall[5,6,7,8,9], MD, PhD; Sharon Johnston[9], MD, LLM; Matthew Hogel[5], PhD; Sean B Rourke[10,11,12], PhD, FCAHS; Clare Liddy[5,6,7,9], MD, MSc

[1]Primary Healthcare Research Unit, Department of Family Medicine, Faculty of Medicine, Memorial University of Newfoundland, St. John's, NL, Canada

[2]School of Pharmacy, Memorial University of Newfoundland, St. John's, NL, Canada

[3]Health Sciences Library, Faculty of Medicine, Memorial University of Newfoundland, St. John's, NL, Canada

[4]Division of Community Health and Humanities, Faculty of Medicine, Memorial University of Newfoundland, St. John's, NL, Canada

[5]C.T. Lamont Primary Health Care Research Centre, Bruyere Research Institute, Ottawa, ON, Canada

[6]Department of Family Medicine, University of Ottawa, Ottawa, ON, Canada

[7]Ottawa Hospital Research Institute, Ottawa, ON, Canada

[8]Institute of Clinical Evaluative Sciences, Toronto, ON, Canada

[9]Bruyere Research Institute, Department of Family Medicine, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada

[10]Ontario HIV Treatment Network, Toronto, ON, Canada

[11]Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada

[12]Department of Psychiatry, University of Toronto, Toronto, ON, Canada

Corresponding Author:
Shabnam Asghari, MD, MPH, PhD
Primary Healthcare Research Unit
Department of Family Medicine, Faculty of Medicine
Memorial University of Newfoundland
Agnes Cowen Hostel, Health Sciences Centre
300 Prince Philip Dr.
St. John's, NL, A1B 3V6
Canada
Phone: 1 709 777 2142
Fax: 1 709 777 2965
Email: shabnam.asghari@med.mun.ca

Abstract

Background: Strategies to improve access to health care for people living with human immunodeficiency virus (PLHIV) have demonstrated limited success. Whereas previous approaches have been informed by the views of health providers and decision-makers, it is believed that incorporating patient perspectives into the design and evaluations of health care programs will lead to improved access to health care services.

Objective: We aim to map the literature on the perspectives of PLHIV concerning access to health care services, to identify gaps in evidence, and to produce an evidence-informed research action plan to guide the Living with HIV program of research.

Methods: This scoping review includes peer-reviewed and grey literature from 1946 to May 2014 using double data extraction. Variations of the search terms “HIV”, “patient satisfaction”, and “health services accessibility” are used to identify relevant literature. The search strategy is being developed in consultation with content experts, review methodologists, and a librarian, and validated using gold standard studies identified by those stakeholders. The inclusion criteria are (1) the study includes the perspectives of PLHIV, (2) study design includes qualitative, quantitative, or mixed methods, and (3) outcome measures are limited to patient satisfaction, their implied needs, beliefs, and desires in relation to access to health care. The papers are extracted by two independent reviewers, including quality assessment. Data is then collated, summarized, and thematically analyzed.

Results: A total of 12,857 references were retrieved, of which 326 documents were identified as eligible in pre-screening, and 64 articles met the inclusion criteria (56% qualitative studies, 38% quantitative studies and 6% mixed-method studies). Only four studies were conducted in Canada. Data synthesis is in progress and full results are expected in June, 2016.

Conclusions: This scoping review will record and characterize the extensive body of literature on perspectives of PLHIV regarding access to health care. A literature repository will be developed to assist stakeholders, decision-makers, and PLHIV in developing and implementing patient-oriented health care programs.

(JMIR Res Protoc 2016;5(2):e71) doi:10.2196/resprot.5263

KEYWORDS

HIV; HIV Infections; Attitude to Health; Patient Satisfaction; Perspective; Health Services Accessibility; Health Services/Utilization; Access to Health Care

Introduction

Within the topic of access to health care for people living with human immunodeficiency virus (PLHIV) there are four key ideas which are very important to the conception and planning of research in this area. These ideas are used to guide research in an effective manner to be able to produce the best results and initiate change. These ideas are (1) efforts to improve health care will be wasted unless they reflect what patients want from the service [1], (2) access is a major concern in health care policy and is one of the most frequently used words in discussions of the health care system [2], (3) engagement in care is vital for the prognosis of PLHIV or acquired immune deficiency syndrome (AIDS), and to reduce the transmission of HIV [3], and (4) access and delivery of health care services to PLHIV is challenging and requires a characterization of these people and their perspective of access to health care [4-6].

Access to Health Care for People Living with HIV

In developed countries, the number of PLHIV is increasing. With advances in HIV treatment and health care services, PLHIV are living longer, necessitating a wider range of preventive, acute, and long-term health care services to meet the needs of PLHIV across their lifetimes [4,5]. The complexity of responses to meet the needs of PLHIV is heightened as HIV continues to disproportionally affect vulnerable populations.

Providing health care for a patient population that experiences complex needs requires societies to develop and sustain appropriate health care, as well as improve access to health care services that ensure engagement and ongoing retention in care [4,7-9]. The positive impact of accessible health care on the health and quality of life of PLHIV has been previously identified [4,7-9]. In a system such as Canada's (that provides universal health care), it is often assumed that there are few barriers to accessing care and treatment, such as antiretroviral therapies. Indeed, Canadian studies show that most people diagnosed with HIV have had encounters with health care providers within one month of their diagnosis [5]. However, there are many people with HIV who have not engaged with care to adequately monitor and treat infection [5]. Access to required services for HIV care also varies across jurisdictions, and many PLHIV report continued difficulty accessing health care services [5]. Previous studies have revealed barriers to access, disparities in health care delivery, and factors contributing to underutilization of services among this population [4]. In addition, there have been attempts to mitigate these barriers, including strategies such as eHealth or outreach programs to improve access and engagement in health care [7]. However, most of these studies were developed and conducted based on the perspective of health care decision-makers, while patients' views of access to health care may differ from health professionals, managers, and policymakers [10]. Incorporating patients' perspectives into the implementation and evaluation of health care programs is essential [11]. This study represents the first attempt to broadly and systematically identify, classify, and synthesize literature on PLHIV's perspectives on access to health care.

Concept of End-Users and Patients' Perspectives

It is increasingly recognized that patients' beliefs and desires influence their involvement in their own health, access to health care, and communication with their health care providers. Recent studies also emphasize that patients' perceptions of their access to health care services should be taken into account when implementing health programs [12-14]. However, there is no unique consensus for patients' perspectives that can span all conditions and all populations [10,11].

Most existing literature has documented patients' perspectives by assessing patient satisfaction using questionnaires and surveys; others suggest first identifying a common definition for the end-users of the health care system, including patients, consumers, citizens, and the general public. These studies classify the end-users into two categories. The first group includes individuals *whose role is to provide a societal or lay perspective about health services/technologies* [15]; this category includes groups representing citizens and elected officials. The second category includes *those individuals directly affected by a given health condition or health service/technology* [15]. One study by Cayton suggests that these two categories represent different roles that individuals take on while engaging with health care services, and identifies these categories as two sides of the same coin [16].

Finally, consumer-perspective studies suggest visualizing issues through the eyes of the service users. These investigations include consumers' insights and *experiential* evidence of the totality of features of a product, and consumer-stated satisfaction (or their implied needs) with the products. The challenge in these studies is the implicit assumptions of people's interpretation of quality and their individual values [1,11].

Concept of Access to Health Care

Access to health care is a complex concept that is usually measured using multiple dimensions, including the characteristics and expectations of health care providers, customers, or patients. A growing body of research has grouped these characteristics into the five A's of access to health care (affordability, availability, accessibility, accommodation, and acceptability) [2]. Many investigators suggest distinguishing between the *potential of having access* and *gaining access*, by identifying whether people who require health care get into the health care system or not.

Individuals' perceptions of their needs for health care, and their decisions to seek health care services, are the first steps in the process of gaining access to health care. Access to health care services suggests that a person distinguishes and accepts his or her needs for health care, consents to be a service user, recognizes resources, and is willing to use the services available [17]. This process is further influenced by demographic, socioeconomic, cultural, and environmental factors. Individuals' anticipation and recognition of a health care service may differ from those of health care professionals [17]. In recent years, efforts to change people's attitudes and behaviors regarding health care services have increasingly shifted to acknowledging the importance of the views of users and their demands in developing services. Some of these advances extend the concept of access (beyond physical access) to the development of remote access via electronic devices and the Internet [18].

Scope of the Review

We aimed to summarize the perspectives of PLHIV concerning access to health care, as identified in previous studies. In order to provide a more comprehensive overview of the existing knowledge, a scoping review will be conducted instead of a systematic review. Findings from the scoping review will enable us to examine the extent, range, and nature of research activity on this topic, and to evaluate the value and feasibility of performing a full systematic review [19].

Protocol of the Review

The standard process for this scoping review will include the stages suggested by Arksey and O'Malley, among others [19-23]. The draft protocol is being circulated to knowledge translation experts, systematic review methodologists, a librarian, clinicians, and decision-makers for their review, and the protocol will be modified as required. The quality of individual studies will also be assessed, scored, and synthesized to gauge the overall quality of studies being done [19,21-23].

Stage 1: Identifying the Research Question

The research question for this review was developed by members of Advancing Primary Healthcare for People Living with HIV (LHIV Innovation Team), a team of researchers, primary and specialist health care providers, policy-makers, and HIV-positive people with experience accessing health care, aiming to improve the community-based care of PLHIV in Canada. Our research question is summarized as: What is the extent of knowledge on the perspectives of PLHIV about access to health care services?

Goals and Aims

In response to the research question, the main goal of this review is to explore the depth, breadth, and quality of evidence about the perspectives of PLHIV regarding access to health care services internationally, with a particular focus on Canadian studies. The aims of this scoping review are to orient our research team, to provide evidence-based information for the team to conduct the research, and to advance the primary health care for PLHIV in Canada.

Objectives

We have five main objectives in this study:

1. Map the literature on the perspectives of PLHIV about access to health care services.
2. Describe what is known about the perspectives of PLHIV regarding access to health care services, to identify the gaps in evidence, and to highlight research priorities based on these results.
3. Establish the themes of the perspectives of PLHIV regarding access to health care.
4. Prepare an evidence-based summary of Canadian and international research literature on the perspectives of PLHIV related to health care access.
5. Produce an action plan and a research agenda for the LHIV Innovation Team.

Methods

Participants

The participants that will be targeted include anyone living with HIV/AIDS. There will be no exclusion criteria based on age, sex, ethnicity, or geographic location, although sub-populations may be discussed separately depending on our findings.

Outcomes

Outcomes will be restricted to any measures of PLHIV-stated satisfaction, implied needs, beliefs, and desires concerning access to health care. No restrictions on the type of health care services are to be applied to our search, including traditional and non-traditional services for the diagnosis and treatment of disease or the maintenance of health, in order to include all outcomes in the literature. To distinguish access from other attributes of health care services, including continuity of care and retention, the definitions suggested by Haggerty et al will be used [24,25].

Stage 2: Identifying Relevant Studies

Selection of Search Terms

Significant terms from the research question will be selected, and a list of possible synonyms or alternate terms will be compiled. To find the best search terms, Medical Subject Heading (MeSH) terms, MeSH tree, and related words found in key words and references will also be searched.

Building Search Terms Strategy

To determine the best search strategy, different combinations of words will be tested across databases. The search will include an iterative process to refine the search terms through testing

of different terms, and combining new terms, as new related citations are identified. The search will include a combination of MeSH and keywords searched in the title and abstract (tiab) fields. Search strategies will be modified for other databases as required.

Sources of Relevant Studies

To identify all sources of information, this review will begin with a comprehensive mapping of peer-reviewed publications referenced in electronic databases. The search for studies will be in the following databases, and will be guided by a librarian: EMBASE (1947 to May 5, 2014); MEDLINE vis PubMed (1946 to May 5, 2014); CINAHL (1937 to May 5, 2014); Cochrane (1993 to May 5, 2014); and PsycINFO (1880s to May 5, 2014).

Cited references of articles chosen for inclusion in the scoping review will also be searched, as well as additional sources, including the reference lists of included studies, searching ProQuest for PhD theses, contacting experts to request details of any known studies (eg, known Canadian researchers in this subject area), HIV Conferences and Symposia, and all sources identified in Multimedia Appendix 1.

Validation of Search Protocol

To validate the search protocol and calibrate our search strategy, the protocol will be tested on the gold standard studies and journals suggested by content experts. The eligibility criteria will be modified as required.

Directory of the Identified Studies

A directory of publications and grey literature will be created in Refworks [26]. To capture and tag the web-pages' information, other reference manager software will also be used, including Zotero [27] and Mendeley [28]. The tagged webpages will then be imported into Refworks.

Stage 3: Study Selection

Study selection will be an iterative process consisting of searching the literature, refining the search strategy, assessing the eligibility criteria, pre-screening and reviewing the full text of the literature for inclusion, and retaining only articles concerning PLHIV's perspectives on access to health care.

Eligibility Criteria

Decisions about review process methodology will be undertaken by members of our team who will be blinded to the results of the studies in question, and who have expertise in health care services for PLHIV. Inclusion criteria will ensure a wide range of literature from varying resources, but only French and English articles will be used, as reviewers are fluent in these languages. To ensure a good standard of evidence and clinical relevance to the review, the types of articles found under exclusion criteria will not be included.

Inclusion criteria will include (1) literature from peer-reviewed journals, (2) grey literature, such as unpublished theses and reports from relevant websites, and (3) the use of only French and English articles for full-text review. Exclusion criteria will include (1) audits or anecdotal information, (2) research at the planning stage (although this will be included in the research directory), (3) pilot studies, (4) undergraduate and MSc dissertations, (5) book reviews, and (6) policy analyses.

Qualitative and quantitative studies will be examined. Qualitative studies will include any kind of qualitative study (eg, phenomenology, ethnography, grounded theory, historical and case studies) as identified by the authors. Quantitative studies encompass reviews (systematic reviews, meta-analyses, narrative reviews, scoping reviews), observational studies (cohort, case control, cross-sectional studies, case series, case reports), and interventional studies (field trials, randomized controlled trials, community trials, quasi-experimental).

Study Selection Process

Step 1: Pre-screening

The titles and abstracts of all articles identified during database searches will be examined by a trained undergraduate student to evaluate eligibility, after duplicates are removed. Studies will be considered unrelated if the articles and abstracts are not related to the search subject, or if the articles are commentaries or editorials. The number of all articles deemed eligible by title and abstract will be recorded for further reference, but only French and English articles are subject to full-text reviews.

Step 2: Verification of Results

A random sample of 5% of the articles that are excluded by title and abstract will then be re-examined by one of the two reviewers to ensure that all relevant articles are considered. If more than 5% of the sample is found to be relevant, all excluded articles will be re-examined.

Step 3: Full Text Review

The full texts of retained references will be linked to the PLHIV Perspective Directory in Refworks using the Memorial University Library Services. The number of articles without full texts will also be recorded for further reference. Before commencing the full text review and data extraction, a calibration exercise will be undertaken. Two independent reviewers will be assigned a random selection of 5% of included citations. The eligibility criteria will then be modified if the agreement between the two reviewers is low ($\kappa<0.5$). The reviewers will also screen the remainder of the citations and discrepancies will be resolved by a third reviewer.

Stage 4: Data Extraction

A data extraction tool in Excel will be prepared for data abstraction to systematically collect data from identified articles. The tool will be designed to extract information on the citation type (eg, original research), country, date of study, methodological aspects of the study, design, characteristics of the participants, participants' perspectives on access to health care, and the quality of the study. The data extraction tool will be assessed on a random sample of 10 articles. The data extraction tool will also be revised iteratively, as required. Two trained graduate students will independently review and extract the information.

Stage 5: Collating, Summarizing and Reporting the Results

Collating and summarizing results will include a descriptive summary of the number of identified articles, and an interpretive synthesis using the Arksey and O'Malley framework [19]. It is anticipated that the identified studies will incorporate different methodologies; qualitative and quantitative analyses will then be undertaken. The quality of original studies (both quantitative and qualitative) will be evaluated using a scoring system for Systematic Evaluation of Mixed Studies Review [23]. The quality of the screened articles will be graded, not with the intention of excluding the poorer studies or weighting the studies, but rather to identify the overall quality of studies in the sample. The studies and their characteristics will also be summarized. The frequency of studies will be reported by the study design, including place and date of publication, quality score, identified outcomes (PLHIV's perspectives on access to health care), the positive and negative perspectives, and the PLHIV's reported barriers and facilitators to accessing health care.

Quantitative studies will be reviewed and evaluated using a descriptive summary of key findings (eg, PLHIV's reported facilitators and barriers, PLHIV's views, satisfaction, attitudes, and opinions on access to health care) as well as the measurement tools (see Multimedia Appendix 2). Qualitative studies will be reviewed and evaluated by identifying the key findings and themes (eg, PLHIV's reported barriers and facilitators, PLHIV's views on access to health care). The findings will then be presented as an initial concept and further broken down into the emerging and final themes within that concept (see Multimedia Appendix 2).

Analysis will focus on detecting the key concepts among studies. The concepts will then be synthesized and refined to determine core themes; directed content analysis and thematic analysis will be undertaken to classify the data [29-31]. It is also anticipated that this multi-layer synthesis will identify novel concepts not suggested by the individual studies. Using this approach, we will identify research available in this area, the gaps in literature, and whether there is a need for a systematic review of the literature or other future reviews. Need for a systematic review will be determined by the content and methods of the studies and whether they are conducive to performing a systematic review, as the topic is very broad.

The results will then be reported in descriptive tables, frequency tables, and diagrams. The characteristics of the studies, including participants, study setting, study design, and study outcomes will be described. A summary table will also provide the identified themes.

Knowledge-User Consultation

To ensure applicability, usability, and a clear purpose, the review is being conducted using an integrated knowledge translation approach and knowledge-users will be involved throughout the review's duration. This approach will involve a series of consultations with research experts and the community advisory committee in our team to engage them in the development of the study outcome, action plan and research agenda, and to provide opportunities for knowledge exchange. The team includes researchers, educators, PLHIV, policymakers, clinicians, and trainees.

Preliminary findings of the review will be shared with our team, to validate our findings and guide the review's completion, on a regular basis [20]. We will present the preliminary results and list of findings in the annual meetings of the LHIV Innovation Team. All comments and feedback will be recorded and will be integrated into the study. We will also ask the LHIV Innovation Team whether they can suggest any additional issues related to PLHIV's access to health care from the patients' perspective, which has not yet been identified in our review. Using the final results, a summary of possible implications to practice, including the areas that may require action in the medium and longer term, will be developed. The summary will be presented in the annual meeting of the LHIV Innovation Team for brainstorming, developing the research questions, identifying appropriate strategies, and the production of an action plan and research agenda for the LHIV Innovation Team.

Results

Stage 2: Identifying Relevant Studies

The search terms that were selected for the literature search can be found in Multimedia Appendix 3. The literature search strategy for PubMed is outlined in Table 1 (see Multimedia Appendix 4 for search strategies for all other databases). After an extensive literature search, 20,687 articles were found using the appropriate search terms. 7829 of these articles were duplicates which left 12,858 references to be screened.

Table 1. The literature search strategy for PubMed and number of identified articles.

#	Searches	
1	"HIV"[Mesh] OR "HIV Infections"[Mesh] OR HIV[tiab] OR AIDS[tiab] OR "Acquired Immunodeficiency Syndrome"[tiab] OR "Human Immunodeficiency Virus"[tiab] OR "Human Immunodeficiency Viruses"[tiab] OR "Acquired Immune Deficiency Syndrome"[tiab]	
2	Satisfaction[tiab] OR satisfy[tiab] OR perspective[tiab] OR perspectives[tiab] OR attitude[tiab] OR attitudes[tiab] OR opinion[tiab] OR opinions[tiab] OR view[tiab] OR views[tiab] OR preference[tiab] OR preferences[tiab] OR experience[tiab] OR experiences[tiab] OR "Attitude to Health"[Mesh:NoExp] OR "Patient Satisfaction"[Mesh]	
3	(access[tiab] OR accessibility[tiab] OR accessible[tiab] OR barrier[tiab] OR barriers[tiab] OR facilitator[tiab] OR facilitators[tiab] OR utilize[tiab] OR utilize[tiab] OR utilization[tiab] OR use[tiab] OR utilization[tiab] OR provision[tiab] OR provide[tiab]) AND ("health services"[tiab] OR "health service" [tiab] OR "health care"[tiab] OR healthcare[tiab] OR care[tiab] OR treatment[tiab] OR therapy[tiab] OR therapies[tiab] OR service*[tiab] OR clinic*[tiab] OR "medical care"[tiab] OR "medical services"[tiab] OR program*[tiab])	
4	"Health Services Accessibility"[Mesh] OR "Health Services/utilization"[Mesh]	
5	#3 OR #4	
6	#1 AND #2 AND #5	N=5858

Stage 3: Study Selection

After assessing eligibility based on title and abstract, a total of 317 articles were deemed to be relevant (Figure 1). Of the 12,532 articles which were not relevant based on title and abstract, 700 (5%) were randomly selected to verify the results of the exclusion/inclusion process. These articles were re-assessed based on title and abstract. Of the 700, 9 articles were found to be relevant and therefore added to the 317 to be reviewed by full text. This was less than 5% of the sample and therefore verifies the process (Figure 1).

A total of 326 articles were reviewed in full text. Based on the inclusion/exclusion criteria, 260 of these articles were not about patients' perspectives on their access to care, which left 66 articles that met eligibility. A full description of the exclusion process can be found in Figure 1.

Stage 4: Data Extraction

The final version of the data extraction tool can be viewed in Multimedia Appendix 5. During extraction, two articles were found to not be relevant to this scoping review and therefore were not included in any analysis, which left a total of 64 articles. Of these 64, 36 (56%) were qualitative, 24 (38%) were quantitative and 4 (6%) were mixed methods by design. Throughout the extraction process, a comparison of quality assessment and extraction were done by two independent reviewers. Quality assessment scores were deemed comparable if they were within 1 point of each other. If differences in extraction results were found, a discussion between the two reviewers was initiated and either a common conclusion was made, or a third party was consulted. Overall, the agreement between the two reviewers was good (κ=.75). The majority of assessments and extractions were similar between the reviewers, with all differences being discussed and decided upon together.

Stage 5: Collating, Summarizing and Reporting the Results

Looking at the articles more closely, there were some general initial quantitative results available. The majority of articles were published within the past 10 years, with the most being published in 2009 (n=9); a breakdown of all publication years can be found in Figure 2. Of the 20 different countries in which research was performed, a substantial number of the studies were conducted in the United States (n=27), with other countries such as Nigeria, Canada, India, and South Africa adding studies to the body of literature. In Figure 3, it is possible to see a visual representation of the proportion of research there has been in each country. The *other* category includes the 11 countries that are only represented in one article of this review. Data synthesis is in progress and full results are expected in June, 2016.

Figure 1. Stepwise exclusion of articles.

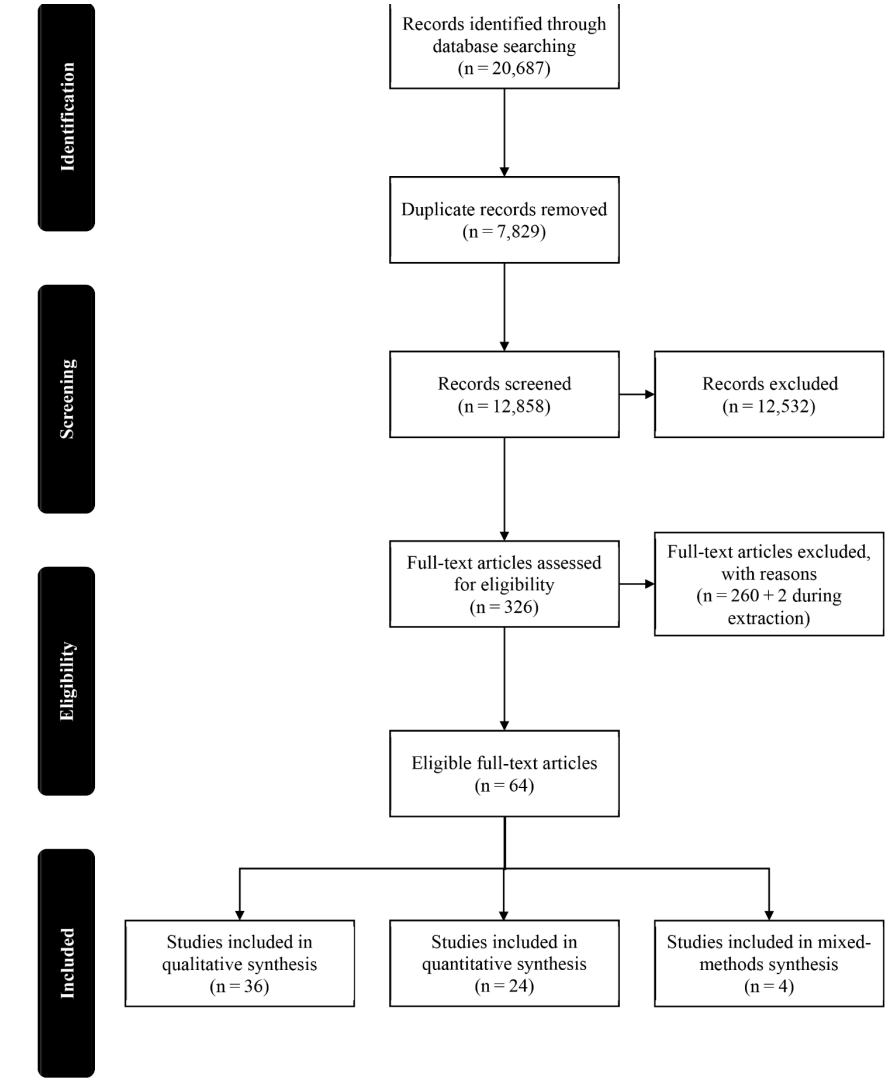


Figure 2. Year of publication of research.

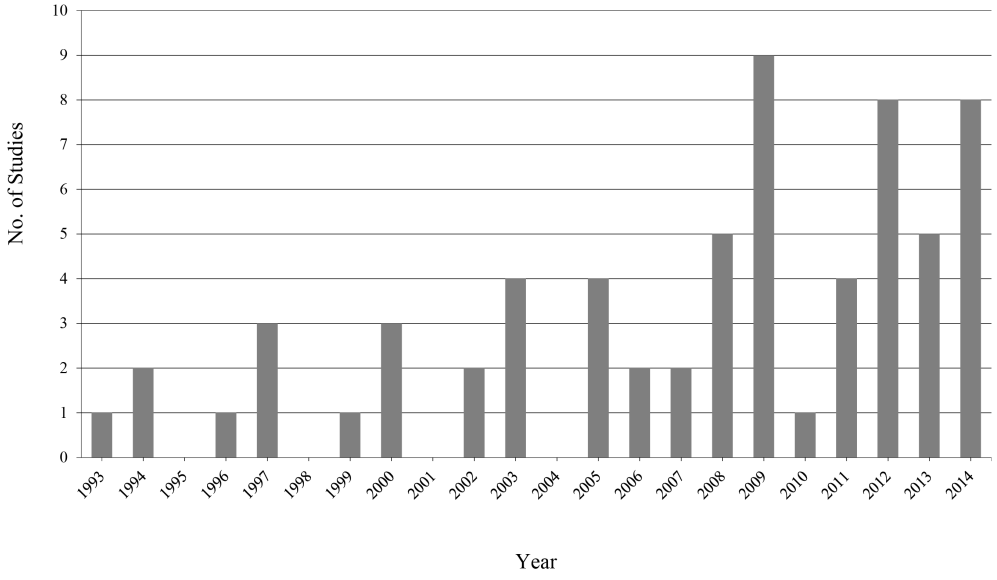
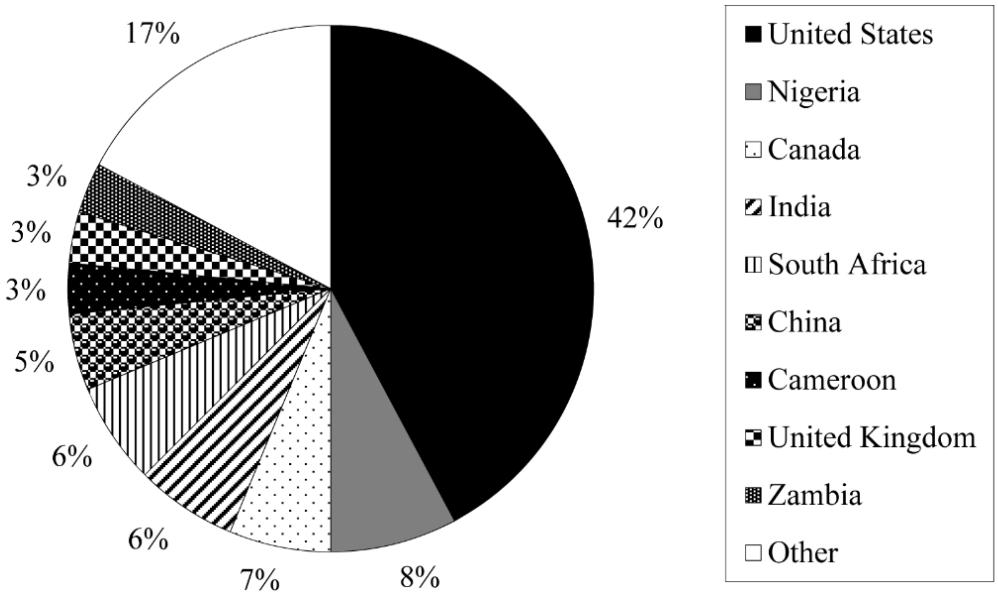


Figure 3. Country of study.



Discussion

Anticipated Challenges

A large number of search results are anticipated, so proactive steps are taken during the review, including (1) working closely with a librarian at Memorial University of Newfoundland to ensure that the review will be manageable, and (2) categorizing the studies in terms of their quality and the proper knowledge synthesis methods. We have a strong team with expertise in research methods, review methods, and content. Our team conducts regular meetings and communications with stakeholders to obtain their comments and iteratively modify the study methodology as required.

Throughout the process there have been some challenges. As there are a large number of articles identified for review, not all are initially accessible electronically through databases, and many have to be found individually. This issue adds to the workload of the research librarian, who has to manually obtain these records. Due to the wide selection of possible outcomes and the adding of new possibilities (due to an iterative process to include all aspects of patients' perspectives of care), there may be slight variation in how results are classified between graduate students. However, the core results sections (eg, *5 A's*) remain the same, so all important results will be accounted for.

Next Steps

Data extraction has been completed and compared by both graduate student reviewers. The next step in the process is to collate and summarize that data found, in order to answer the objectives within this study.

Conclusion

A scoping review will record and characterize the extensive body of literature on perspectives of PLHIV regarding access to health care. Without a systematic and well-documented protocol, the scoping reviews are subject to biases. A repeatable and evidence-based protocol is required to broadly and systematically identify, classify, and synthesize literature. A valid protocol will help to identify the issues, resolve some problems, and reduce the risk of bias.

Acknowledgments

We would like to thank the LHIV Innovation Team for all their work on this project, as well as the Canadian Institutes of Health Research grant for the Advancing Primary Healthcare for PLHIV in Canada project to allow for this research to happen.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Additional sources of information pertaining to PLHIV.

[PDF File (Adobe PDF File), 30KB - resprot_v5i2e71_app1.pdf]

Multimedia Appendix 2

Data summation charts.

[PDF File (Adobe PDF File), 297KB - resprot_v5i2e71_app2.pdf]

Multimedia Appendix 3

Search terms.

[PDF File (Adobe PDF File), 346KB - resprot_v5i2e71_app3.pdf]

Multimedia Appendix 4

Search strategies.

[PDF File (Adobe PDF File), 453KB - resprot_v5i2e71_app4.pdf]

Multimedia Appendix 5

Data extraction tool.

[PDF File (Adobe PDF File), 366KB - resprot_v5i2e71_app5.pdf]

References

1. Wensing M, Elwyn G. Methods for incorporating patients' views in health care. BMJ 2003 Apr 19;326(7394):877-879 [FREE Full text] [doi: 10.1136/bmj.326.7394.877] [Medline: 12702627]
2. McLaughlin CG, Wyszewianski L. Access to care: remembering old lessons. Health Serv Res 2002 Dec;37(6):1441-1443 [FREE Full text] [Medline: 12546280]
3. Siegfried N, Uthman OA, Rutherford GW. Optimal time for initiation of antiretroviral therapy in asymptomatic, HIV-infected, treatment-naive adults. Cochrane Database Syst Rev 2010(3):CD008272. [doi: 10.1002/14651858.CD008272.pub2] [Medline: 20238364]
4. Uphold CR, Mkanta WN. Review: use of health care services among persons living with HIV infection: state of the science and future directions. AIDS Patient Care STDS 2005 Aug;19(8):473-485. [doi: 10.1089/apc.2005.19.473] [Medline: 16124841]
5. The Ontario HIV Treatment Network. Rapid Response Service. 2014. Demographic characteristics associated with access to HAART, HIV care and HIV viral load testing URL: http://63.135.124.232/ /Pages/Knowledge-Exchange/Rapid-Responses/Documents/RR62-2012-Demographics-Access-HAART.pdf [accessed 2015-10-19] [WebCite Cache ID 6cOniHhpA]
6. Carman M, Grierson J, Hurley M, Pitts M, Power J. Australian Research Centre in Sex, Health & Society. 2009 Jul. HIV populations in Australia: implications for access to services and delivery URL: https://www.latrobe.edu.au/arcshs/downloads/arcshs-research-publications/hiv_populations_australia_implications_access_delivery.pdf [accessed 2015-10-19] [WebCite Cache ID 6cOo0tFbh]
7. Cunningham WE, Sohler NL, Tobias C, Drainoni M, Bradford J, Davis C, et al. Health services utilization for people with HIV infection: comparison of a population targeted for outreach with the U.S. population in care. Med Care 2006 Nov;44(11):1038-1047. [doi: 10.1097/01.mlr.0000242942.17968.69] [Medline: 17063136]
8. Cunningham CO, Sohler NL, McCoy K, Heller D, Selwyn PA. Health care access and utilization patterns in unstably housed HIV-infected individuals in New York City. AIDS Patient Care STDS 2005 Oct;19(10):690-695. [doi: 10.1089/apc.2005.19.690] [Medline: 16232053]
9. Helleberg M, Engsig FN, Kronborg G, Larsen CS, Pedersen G, Pedersen C, et al. Retention in a public healthcare system with free access to treatment: a Danish nationwide HIV cohort study. AIDS 2012 Mar 27;26(6):741-748. [doi: 10.1097/QAD.0b013e32834fa15e] [Medline: 22156974]
10. Van Berckelaer A, DiRocco D, Ferguson M, Gray P, Marcus N, Day S. Building a patient-centered medical home: obtaining the patient's voice. J Am Board Fam Med 2012;25(2):192-198 [FREE Full text] [doi: 10.3122/jabfm.2012.02.100235] [Medline: 22403200]
11. Cleary PD, Edgman-Levitan S. Health care quality: incorporating consumer perspectives. JAMA 1997 Nov 19;278(19):1608-1612. [Medline: 9370508]
12. Kairy D, Tousignant M, Leclerc N, Côté A, Levasseur M, Researchers TT. The patient's perspective of in-home telerehabilitation physiotherapy services following total knee arthroplasty. Int J Environ Res Public Health 2013 Sep;10(9):3998-4011 [FREE Full text] [doi: 10.3390/ijerph10093998] [Medline: 23999548]
13. Van Berckelaer A, DiRocco D, Ferguson M, Gray P, Marcus N, Day S. Building a patient-centered medical home: obtaining the patient's voice. J Am Board Fam Med 2012;25(2):192-198 [FREE Full text] [doi: 10.3122/jabfm.2012.02.100235] [Medline: 22403200]

14. Gagnon M, Lepage-Savary D, Gagnon J, St-Pierre M, Simard C, Rhainds M, et al. Introducing patient perspective in health technology assessment at the local level. BMC Health Serv Res 2009;9:54 [FREE Full text] [doi: 10.1186/1472-6963-9-54] [Medline: 19327160]
15. Gauvin FP, Abelson J, Giacomini M, Eyles J, Lavis JN. It all depends: conceptualizing public involvement in the context of health technology assessment agencies. Soc Sci Med 2010 May;70(10):1518-1526. [doi: 10.1016/j.socscimed.2010.01.036] [Medline: 20207061]
16. Cayton H. Patient and public involvement. J Health Serv Res Policy 2004 Oct;9(4):193-194. [doi: 10.1258/1355819042250195] [Medline: 15511317]
17. Gulliford M, Figueroa-Munoz J, Morgan M, Hughes D, Gibson B, Beech R, et al. What does 'access to health care' mean? J Health Serv Res Policy 2002 Jul;7(3):186-188. [Medline: 12171751]
18. Bryan C, Boren SA. The use and effectiveness of electronic clinical decision support tools in the ambulatory/primary care setting: a systematic review of the literature. Inform Prim Care 2008;16(2):79-91. [Medline: 18713524]
19. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol 2005 Feb;8(1):19-32. [doi: 10.1080/1364557032000119616]
20. Kastner M, Tricco AC, Soobiah C, Lillie E, Perrier L, Horsley T, et al. What is the most appropriate knowledge synthesis method to conduct a review? Protocol for a scoping review. BMC Med Res Methodol 2012;12:114 [FREE Full text] [doi: 10.1186/1471-2288-12-114] [Medline: 22862833]
21. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implement Sci 2010;5:69 [FREE Full text] [doi: 10.1186/1748-5908-5-69] [Medline: 20854677]
22. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535 [FREE Full text] [Medline: 19622551]
23. Pluye P, Gagnon MP, Griffiths F, Johnson-Lafleur J. A scoring system for appraising mixed methods research, and concomitantly appraising qualitative, quantitative and mixed methods primary studies in Mixed Studies Reviews. Int J Nurs Stud 2009 Apr;46(4):529-546. [doi: 10.1016/j.ijnurstu.2009.01.009] [Medline: 19233357]
24. Haggerty J, Burge F, Lévesque JF, Gass D, Pineault R, Beaulieu MD, et al. Operational definitions of attributes of primary health care: consensus among Canadian experts. Ann Fam Med 2007;5(4):336-344 [FREE Full text] [doi: 10.1370/afm.682] [Medline: 17664500]
25. Haggerty JL, Reid RJ, Freeman GK, Starfield BH, Adair CE, McKendry R. Continuity of care: a multidisciplinary review. BMJ 2003 Nov 22;327(7425):1219-1221 [FREE Full text] [doi: 10.1136/bmj.327.7425.1219] [Medline: 14630762]
26. ProQuest. Refworks. 2014. Refworks URL: https://www.refworks.com/refworks2/default.aspx?r=authentication::init [accessed 2015-10-19] [WebCite Cache ID 6cOrVhABD]
27. Roy Rosenzweig Center for History and New Media. 2014. Zotero URL: https://www.zotero.org/ [accessed 2015-10-19] [WebCite Cache ID 6cOrlnLXg]
28. Mendeley Ltd. Mendeley. 2014. Mendeley URL: https://www.mendeley.com/ [accessed 2015-10-19] [WebCite Cache ID 6cOs08T9l]
29. Walsh D, Downe S. Meta-synthesis method for qualitative research: a literature review. J Adv Nurs 2005 Apr;50(2):204-211. [doi: 10.1111/j.1365-2648.2005.03380.x] [Medline: 15788085]
30. Jones ML. Application of systematic review methods to qualitative research: practical issues. J Adv Nurs 2004 Nov;48(3):271-278. [doi: 10.1111/j.1365-2648.2004.03196.x] [Medline: 15488041]
31. Evans D, Pearson A. Systematic reviews of qualitative research. Clin Eff Nurs 2001 Sep;5(3):111-119. [doi: 10.1054/cein.2001.0219]

Abbreviations

AIDS: acquired immune deficiency syndrome
HIV: human immunodeficiency virus
LHIV: living with human immunodeficiency virus
MeSH: Medical Subject Heading
PLHIV: people living with human immunodeficiency virus
Tiab: title and abstract

Edited by G Eysenbach; submitted 22.10.15; peer-reviewed by K O'Brien, L Perrier; comments to author 20.12.15; revised version received 13.01.16; accepted 17.01.16; published 18.05.16.

Please cite as:
Asghari S, Maybank A, Hurley O, Modir H, Farrell A, Marshall Z, Kendall C, Johnston S, Hogel M, Rourke SB, Liddy C
Perspectives of People Living with HIV on Access to Health Care: Protocol for a Scoping Review
JMIR Res Protoc 2016;5(2):e71
URL: http://www.researchprotocols.org/2016/2/e71/
doi:10.2196/resprot.5263
PMID:27193076

Publisher:
JMIR Publications
130 Queens Quay East.
Toronto, ON, M5A 3Y5
Phone: (+1) 416-583-2040
Email: support@jmir.org