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Protocol

An App to Help Young People Self-Manage When Feeling Overwhelmed (ReZone): Protocol of a Cluster Randomized Controlled Trial

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Abstract

Background: The association between behavioral difficulties and academic attainment is well established. Recent policy advising schools on managing behavior has promoted the early identification of behavioral difficulties. There is also increasing research into mHealth interventions to provide support for emotional and behavioral difficulties for young people.

Objective: The primary aim of the proposed research is to examine the effectiveness of an mHealth intervention, ReZone, in reducing emotional and behavioral difficulties in young people.

Methods: The protocol is a cluster trial of 12 classes with N=120 students with classes randomized to ReZone or management as usual. Multilevel modeling will be used to compare ReZone versus management as usual accounting for classroom-level variation.

Results: Baseline data collection started in February 2017 and ended in April 2017. Follow-up data collection started in April 2017 and ended in June 2017.

Conclusions: The proposed research will provide evidence as to whether ReZone is effective at helping young people to self-manage when feeling overwhelmed.

Trial Registration: ISRCTN 13425994; http://www.isrctn.com/ISRCTN13425994 (Archived by WebCite at http://www.webcitation.org/6tePwwiHk)

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KEYWORDS

cluster trial; behavioral difficulties; schools

Introduction

Background

In England, between 3% and 7% of school-aged children experience behavioral difficulties [1]. The association between behavioral difficulties and academic attainment is well established [2]. In particular, increasing levels of behavioral difficulties have been shown to predict negative change in academic attainment [3], and a systematic review showed a consistent association between behavioral difficulties and early school leaving [4]. Correspondingly, recent policy advising schools on managing behavior has promoted the early identification of behavioral difficulties [5]. Behavioral difficulties may interfere with school engagement, and local government bodies in England are responsible for providing alternative provision schools. Alternative provision is defined as "education arranged by local authorities for pupils who, because of exclusion, illness or other reasons, would not otherwise receive suitable education; education arranged by schools for pupils on a fixed period of exclusion; and pupils being directed by schools to off-site provision to improve their behavior" [6].

A range of programs exist to support social and emotional aspects of learning (SEAL) in students, with a systematic review identifying 113 school interventions and 222 out-of-school interventions in the United Kingdom [7]. SEAL interventions are centered on reducing risk factors and fostering protective mechanisms and focus on the development of 5 essential skills and competencies: self-awareness, self-management, social awareness, relationship skills, and responsible decision making [8]. A review identified that the majority of children targeted for these interventions were aged 5 to 10 years (56%) and were classroom-based (74%) [9]. A review of meta-analyses of SEAL interventions concluded that high-quality SEAL programs can successfully increase children's socioemotional and language skills, along with fostering positive outcomes and preventing negative ones [10]. When compared to other youth development programs offered to school-age youth, SEAL programs are among the most successful [11].

Technology-Enabled Mental Health Care

In terms of mental health, delivering services using new technologies is a developing area of interest in the English government, which recommends the increased use of technology-enabled interventions to improve access to services [12]. This trend is particularly relevant to young people, a group with disproportionate levels of mental health problems and the highest use of technology. For example, 8 in 10 children aged 12 to 15 years have access to a mobile phone, with the majority (59%) using them to access the Internet. The proportion of children aged 5 to 10 years having access to a tablet computer has increased from 51% to 71% in the past 3 years [13]. Correspondingly, there has been an increase in the use of technology (eHealth) and mobile and wireless technologies (mHealth) for health care promotion and service delivery.

Technology-enabled health care is "not just about technology, but about empowering patients to exercise greater choice and control" [12] through increasing their sense of agency [14]. Some argue that it results in patients having a better understanding of their conditions [15]. Mobile phone apps particularly enable real-time recording of moods, behaviors, and activities, which can then be shared with others to improve engagement [16]. The use of mobile phone and tablet technology for service provision has a range of potential benefits, including the ability to record information, portability, acceptability, relatively low costs, and near constant connectivity to young people and carers [17]. In addition, apps provide real-life instruction to enable self-management (eg, breathing techniques like Breathe 2 Relax [18]).

There is increasing research into mHealth interventions [19,20]. One study highlighted limitations in the security of apps in a health library [21]. A systematic review of youth mental health interventions via mobile phones [22] discovered key gaps in the literature in terms of the feasibility of apps, with little research being conducted on the attractiveness of apps for target users. The largest gap identified in the literature was evidence-based testing into the efficacy of apps, as the rapidity of technological advancement presents challenges for researchers in terms of testing newly developed apps [23].

Aims of This Research

The aims of this research are to bridge research gaps by developing an mHealth self-management support intervention to help students engage with learning and ensuring the intervention is evidence-based. Therefore, the primary aim of the proposed research is to examine the effectiveness of an mHealth intervention, ReZone, in reducing emotional and behavioral difficulties in young people to support engagement with school. The secondary aims are to examine the effectiveness of ReZone in improving self-management, well-being, and health-related quality of life in young people.

Methods

Participants and Procedures

The sample size calculation was performed using the clustersampsi command [24] in Stata 12 (StataCorp LLC). The primary outcome measure is behavioral difficulties [25].

A minimum of 12 clusters (classes) of 10 students will be recruited. This is based on a mean effect size for universal classroom management programs of d=0.80 and an intraclass correlation coefficient (ICC) of 0.05 [26], a mean (standard deviation) in the intervention arm of 2.42 (2.05) indicating that behavioral difficulties are in the nonclinical range and a mean in the control arm of 5.13 (2.74) indicating that behavioral difficulties are in the clinical range [25], an average cluster size of 10 students and a coefficient of variation of cluster sizes of 0.42 [27], and a correlation between before-and-after measurements of 0.5. As the sample is being stratified by alternative provision versus mainstream school, 3 classes of each type per arm are being recruited across South East England.

All students aged 10 to 15 years in the schools taking part in the project will be eligible to participate. To ensure matched ages across the conditions, 5th grade students (aged 10 to 11 years) will be recruited from mainstream schools; the alternative provision schools have classes with mixed ages, and, therefore,

students aged 10 to 15 years will be recruited from these schools. Students will be informed about the study by schools, which will disseminate information sheets and consent forms. Consent will be recorded in writing from parents with assent recorded from young people. Participants will be assigned a unique number and their data will only be identified by this number; consent forms and contact details will be stored securely and separately from anonymized study data. Participant lists of all classes and students will be obtained from schools.

An independent trials unit will randomize classes to management as usual or ReZone stratified by school type (alternative provision vs mainstream) using random sequence generation after classes have been recruited and baseline measures assessed. To reduce the predictability of randomization, classes will be randomized in blocks of 2, and allocation will be implemented via a secure online portal.

Management as usual was deemed an appropriate comparator as there is no routinely used mHealth intervention in classes when students feel overwhelmed. The trial will be open label.

Research assistants will attend classes, and students will complete baseline paper questionnaires (this took place from February to April 2017). Classes will then begin management as usual or download and start using ReZone. Research assistants will attend classes to collect follow-up paper questionnaires 3 months later (this took place from April to June 2017).

A favorable opinion has been received from University College London (UCL) Research Ethics (number 7969/001), and the study is adhering to relevant ethical guidelines from the British Psychology Society [28]. The study is sponsored by UCL, and trial materials will be made available to the sponsor for auditing upon request. The trial is registered with ISRCTN [ISRCTN13425994], and the protocol is reported in line with Standard Protocol Items: Recommendations for Interventional Trials guidelines [29]. ReZone is reported according to guidelines for reporting mHealth interventions [30].

Intervention

Infrastructure (Population Level)

There are 3.6 million school students aged 10 to 15 years old in the United Kingdom [31]. The rapid increase of teledensity—56% of children aged 8 to 12 years [32] and 88% of adolescents aged 13 to 17 years own or have access to a mobile phone [33]—combined with the increase in access to a tablet or e-reader—58% of adolescents have access to a tablet computer and 35% of teachers have access to a tablet computer or e-reader in the classroom (compared to only 20% of teachers in 2012) [34]—allows ReZone to reach a large population.

Technology Platform

ReZone was made for Apple iOS, Google Android, and Google ChromeBook. It was developed using HTML, Cascading Style Sheets, and JavaScript and using Phonegap to convert into iOS and Android apps. The server querying was performed using hypertext preprocessor (PHP) and a MySQL database. The server is a Dell PowerEdge R210 with Quad Core 2.40 Ghz Linux-based dedicated server with 1 TB bandwidth. The ChromeBook app is kept as a packaged HTML app.

Interoperability and Health Information System Context

As ReZone is being used in a classroom setting, it is not necessary to connect or interact with national or regional health information systems at this stage.

Intervention Delivery

Students are able to download the ReZone app from the iTunes, Google Play, and Windows app stores. Students can then use the app as much as they like, using the tools on the platform as well as being able to download and email the flat graphics of tools without personal data. Students can use ReZone on their own accord or be directed by teachers to use it during classes at times the student is becoming overwhelmed.

Intervention Content

The app aims to help students manage their emotional well-being in the classroom by encouraging them to refocus if they are feeling angry, stressed, or anxious. ReZone contains a series of tools designed to improve concentration, help relieve stress, and help students to reflect and think through problems logically. Consultations with staff from alternative provision schools were conducted where researchers discussed the therapeutic tools already being used within the school and which elements of the tools they felt were important. ReZone was then reviewed as part of the App Approval Application panel at the Anna Freud National Centre for Children and Families. This feedback, along with mentalization-based therapy, cognitive behavioral therapy (CBT), mindfulness breathing, and evidence-based training such as attention bias modification training (ABMT) aided the design of ReZone.

Functions

There are 6 functions of Rezone (stress bucket, chill out, art therapy, timeout, happy faces, and games) (Figure 1) which are based in CBT, mindfulness, and ABMT.

- Stress bucket (Figures 2 and 3): The stress bucket lets the user add any stressors that they are experiencing to a bucket. They are then able to introduce activities that help them cope with each stressor. They can see the water in the bucket rise and fall as they add and relieve stressors. If the bucket reaches 50 stress points, it will overflow.
- Timeout: Timeout asks the user to think through a time when they have felt stressed, angry, or upset. The user then works through on the app all the events that led up to feeling this way and what happened afterwards. The user can also think through what they could have done differently to help the situation as a behavioral plan. The visualization is a rocket, and each thought process creates a cloud.
- Chill out (Figure 4): Chill out uses breathing to help the user calm down and relax. Each chill out activity is based around an object or animal (rabbit, jellyfish, ball, or square) using breathing in different ways.
- Art therapy: The user can choose between a castle, dinosaur, fish, goat, heart, helicopter, unicorn, rocket, footballer, sea, or turtle to color in. There is a range of colors and utensils to complete the drawing.

- Happy faces: The user is given 30 seconds to find as many happy faces as they can among other faces depicting negative emotions.
- Game: There is game of Balloon Blast on the app. The user taps the screen to move the balloon up, trying to avoid all the obstacles, as hitting one will mean the game is over. This is a game created to provide a break or reward for the user in between the other features.

Figure 1. ReZone home page.

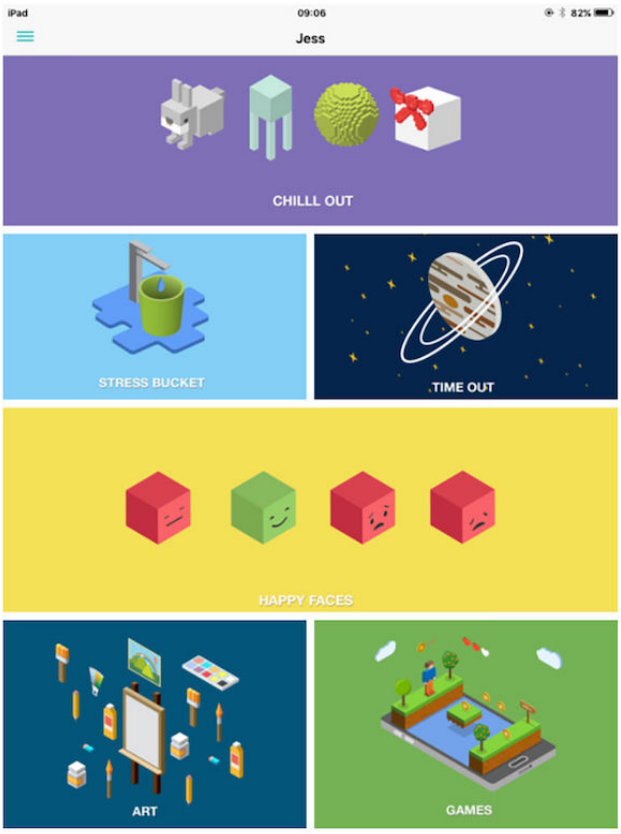


Figure 2. ReZone stress bucket (before).

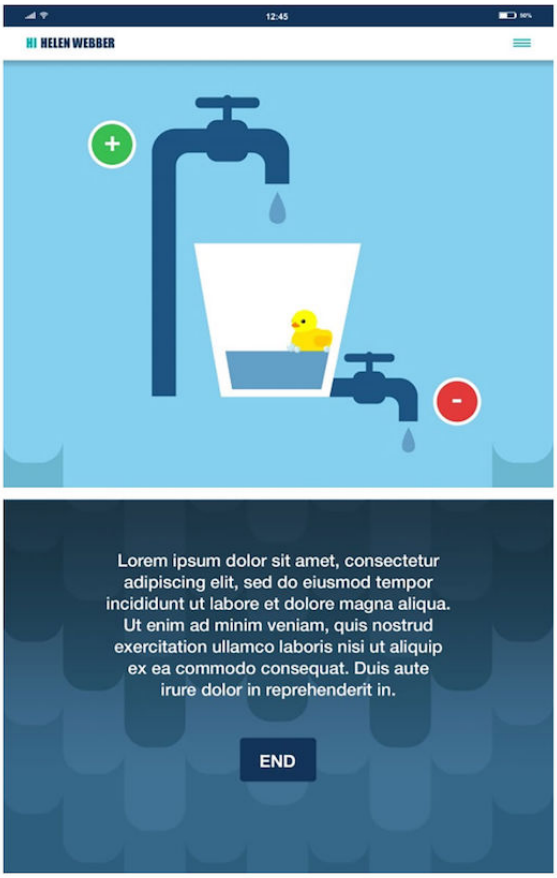


Figure 3. ReZone stress bucket (after).

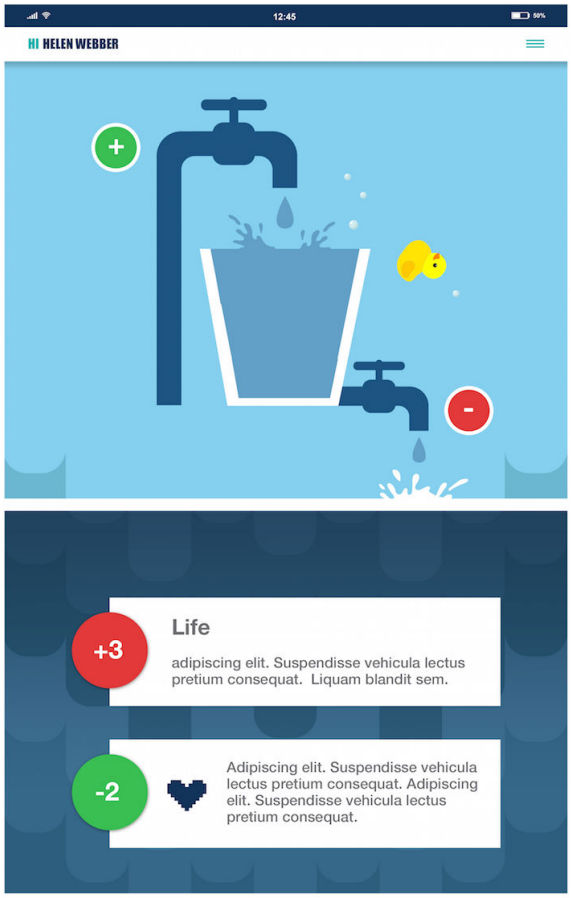
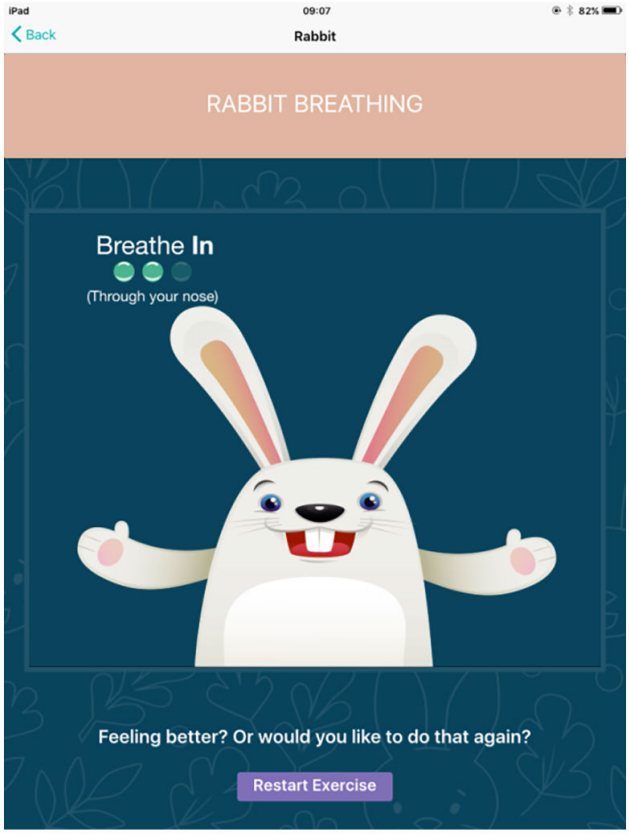


Figure 4. ReZone chill out function; breathing exercise.



Theory

Cognitive Behavioral Therapy

The stress bucket and timeout are based on the mechanism of CBT, a widely used technique looking at how a person thinks about a situation and how this affects the way they act [35]. It has been shown to successfully treat many conditions including depression and anxiety in young people in a variety of settings and formats when delivered through a digital platform [36].

Mindfulness

Chill out and art therapy are based on the concept of mindfulness [37,38]. This can be defined as the self-regulation of attention and orientation so that it is maintained on immediate experiences, allowing for increased recognition of mental events in the present moment, curiosity, openness, and acceptance. Mindfulness has been shown to have many benefits for children and young people [38]. For example, evidence suggests that mindfulness can improve the mental, emotional, social, and physical health of young people. It can also increase the ability to manage behavior and emotions while reducing stress and anxiety [39,40].

Attention Bias Modification Training

Happy faces uses techniques from ABMT, which aims to alter cognitive biases that selectively focus on negative emotional cues in the environment [41]. It has been shown that if children search for happy faces among angry faces, greater posttraining attention bias toward happy faces is evident. It also has significantly reduced clinician-rated anxiety [42].

Usability and Content Testing

Designing the app began with formative research with alternative provider schools to elicit feedback about the current use of tools when feeling angry, stressed, or anxious and current mobile phone and tablet use in and outside of the classroom. Students were also recruited to test prototypes and provide feedback on the usability, content, and design of the app. We will also be conducting focus groups and interviews with teachers and students at the end of the trial to gather further feedback on usability and content.

User Feedback

In the initial feedback on the designs, students reported that the tools were useful and easy to understand, and they appreciated the ability to have a range of tools in one place. Students offered their opinions on the design and wording of the app for their age range and on how best to share their data with their teachers. Given the existing user feedback, it is not anticipated that ReZone will cause distress. However, if students were to experience distress from using ReZone, it would be recorded as a serious adverse event, the ethics committee and sponsor would be notified, and the trial would be stopped if necessary.

Access of Individual Participants

ReZone is designed to be used in school settings with 10- to 15-year-old students, who commonly have access to tablets within school. Access could be affected by socioeconomic status due to the cost of a mobile phone or tablet to families or schools.

Cost Assessment

ReZone is free to download from the relevant app stores and, therefore, the cost of the intervention to the school is for Internet access in order to download and run the app and the cost of the tablets and/or phones. The financial strategy of ReZone and other digital products in our center is to cover ongoing technical maintenance of the app and systems through costed training for schools and mental health services in using specific products such as ReZone, using digital products in these settings in general, and developing and evaluating in-house digital products.

Adoption Inputs and Program Entry

ReZone has information points and examples throughout the app and the 6 individual functions so that the intervention use is clear to both students and staff. Students were recruited to give feedback on the information points and usability of the app. Additional training will not be provided as ReZone has been developed to be used as a standalone intervention.

Limitation for Delivery at Scale

Access to mobile phones and tablets at school is the main limitation for delivery at scale, but this is more applicable to mainstream schools than alternative provider schools where mobile phones and tablets are routinely used during learning.

Contextual Adaptability

The functionality of ReZone applies to a range of school settings. The intervention is free and easily downloaded from various app stores; it is not limited to specific users or geographical localities. It will be important to examine how best to adapt ReZone for other cultures, groups, and settings as part of other projects.

Replicability

Screenshots of content are included in Figures 1 to 4 to provide information and further context for replicating the study.

Data Security

Students are asked to enter their name, school, and date of birth each time they start using the app. The app combines the 3 sets of data encryption before submitting to the server using an Internet connection. These data are encrypted again at server level using PHP and saved in encrypted format inside a MySQL database with a unique identifier. Name, school, and date of birth are not stored as plain text in the database. If the data were to be intercepted, the data would be meaningless because they are encrypted before leaving the app. With regard to the ChromeBook app, a SHA256 Secure Sockets Layer certificate will be added to encrypt the data further. The server itself has physical and software-based security such as cameras around the hardware, daily backups, and a firewall.

Compliance With National Guidelines or Regulatory Statutes

The tools used on ReZone are based on the relevant supporting evidence base for mentalization-based therapy, CBT techniques, and ABMT. They are evidence-informed tools that have been previously created and align with relevant recommendations,

such as CBT for anxiety as recommended by National Institute for Health and Care Excellence guidelines [43].

Fidelity of the Intervention

Activity data are stored on the app and will be reviewed to determine how long students spend on ReZone, which tools they use the most, and for how long they use each tool. Metrics of participant engagement with the intervention will also be measured by teachers on self-reported forms. Teachers will record fidelity (eg, the number of times ReZone is used per class, the number of students using ReZone), class disruption, other SEAL interventions being used, and length of time to reinstate student to the class. Participants can also print off activities completed on the app to show teachers or family members.

Measures

Demographic Characteristics

Age, gender, and ethnicity will be self-reported by young people at baseline. Ethnicity will be captured using the categories from the 2001 Census. Special educational needs will be obtained from school records.

Emotional and Behavioral Difficulties

To measure emotional and behavioral difficulties, the 16-item Me and My School (M&MS) [25] will be used. The M&MS measure comprises 2 subscales assessing emotional difficulties (10 items; eg, “I feel lonely,” “I worry a lot”) and behavioral difficulties (6 items; eg, “I lose my temper,” “I break things on purpose”). Young people respond to all items on a 3-point scale from 0=never to 2=always. The M&MS has been used in previous studies and demonstrated reliability and validity [25]. Moreover, clinical cut-off scores have been established of 10 or more for emotional difficulties and 6 or more for behavioral difficulties.

Mental Well-Being

To measure mental well-being, the 7-item Short Warwick-Edinburgh Mental Well-being Scale (SWEMWBS) [44] will be used. The SWEMWBS measures positive mental well-being (eg, “I’ve been feeling useful,” “I’ve been feeling relaxed”). Young people respond to all items on a 5-point scale from 1=none of the time to 5=all of the time. The SWEMWBS has been used in previous studies and demonstrated reliability and validity [44].

Self-Management

To measure self-management, the 6-item self subscale of the Youth Empowerment Scale–Mental Health (YES-MH) [45] will be used. The self subscale captures empowerment to self-manage mental health difficulties (eg, “I know how to take care of my mental or emotional health,” “I feel my life is under control”). Young people respond to all items on a 5-point scale from 1=never or almost never to 5=always or almost always. The YES-MH has been used in a previous study and demonstrated reliability and validity [45].

Health-Related Quality of Life

To measure health-related quality of life, the 6-item EuroQol 5-Dimension–Youth (EQ-5D-Y) [46] will be used. The EQ-5D-Y captures current health states regarding 5 specific health domains (eg, mobility, self-care) on a 3-point scale from 1=no problems to 3=a lot of problems and global health on a visual analog scale. The EQ-5D-Y has been used in previous studies and demonstrated reliability and validity [46].

Analytic Strategy

Data will be entered into an Excel (Microsoft Corp) spreadsheet by research assistants with a random 20% double-entered for cross-checking. Data will only be stored on the organization’s secured servers, accessible only by members of the research team. Data will be analyzed using Stata 12 (StataCorp LLC) in order to examine the effectiveness of ReZone in reducing emotional and behavioral difficulties and improving self-management, well-being, and health-related quality of life in young people in need of targeted support to engage with learning. Three models will be tested for each of the outcome variables with time nested within students within classrooms. In model 0, the null model without predictors will be computed to examine change in outcome (eg, behavioral difficulties) over time, and the ICC will be calculated. In model 1, the association patient-level grand mean centered age, ethnicity, and special educational needs will be entered as a level-1 predictor. In model 2, the condition (ReZone vs management as usual) will be entered. School-type (ie, alternative provision vs mainstream) will be entered as a fixed effect. The likelihood ratio test will be used to compare the fit of subsequent models. An intention-to-treat analysis will be performed with last-item carried forward imputation.

Results

Funding for the trial has been secured from University College London (UCL). Baseline data collection started in February 2017 and ended in April 2017. Follow-up data collection started in April 2017 and ended in June 2017. Data analysis and write-up will be completed by December 2017.

Any updates to this protocol will be published, and the findings of the proposed research will be submitted for publication in a peer-reviewed journal by the current authors in line with International Committee of Medical Journal Editors’ guidelines. The research team will also disseminate findings to the participating schools, the study sponsor, and relevant conferences. A public summary of the findings will be available on our organization’s website (www.ucl.ac.uk/ebpu).

Discussion

The trial and its findings will develop an evidence-based mHealth self-management support intervention to help students engage with learning and manage their emotions. The findings will contribute to the growing use of technology to support children and young people with their mental health. Anticipated limitations of the proposed research include the fidelity of the intervention, assessed through teacher self-report and activity data; the content of management as usual, as different classes

in this arm may use a variety of different social and emotional learning interventions despite not using ReZone, assessed through teacher self-report; and attrition, addressed by designing ReZone with young people to ensure it is usable and through using existing questionnaires that balance length with capturing the necessary range of relevant outcomes. Notwithstanding the above limitations, the proposed research will provide evidence as to whether ReZone is effective in helping young people to self-manage when feeling overwhelmed.

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Conflicts of Interest

None declared.

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Abbreviations

ABMT: attention bias modification training
CBT: cognitive behavioral therapy
EQ-5D-Y: EuroQol 5-Dimension–Youth
ICC: intraclass correlation coefficient
M&MS: Me and My School
PHP: hypertext preprocessor
SEAL: social and emotional aspects of learning
SWEMWBS: Short Warwick-Edinburgh Mental Well-being Scale
UCL: University College London
YES-MH: Youth Empowerment Scale–Mental Health

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Protocol

The Effect of the Move More Pack on the Physical Activity of Cancer Survivors: Protocol for a Randomized Waiting List Control Trial with Process Evaluation

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Abstract

Background: Physical activity can improve many common side effects of cancer treatment as well as improve physical function and quality of life (QOL). In addition, physical activity can improve survival rate and reduce cancer recurrence. Despite these benefits, only 23% of cancer survivors in England are active to recommended levels. Cancer survivors are interested in lifestyle behavior change. Home-based interventions offer a promising means for changing physical activity behavior. Prediagnosis levels of physical activity and self-efficacy have been reported to be predictors of physical activity behavior change. The Move More Pack, which has undergone revision, is a printed resource with supporting Internet-based tools that aims to increase the physical activity of cancer survivors in the United Kingdom. The revised Move More Pack is underpinned by the theory of planned behavior and the social cognitive theory.

Objective: The aim of this proposed study was to investigate the effect of the revised Move More Pack, supported by Internet-based tools, on physical activity, self-efficacy, and health-related QOL (HRQOL) of cancer survivors in the United Kingdom.

Methods: This study is a two-arm waiting list randomized control trial with embedded process evaluation. A sample of 99 participants per arm will be recruited by invitation through an email database of cancer survivors held by UK charity Macmillan Cancer Support and an advert placed on the Macmillan Cancer Support Facebook page. Each participant is randomized to receive brief physical activity information and the UK guidelines for physical activity, or brief physical activity information and the revised Move More Pack with supporting Internet-based tools. The intervention and control arm will be followed up at 12 weeks to identify changes in self-reported physical activity, self-efficacy, and HRQOL based on Web-based questionnaires. The control arm will receive the revised Move More Pack at 12 weeks with follow-up at 24 weeks. The intervention arm is followed up at 24 weeks to determine maintenance of reported changes. Subgroup analyses will be completed based on participants' prediagnosis level of physical activity and baseline self-efficacy as possible predictors of positive changes. Use of each component of the revised Move More Pack will be assessed using a 4-point Likert scale. Semistructured phone interviews will evaluate the use and perceived usefulness of the revised Move More Pack.

Results: Participant recruitment started in March 2017. Projected completion of this study is October 2018.

Conclusions: This study's findings will identify if the proposed low-cost broad reach intervention improves physical activity, self-efficacy, and the HRQOL of cancer survivors. The process evaluation is designed to contextualize the use and perceived usefulness of the revised Move More Pack, help augment its efficient distribution, and identify potential improvements to its design.

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KEYWORDS

cancer; physical activity; behavior change; health promotion

Introduction

Physical Activity in Cancer Survivors

Two and a half million people are living with or beyond cancer in the United Kingdom [1]. In the last 5 years, this number has grown by almost half a million [1]. The number of cancer survivors, that is, someone living with or after any form of cancer diagnosis [2], is expected to rise to 4 million by 2030 [1].

Developing cancer depends on factors such as age, genetics, and lifestyle behaviors, with a suggested 40% of all cancer diagnosed in the United Kingdom linked to tobacco, alcohol, unhealthy diet, being overweight, and inactivity [3]. Leading a physically active lifestyle reduces people's risk of developing several cancers [4].

Being physically active has multiple benefits for cancer survivors. Physical activity can improve many common side effects of cancer treatments, such as fatigue, psychological distress, and adverse impact on body composition, as well as improving physical function and quality of life (QOL) [5-7]. In addition, increased physical activity is associated with improved survival and reduced disease recurrence [8]. The evidence supports the unequivocal role of physical activity in self-management [5]. Physically active cancer survivors report a sense of regaining control of their lives [9,10] and some normalcy [9-11] following a cancer diagnosis.

Engaging in physical activity is not only recommended but also safe both during and after cancer treatments [7]. The American College of Sports Medicine [7] advises that cancer survivors avoid inactivity and return to typical daily activities as soon as possible after surgery and during and after cancer treatments, working toward the standard age-appropriate physical activity guidelines [7,12]. Despite these benefits, only 23% of cancer survivors in England are active at recommended levels, and 31% are completely inactive [13].

Wang and colleagues [14] report that cancer survivors in Scotland are less likely to smoke, more likely to eat a healthy diet, and more liable to drink alcohol responsibly, although the odds ratios for these conclusions are not compelling. Wang and colleagues [14] also report that cancer survivors in Scotland are less likely to take part in at least 2 hours of physical activity than those who have not had a cancer diagnosis. A cancer diagnosis may offer a teachable moment in which people may be more receptive to changing their lifestyle behaviors [15-18]. McBride and colleagues [18] suggest that low-level interventions may facilitate such an opportunity.

Self-Efficacy and Self-Identity

Self-efficacy is central in overcoming the barriers faced by cancer survivors in becoming physically active [19]. Self-efficacy is defined in this context as the confidence of a cancer survivor that he or she has the ability and capacity to be more physically active. Self-efficacy has been reported to be a predictor of intentions to change physical activity in cancer survivors [9,20], consistent with the extant general literature on health behavior change [21]. In addition, identifying as a physically active individual has been reported to be an indicator of physical activity engagement, with those cancer survivors who are physically activity before their diagnoses being more likely to be so afterwards [9]. However, physical activity tends to decrease following diagnosis [22] and is unlikely to reverse without intervention. These predictors of physical activity are reported to be consistent across cancer survivors regardless of age, stage, type of cancer, comorbidity, or treatment received [9].

Remote Support to Facilitate Physical Activity Behavior Change

Cancer survivors report a high level of interest in lifestyle interventions [20,23-25]; however, access to face-to-face programs is not always possible because of transportation issues and geographic and access considerations [24]. There is a demand for written health information to support behavior change [24,26-28]. Advantages include message consistency, ease of delivery, self-paced learning, and the permanence of information with low production costs [29].

Home-based interventions using printed materials offer a cost-effective, potentially promising means of intervening regardless of location [23,24]. At a time when spending on public health and health care in the United Kingdom continues to be constrained, with demand for services increasing, the need for home-based interventions is growing. Randomized control trials (RCTs) have been, and continue to be, conducted on the efficacy of such interventions [23,30]. However, none has included a process evaluation to contextualize the use of such interventions in a real-world setting removed from the health care environment.

The Move More Pack and its Revision

The UK charity, Macmillan Cancer Support, developed a printed resource in 2011 called the Move More Pack that aimed to effect change in physical activity in cancer survivors. The Move More Pack consisted of a physical activity and cancer booklet and a series of written assignments to support behavior change. No additional assistance or follow-up was provided. The effectiveness of the Move More Pack in effecting change in physical activity in cancer survivors has not yet been investigated.

The principal investigator led the redevelopment of the Move More Pack in 2016 to become a printed resource supported by a series of Internet-based tools. Following discussions with cancer survivors [9,31], a systematic search and critical appraisal of the literature, a review of the original Move More Pack with respect to its underlying theoretical constructs, and an inventory

of the behavior change techniques (BCTs) it advocates, recommendations were made.

The theory of planned behavior (TPB) [15,32] and the social cognitive theory (SCT) [33-35] were identified as appropriate theories upon which to base the redevelopment of the Move More Pack. The original Move More Pack was assessed using the constructs of the TPB and the SCT. The BCT taxonomy version 1 (BCTTv1) [36] identified the active ingredients that aimed to effect change and those that might be missing from the original design. Following an iterative process, a group of six subject experts including the principal investigator, in partnership with Macmillan Cancer Support's information development team, refined the structure, content, and BCTs included within the revised Move More Pack. Macmillan Cancer Support's information development team wrote the final copy of the revised Move More Pack. Dr Tim Iverson, Macmillan Cancer Support's chief medical editor, approved the final version. The revised Move More Pack received the National Health Service England (NHS England) Information Standard [37]. A PDF of the revised Move More Pack is included as Multimedia Appendix 1.

The revised Move More Pack retained the physical activity and cancer booklet (Multimedia Appendix 2). A pull-out wall chart is included in the revised Move More Pack for users to track their progress, record achievements, and serve as a visual prompt to be more active (Multimedia Appendix 3). Furthermore, five activity leaflets (Multimedia Appendix 4) are included on popular activities of gardening, walking, and recreational swimming; the sports of badminton, bowls, cycling, golf, and walking football; and finally, on how to be generally active in daily life [38]. A digital versatile disc that focuses on exercise specifically for cancer survivors is included and is also available to view on the Web [39].

Tailored multi-component interventions are likely to be most effective in effecting lifestyle behavior change in cancer survivors [35,40,41]. Users of the revised Move More Pack can sign up to receive e-newsletters, with messages tailored to their reported prediagnosis levels of physical activity, and influenced by the stages of physical activity behavior change advanced by Marcus and Forsyth [42]. Prediagnosis levels of physical activity are collected using the Godin Leisure Time Exercise Questionnaire (GLTEQ) [43]. Case studies included within the e-newsletters are tailored to the age and gender of the user of the revised Move More Pack. A welcome email is sent to users of the revised Move More Pack, followed by e-newsletters sent during months 1, 2, 3, 6, 9, and 12. Details are outlined in Table 1, with an example e-newsletter included as Multimedia Appendix 5.

An online social community aims to link users of the revised Move More Pack, enabling social learning and enhancing social norms [44]. An online *ask the physio* group is available and allows users of the revised Move More Pack to post questions on an open forum to a registered cancer specialist physiotherapist [45]. Details of how to find local physical activity opportunities are also included on the Web [46].

The use of a pedometer combined with a printed resource has been reported to be effective in increasing physical activity in breast cancer survivors [32]. Consequently, details are provided on how to download a straightforward and easy to use digital pedometer app, as well as an app to reduce sitting time [47]. Finally, a series of video case studies of cancer survivors who have become more active are included [48]. A Web page dedicated to users of the revised Move More Pack links to these Internet-based tools (Multimedia Appendix 6) [49].

The revised Move More Pack and Internet-based tools have been developed based on the best available evidence and following guidance on the development of complex interventions from the United Kingdom based Medical Research Council (MRC) [50]. The revised Move More Pack does not prescribe physical activity; rather, it aims to empower cancer survivors to increase control over their physical activity behavior.

Aims

This study aims to investigate the effect of the revised Move More Pack over 24 weeks. It is hypothesized that use of the revised Move More Pack increases physical activity in cancer survivors, and the proportion of cancer survivors who are classified as active over 12 weeks increases with its use, with changes being maintained at 24 weeks. The primary aim is to test the effectiveness of the revised Move More Pack in reclassifying cancer survivors categorized as inactive or moderately active at baseline, to being more active over 12 weeks, with increases maintained at 24 weeks.

The secondary aims include:

- Test the effect of the revised Move More Pack on the self-efficacy and health-related QOL (HRQOL) of cancer survivors.
- Analyze subgroups to elucidate for whom the revised Move More Pack has a positive effect on physical activity, self-efficacy, and HRQOL in the context of prediagnosis levels of physical activity and baseline self-efficacy.
- Conduct a process evaluation to contextualize the use and perceived usefulness of the revised Move More Pack.

Table 1. The theme and behavior change techniques used in the e-newsletters sent to users of the revised Move More Pack.

Newsletter	Stage of change[a]	BCTs[b] used[c]
For those active before diagnosis [d]		
Month 1	Doing some physical activity	Information about others' approval; Information about health consequences; Information about emotional consequences; Graded tasks; Social comparison; Goal setting (behavior)
Month 2	Doing some physical activity	Information about others' approval; Information about health consequences; Information about emotional consequences; Framing or reframing; Graded tasks
Month 3	Doing enough physical activity	Information about others' approval; Social support (unspecified); Self-reward; Action planning
Month 6	Making physical activity a habit	Self-monitoring; Action planning; Habit reversal; Habit formation
Month 9	Making physical activity a habit	Self-monitoring; Action planning; Habit reversal; Habit formation; Social support (unspecified)
Month 12	Making physical activity a habit	Self-monitoring; Action planning; Habit reversal; Habit formation; Social support (unspecified); Self-reward
For those inactive before diagnosis [d]		
Month 1	Inactive and thinking about becoming physically active	Information about others' approval; Information about health consequences; Information about emotional consequences; Graded tasks; Social comparison
Month 2	Doing some activity	Information about others' approval; Information about health consequences; Information about emotional consequences; Framing or reframing; Graded tasks
Month 3	Doing some activity	Information about others' approval; Goal setting (behavior); Self-reward; Action planning; Commitment
Month 6	Doing enough physical activity	Self-monitoring; Action planning
Month 9	Making physical activity a habit	Self-monitoring; Action planning; Habit formation; Social support (unspecified)
Month 12	Making physical activity a habit	Self-monitoring; Action planning; Habit reversal; Habit formation; Social support (unspecified); Self-reward

[a]On the basis of the stage of change constructs offer by Marcus and Forsyth [42].

[b]BCT: behavior change technique.

[c]BCT selected from the BCT Taxonomy version 1 [36].

[d]Prediagnosis levels of physical activity assessed using question two of the Godin Leisure Exercise Time Questionnaire.

Methods

Identifying the underlying theoretical constructs of a health-related program is key when designing its evaluation [51]. A breakdown of the components of the revised Move More Pack based on the constructs of the SCT and the TPB, along with the BCTs used in available as Multimedia Appendix 7.

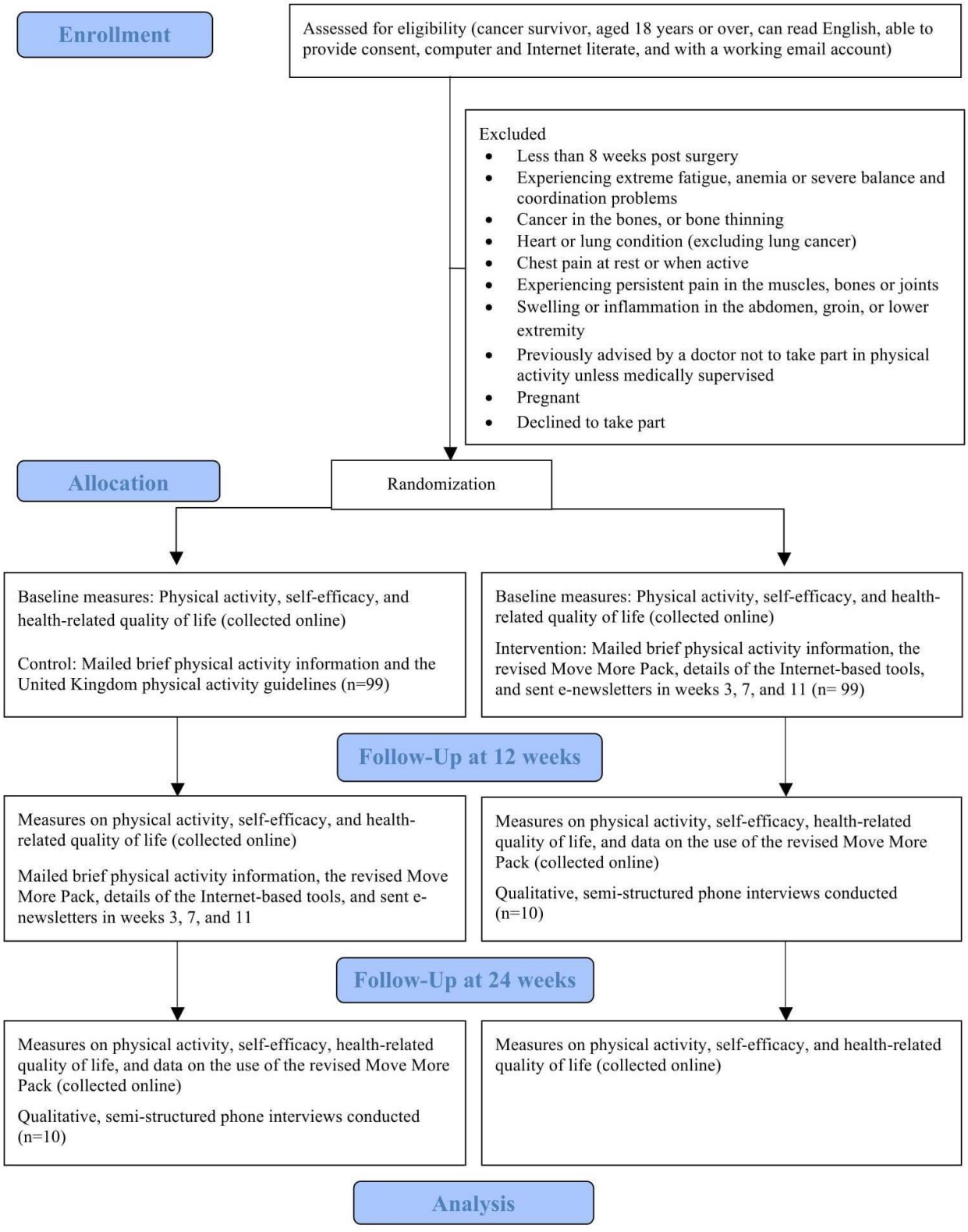
Design

This study is a two-arm waiting list RCT (ISRCTN 66418871) with embedded process evaluation, designed following guidance from the MRC for evaluating complex interventions [52]. Figure 1 shows the progress through the phases of this study. The control arm participants receive brief physical activity information and details of the UK guidelines for physical activity. Intervention arm participants receive brief physical activity information, the revised Move More Pack, directions to the Internet-based tools, as well as the e-newsletters as outlined in Table 1, up to and including the newsletter sent in month 3.

Sample size

NHS England [13] report that 23% of cancer survivors are active to the recommended levels for aerobic activity, 31% are inactive, and 46% are physically active but not to the recommended levels. NHS England [13] also reported that 18% of cancer survivors are interested in becoming more active. The sample size for this study has been calculated based on the assumption that the revised Move More Pack will increase the proportion of the sample achieving the aerobic physical activity guidelines by 18%. A sample of 82 participants will be required per arm for a one-tailed test, power of 80% with alpha set at 5%. A total of 99 participants will be recruited per arm to allow for a 20% dropout.

Figure 1. Participant flow through this waiting list randomized control trial with embedded process evaluation.



Recruitment

Participants will be recruited by email invitation through the Macmillan Cancer Support database of cancer survivors. An advert will also be placed on the Macmillan Cancer Support Facebook page [53]. Those that express an interest will be sent further participant information by email, with consent provided digitally by check box, following the British Psychological Society ethics guidance for Internet-mediated research [54]. Participants will be informed that the study aims to investigate the impact of health promotion information on lifestyle behaviors, with no specific reference made to physical activity. Participants will be notified that they will be randomized to receive guidelines for a lifestyle behavior or a health promotion

pack with Internet-based tools relating to a lifestyle behavior. Recruited participants will be randomized based on simple randomization. Recruitment will continue until 99 participants are randomized to either the control or intervention arm.

Inclusion Criteria

This study will include cancer survivors regardless of cancer stage, cancer type, or comorbidity. Participants will be aged 18 years or over, who can read English, can provide consent, are computer and Internet literate, and have a working email account.

Exclusion Criteria

There are greater risks from being inactive than taking part in physical activity. The revised Move More Pack does not prescribe exercise in any way, and the relevant safety information is sent in the post to participants at the start of the study. The safety information is taken from the Macmillan Cancer Support Web pages [55] and has received the NHS England Information Standard [37]. However, those participants considered at high risk of injury are excluded from this study. On the basis of guidance on exercise and cancer survivorship from the American College of Sports Medicine [7,56], reviewed and approved by subject experts from Macmillan Cancer Support's physical activity team, the following screening questions will be asked of participants, with an answer of yes to any question resulting in exclusion from the study:

- Are you less than 8 weeks postsurgery?
- Are you experiencing extreme fatigue, anemia, or severe balance and coordination problems?
- Do you have cancer in your bones or bone thinning?
- Do you have a heart or lung condition (excluding lung cancer)?
- Do you feel pain in your chest at rest, during your daily activities, or when becoming active?
- Do you have persistent pain in your muscles, bones, or joints?
- Do you have swelling or inflammation in the abdomen, groin, or lower extremity?
- Has your doctor ever said that you should only do medically supervised physical activity?
- Are you pregnant?

Excluded participants will be informed that they will need medical approval before becoming more physically active and, therefore, are not eligible for this study. They will be thanked for their time and given the details of how to order the free resources offered to participants in this study, for use after receiving permission from their general practitioners or cancer care teams, should they decide to become more active.

Procedures and Assessment Tools

Effectiveness

Physical activity will be assessed using the GLTEQ, a reliable and validated tool [43] used previously with cancer survivors [57]. The cancer specific 7-item Functional Assessment of Cancer Therapy Questionnaire (FACT-G7), also a reliable and validated tool, will be used to assess HRQOL [58].

The GLTEQ and the FACT-G7 will be administered electronically at baseline in the intervention and control arms of the study. Participants will be asked to complete the GLTEQ twice:

1. To consider their levels of activity in a standard week before their cancer diagnosis, to allow for the tailoring of the e-newsletters, and to provide a context for the use of the revised Move More Pack.
2. To consider their levels of activity in a standard week after diagnosis, as a baseline assessment of physical activity.

Self-efficacy will be assessed using the following single-item assessment tool: "On a scale of 1 to 10 (1=not at all confident and 10=very confident), how confident are you that you will be physically active in situations such as the following: feeling tired, bad mood, not having the time, on vacation, bad weather?" A similar measure has been used previously with cancer survivors [59]. A single-item assessment tool is selected for its practical application to a real-world setting, and furthermore, single-item assessment tools can perform just as well as multi-item assessment tools [60].

Additional participant information will be collected on date of birth, gender, primary cancer site (type), time since diagnosis, treatment received, time since completion of treatment, response to treatment, and ethnic group. The structure of these questions is that used by NHS England [13]. These questionnaires and participant data will be collected using software from Qualtrics, USA.

12-Week Follow-Up

The effectiveness of the revised Move More Pack at effecting change in physical activity, self-efficacy, and HRQOL in the intervention arm will be evaluated after 12 weeks using the assessment tools used at baseline. The control arm will also be assessed at this 12-week time point. Participants will not have access to their previous scores.

At the 12-week time point, participants in the control arm will be mailed the revised Move More Pack, directed to the Internet-based tools, and will receive the e-newsletters as outlined. The control arm will be followed up a further 12 weeks later, at 24 weeks, to evaluate change in physical activity, self-efficacy, and HRQOL. Participants in the intervention arm will continue to have access to the Internet-based tools, although they will no longer receive e-newsletters after the 12-week time point.

Maintenance

The maintenance of reported changes in physical activity, self-efficacy, and HRQOL for participants in the intervention arm will be evaluated after 24 weeks with the same assessment tools. Participants will not have access to their previous scores.

Participants will be informed that they can withdraw from the study at any time by contacting the principal investigator. In such cases, the reason for withdrawal from the study will be ascertained and recorded. Nonresponders to the questionnaire will be followed up by email to record their reasons for dropping out of the study.

Process Evaluation

Use of each component of the revised Move More Pack will be assessed using a 4-point Likert scale of often, sometimes, rarely, and never. The 4-point Likert scale is included as part of the questionnaire administered to the intervention arm at 12 weeks and the control arm at 24 weeks. Participants will also have the opportunity to add comments about their use and their perceived usefulness of the revised Move More Pack. At the 12-week time point, participants from the intervention arm will be stratified into two groups, those inactive before diagnosis and those moderately active or active before diagnosis. Five participants from each group will be randomly selected and interviewed by phone to gain a deeper understanding of their interaction with, and views of, the revised Move More Pack. This interview process is repeated in the control arm at 24 weeks.

Interviews will follow a semistructured format and will be conducted by the principal investigator. This format has been selected to ensure that data are collected on central topic areas of use and perceived usefulness of the components of revised Move More Pack while not restricting the flow of the conversation. In addition, the interviews will aim to gather data to situate the experience of using the revised Move More Pack within a broad social context. The interview topic guide is included as Multimedia Appendix 8.

Data Analysis

The quantitative data will be analyzed using intention-to-treat analysis. The GLTEQ provides a physical activity score, and these scores can be used to categorize participants into inactive, moderately active, and active groups. The two-proportion *z* test is used to investigate differences between the proportions of participants in the control arm and the intervention arm classified as active.

Secondary analysis of the paired before and after ordinal data within each intervention arm will be analyzed with the Wilcoxon's signed-rank test; across arms, comparisons will be analyzed with the Mann-Whitney *U* test. The mean GLTEQ scores will be analyzed with the independent *t* test and the paired *t* test. The predictors of self-efficacy and prediagnosis physical activity on post-intervention physical activity levels will be assessed by multiple regression analysis. Additional quantitative data will include descriptive statistics such as means, standard deviations, medians, and percentages.

The interviews will be recorded and transcribed verbatim. The interview transcripts and the qualitative comments made by the participants as part of the questionnaires administered at the 12-week and 24-week time points will be thematically analyzed [61] by two of the study investigators, ensuring that identified themes are grounded in the original data. A third investigator will be used where there are differences in opinion. The process of analysis will follow five stages:

1. Familiarization with the data involving reading and rereading the interview transcripts and qualitative comments.
2. Initial coding.
3. Theme identification.
4. Theme review and development of higher level categories.
5. Identification of relationships and patterns.

The investigators will move back and forth through these steps until they concur and are satisfied with the themes, categories, relationships, and patterns identified.

Cost Consequence Analysis

The economics of the revised Move More Pack will take the form of a cost consequence analysis, with costs assessed against a range of outcomes. Although this will not draw definitive conclusions regarding cost effectiveness, it will identify the costs of achieving the reported outcomes. The development costs and other costs needed to make the revised Move More Pack usable will not be included.

Data Management

Web-based questionnaires will be completed using software from Qualtrics, USA. The questionnaire software from Qualtrics, USA, treats data as highly confidential [62] and offers the highest levels of data security [63]. Ownership, control, and management of data remain with the University of Surrey.

Information gathered will be secured on password-locked computers and the servers at the University of Surrey. Hard files will be stored in locked cabinets within the university. Project data, for example, consent forms, will be retained for at least 6 years and research data for at least 10 years as stipulated by the policies of the University of Surrey [64]. Personal data will be secured and processed in the strictest confidence according to the Data Protection Act [65].

Data for analysis and reporting is anonymized. Identifiable data are accessible only by the principal investigator, members of the research team, and authorized personnel from the University of Surrey, and regulatory authorities for monitoring purposes.

Ethical Considerations

The information included in the revised Move More Pack is certified by the NHS England Information Standard [37]. The NHS England Information Standard ensures that publically available information has undergone rigorous assessment, is evidence-based, of high quality, clear, accurate, and appropriate for its intended audience. The revised Move More Pack does not prescribe exercise. The relevant safety information is sent to participants in the first postal communication. Criteria for cessation of physical activity is provided, for example, sudden onset of dizziness, chest pains, a racing heartbeat, breathing problems, nausea, unusual back or bone pain, muscle weakness or a persistent headache, advising participants to contact their doctors for these or other symptoms. Appropriate screening is in place within the study procedures to identify participants needing medical permission before increasing their physical activity, with these participants being excluded from this study. A log of participant issues will be maintained throughout the study, and participants will be offered a phone debriefing session at the end of the study.

Participants in the control arm will not be restricted with regard to being physically active. The participants in the control arm will be asked as part of the questionnaire instructed at the 12-week follow-up time point if they have used the revised

Move More Pack within the previous 12 weeks, with their data omitted from the study if they have. This study received ethical approval from the University of Surrey Research Ethics Committee on March 15, 2017, reference UEC/2017/023/FHMS.

Results

Recruitment for this study began in March 2017. This study has a projected completion date of October 31, 2018.

Discussion

With improvements in treatment, people are now living longer with cancer, and the condition is now in many cases classified as chronic [1]. Cancer survivors, like others with long-term conditions, are heavy users of the NHS. Seventy percent of the NHS's spending is on the 15 million people living with long-term conditions [66]. However, less than 1% of their time is spent in contact with health care professionals [67]. Becoming more physically active has been shown to have many benefits for cancer survivors and has a key role in supporting the self-management of the consequences of cancer and its treatments.

There is a lack of reporting within the literature on how effective physical activity interventions for cancer survivors are developed and designed and their impact on physical activity, self-efficacy, and HRQOL [68]. To the knowledge of the research team, this is the first intervention to combine a printed physical activity behavior change pack with Internet-based tools, including online access to a cancer specialist physiotherapist, to increase physical activity, self-efficacy, and HRQOL in cancer survivors.

Printed materials supported by Internet-based tools are likely to provide a low-cost approach to physical activity behavior change. The process evaluation will contextualize the use and perceived usefulness of the revised Move More Pack, which will augment efficient distribution and identify needed improvements to its design. The revised Move More Pack may offer some promise as a first line intervention to improve the lifestyles of cancer survivors, particularly in relation to physical activity and exercise. If a marked effect size can be demonstrated, the revised Move More Pack could well provide considerable cost-saving to the overstretched NHS funding in the United Kingdom.

The major limitation of this study is the use of self-reported measures to assess and evaluate participants' physical activity, self-efficacy, and HRQOL. The measures selected are validated and reliable. The GLTEQ has been used in previous research with cancer survivors [57], and the FACT-G7 is specifically designed for cancer survivors [58]. The self-reported measures have been selected for their ease of implementation in a real-world setting. Whereas the use of an objective measure of physical activity may be preferable, this would introduce an additional behavior change technique. Furthermore, as the revised Move More Pack aims to enable cancer survivors to monitor their physical activity by directing them to use a pedometer, introduction of an objective measure may influence the effectiveness of this component of the revised Move More Pack.

Some studies of cancer survivors have reported high levels of dropout [69]. Therefore, an additional 20% will be recruited to this study. Furthermore, a combination of strategies will be employed to encourage participants to complete the relevant questionnaires at the data collection points, including email and text reminders.

It is possible that the exclusion criteria for this study may result in a selection bias; however, the safety of the participants will not be compromised. In addition, as participants are recruited through the channels of Macmillan Cancer Support, they may not be representative of the population of cancer survivors in the United Kingdom. The profile of the included participants will be reported and any selection bias identified.

Acknowledgments

Macmillan Cancer Support will provide the revised Move More Packs for the participants, will host the Internet-based tools, and will support recruitment of participants to this study. The postage costs will be covered by the University of Surrey and Macmillan Cancer Support.

Authors' Contributions

This study protocol was written by JW, the principal investigator. CFS and JO acted as supervisors on the development of this study protocol. JF served as an adviser on this study protocol.

Conflicts of Interest

JW is a former member of staff at Macmillan Cancer Support. JF is a member of staff at Macmillan Cancer Support.

Multimedia Appendix 1

The revised Move More Pack.

[PDF File (Adobe PDF File), 1MB - resprot_v6i11e220_app1.pdf]

Multimedia Appendix 2

The Physical Activity and Cancer booklet.

[PDF File (Adobe PDF File), 748KB - resprot_v6i11e220_app2.pdf]

Multimedia Appendix 3

Pull-out wall chart.

[PDF File (Adobe PDF File), 98KB - resprot_v6i11e220_app3.pdf]

Multimedia Appendix 4

Physical activity leaflets.

[JPG File, 2MB - resprot_v6i11e220_app4.JPG]

Multimedia Appendix 5

Example e-newsletter.

[PDF File (Adobe PDF File), 201KB - resprot_v6i11e220_app5.pdf]

Multimedia Appendix 6

Web page dedicated to users of the revised Move More Pack.

[PDF File (Adobe PDF File), 363KB - resprot_v6i11e220_app6.pdf]

Multimedia Appendix 7

A breakdown of the component of the revised Move More Pack.

[PDF File (Adobe PDF File), 41KB - resprot_v6i11e220_app7.pdf]

Multimedia Appendix 8

Interview topic guide.

[PDF File (Adobe PDF File), 38KB - resprot_v6i11e220_app8.pdf]

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Abbreviations

BCT: behavior change technique
BCTTv1: behavior change technique taxonomy version 1
DVD: digital versatile disc
FACT-G7: 7-item Functional Assessment of Cancer Therapy Questionnaire
GLTEQ: Godin Leisure Time Exercise Questionnaire
MRC: Medical Research Council
NHS England: National Health Service England
RCT: randomized controlled trial
SCT: social cognitive theory
TPB: theory of planned behavior
QOL: quality of life
HRQOL: health-related quality of life

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Protocol

Online Self-Management Support for Family Caregivers to Help Them Manage Behavior Changes in Their Relative With Dementia: Study Protocol for a Randomized Controlled Trial and a Process Evaluation

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Abstract

Background: Online interventions are potentially effective ways to support family caregivers in the management of behavior changes in their relative with dementia.

Objective: The objective of this paper is to present the design of a study evaluating and comparing 3 intervention arms for online self-management support.

Methods: A randomized controlled trial (RCT) will be conducted with a total of 81 family caregivers of community-dwelling people with dementia in the Netherlands. Family caregivers will be randomly allocated to one of the following intervention arms: (1) a major self-management support intervention consisting of personal email contacts with a nurse specialized in dementia care, online videos, and electronic bulletins (e-bulletins); (2) a medium self-management support intervention consisting of only online videos and e-bulletins; and (3) a minor self-management support intervention with only e-bulletins. The primary outcome is the self-efficacy of the family caregiver. The secondary outcomes are the behavior problems of the person with dementia as reported by the family caregiver, and positive and negative aspects of the relationship. Background characteristics (eg, type of family relationship) will also be assessed. All data for the RCT will be collected via online questionnaires, administered before the intervention (T0), after 6 weeks (T1), and after 12 weeks (T2). Alongside the RCT, a process evaluation will be conducted, based on a number of evaluation questions and semi-open interviews with family caregivers.

Results: Data collection will be completed in August 2017. Study results will be reported in early 2018.

Conclusions: The study will shed more light on the effect of online self-management support interventions and insights will be gained into whether a major intervention, consisting of personal email contacts with specialized nurses, videos, and e-bulletins, has more effect than smaller online interventions. This is relevant in an age with increasing numbers of people with dementia, growing pressure on family caregivers, more and more people using the Internet, and increasing healthcare costs.

Trial Registration: Nederlands Trial Registry (NTR): NTR6237; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=6237 (Archived by WebCite at http://www.webcitation.org/6v0S4fxTC)

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KEYWORDS

dementia; family caregivers; self-management; behavior problems; Internet; eHealth; RCT; process evaluation

Introduction

Background

Dementia is a progressive disorder characterized by cognitive and physical decline and behavior and mood changes. The most common forms of dementia are Alzheimer's disease and vascular dementia, followed by Lewy body dementia and frontotemporal dementia [1]. There is still no effective treatment that can influence the progression of Alzheimer's disease and other dementia subtypes. Eventually, someone will die with or from dementia [2].

Most people with dementia live at home, often supported by spouses, adult children, or other family members [3]. Although the family often cares for them with love and dedication, family care can be a big burden [4,5]. For family caregivers it can, for instance, be stressful to deal with their relative's behavior changes, such as dependent behavior, aggressive behavior, suspicious behavior, apathy or indifference, night-time restlessness, and masking behavior. These are often symptoms of the disease and are found in up to 90% of people with dementia [6,7]. Changes in behavior are "challenging" when this causes distress to the person with dementia and/or family caregivers and negatively affects the quality of life of at least one of these parties [8]. A Dutch study [9] found that about three quarters of the family caregivers of persons with dementia experienced problems in dealing with changes in the behavior or mood of their relative, in both the initial and later stages of the disease. In a recent focus group study, family caregivers reported that what they found most difficult was constantly having to switch between different strategies and that they had to keep their relative constantly occupied and distracted [10]. Furthermore, they found it stressful that other people often had a different view of the behavior and mood of the relative with dementia. Lastly, they also found it difficult that in theory they knew what to do in caring for their relative, but were often not able to put it into practice [10].

To support family caregivers (eg, in dealing with the relative's behavior changes), an increasing number of self-management support interventions are being developed, some of which are Internet-based [11]. From the perspective of family caregivers, Internet support might be attractive, since they can use it at a time that is suitable for them, without travelling [12]. Boots et al [13] performed a systematic literature study of Internet-based support, such as a website with information and support on various aspects of care giving. The review by Boots et al [13] suggested that Internet-based support had positive effects (eg, regarding self-efficacy or other psychological and psychosocial outcomes for family caregivers). However, the review authors also concluded that the evidence was still scarce because of the low quality of the studies they had identified [13].

Previous research also did not provide a definitive answer about the effectiveness of incorporating personal contacts with a healthcare professional in online interventions, although some relevant studies have been conducted in this area [12,14-16]. For instance, in a study by Boots et al [14], face-to-face sessions with an experienced professional (psychologist or psychiatric nurse) and family caregivers were added to an online support intervention. The face-to-face sessions were seen as a valuable addition, as they provided an opportunity to tailor the support to the needs of the family caregivers and deepened the relationship [14]. In addition, Schaller et al [15] evaluated an interactive Web portal providing individualized information and support by dementia experts to family caregivers via a messaging function [17]. The interaction between family caregivers and experts was found to be useful, particularly because of the timely reaction to symptoms and because of the opportunity to reach immobile caregivers [15]. Comparable results were found in the study by Torkamani et al [16], which evaluated a computerized platform for contacts between the caregivers and health professionals aimed at reducing the burden on the caregiver, improving quality of life, and delaying institutionalization of the person with dementia. Furthermore, Blom et al [12] evaluated Internet-based information combined with online personal support. In this study, a psychologist provided online feedback on assignments about dealing with depression or other psychological problems in relatives of persons with dementia. The study by Blom et al [12] recommended further research to clarify the necessity of personal contacts with a professional; a completely self-help Internet program would be less expensive, which is an advantage in the current era with increasing numbers of persons with dementia and limited healthcare budgets. However, personal contacts with a healthcare professional might help people translate generic information to their own situation [12].

Objectives

The aim of this study is to investigate whether a major intervention, consisting of personal email contacts with a specialized nurse in combination with videos and electronic bulletins (e-bulletins), is more effective than more minor interventions. Based on the results of this study we will be able to inform about which elements of online self-management support are effective (on their own or in combination) for family caregivers when managing changes in the behavior of their relative with dementia.

The research questions are (1) Is a major online self-management support intervention consisting of personal email contacts with a specialized dementia care nurse, videos, and e-bulletins more effective than smaller online interventions without personal email contacts, with regard to self-efficacy of family caregivers in managing the behavior changes of their relative with dementia, behavior problems in the persons with dementia, as reported by family caregivers, and positive and negative aspects of the relationship between the family caregiver and the person with dementia? (2) What background and baseline characteristics of family caregivers or the persons with

dementia (eg, type of family relationship, baseline level of care pressure, and the specific behavior problems of the person with dementia) are associated with effects on the outcome variables mentioned in question 1? (3) How do the family caregivers evaluate the online self-management support intervention, with or without personal email contacts with a specialized nurse, regarding feasibility, usability, and satisfaction with the intervention?

Methods

Design and Randomization

To answer research questions 1 and 2, a randomized controlled trial (RCT) with 3 repeated measurements will be performed, involving the following intervention arms: (1) a major-intervention arm, (2) a medium-intervention arm, and (3) a minor-intervention arm.

Family caregivers will be randomly allocated to 1 of the 3 self-management intervention arms. Block randomization will be used to achieve balance in the allocation of participants to intervention arms [18]. An independent epidemiologist (NJV) prepared a randomization schedule to assign participants to an intervention arm, using several block sizes of 6 and 9. Following this randomization schedule, the researcher (JGH) will allocate participants to an intervention arm. The participants will then receive an email from the researcher (JGH) containing elements of the intervention arm in question. Participant and researcher blinding is not possible due to the nature of the intervention arms and the organization of the study.

Alongside the RCT, a process evaluation will be conducted to answer research question 3. For the process evaluation, a mix of qualitative and quantitative methods will be used.

Power Calculation and Sample

We hypothesize that (1) both the major and medium intervention arms improve the self-efficacy as compared to the minor intervention arm; and (2) the major intervention arm gives better results for self-efficacy compared to the medium intervention arm. Considering a difference of 0.8 standard deviation units between the groups and assuming a significance level of .05, a power of 80%, and a correlation of .6 between the 2 repeated measures, 20 participants are needed per group. Taking into account a drop out percentage of 20%, we will include 24 participants per group.

In this study, providing self-management support through email is a relatively new task for the specialized nurses involved, with possible learning effects during the study. To take this into account, 1 extra block of 9 participants will be added to allow for a brief learning curve. Hence, in total 81 family caregivers of persons with dementia will be included.

The participants will be family caregivers of people with dementia who meet the following inclusion criteria: (1) the family caregiver is a relative of a person diagnosed with dementia (all types of dementia are eligible, with no restriction on the severity of the dementia); (2) the family caregiver must have contact with the person with dementia at least once a week; (3) the family caregiver's relative with dementia has to live at home (not in a care institution); (4) the family caregiver has access to the Internet and has basic skills in using the Internet and email; (5) the family caregiver has to be aged at least 18 years of age; and (6) the family caregiver is able to read and write Dutch.

To recruit family caregivers for our study, we will use several channels. The panel of the Dutch Alzheimer Society (in which more than 3000 informal caregivers participate) will be sent an email with an open call. Open calls will also be posted on the online forum of the Dutch Alzheimer Society (with 7000 monthly visitors), on the Dementie Nederlands website, and on the social media accounts (Facebook/Twitter) of the Dutch Alzheimer Society.

Recruitment via the aforementioned channels of family caregivers will proceed with first, a very short study description in the open call. In this description, family caregivers will be asked if they are interested in participating in the study. If so, they can send their name and email address to the principal researcher (JGH). The principal researcher will then send an email containing an information letter about the aims and procedures of the study to the family caregiver. This email will have a link to an online informed consent form, which the family caregiver can use to give their consent for participation. The participation flow chart is shown in Figure 1.

Intervention Arms and Components

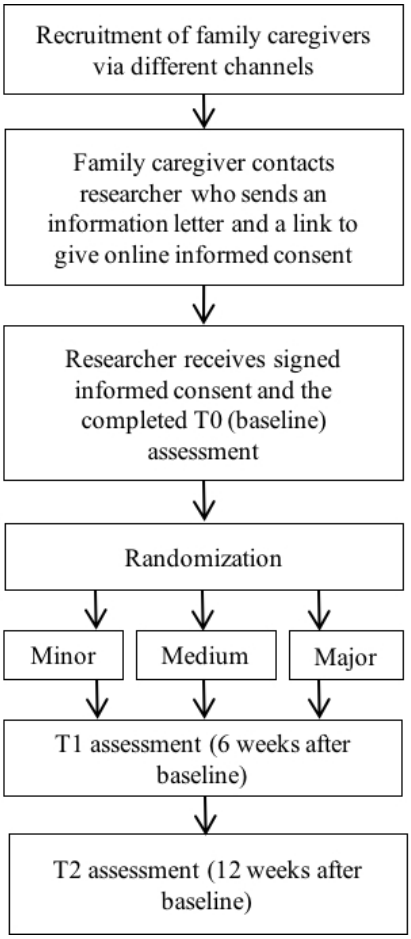
In the RCT, 3 intervention arms will be studied, all focusing on self-management support in dealing with behavior changes, but varying in the number of elements. The intervention arms are referred to as major, medium, and minor.

Major Self-Management Support Intervention

The major intervention arm consists of the following elements: (1) 3 personal email contacts with a nurse specialized in dementia care, (2) provision of online videos about how to manage behavior changes in a relative with dementia and to improve your self-efficacy in managing with this behavior, and (3) provision of e-bulletins with practical information about different types of behavior changes and how to manage them.

The personal email contacts will be handled by a nurse with a Bachelor's or Master's qualification in nursing and with follow-up training in dementia care. In the email contact, the nurse will support the family caregiver in managing behavior changes. The nurse will also give feedback on assignments and will give feedback on the plan that the family caregiver came up with in the assignments. The nurse will tailor their support to the personal needs and questions of the family caregiver, while guided by an intervention protocol developed by project group members (JGH, ALF, PJV, IvA), in consultation with the nurses who had to use the intervention protocol. The number of email contacts was discussed and agreed with experts in dementia care who have experience with online support. Three email contacts are thought to be sufficient and feasible.

Figure 1. Study flow chart.



The Dutch-language intervention protocol (available on request from the first author) is based on the 5 steps of the "5A model" of self-management support [19] and the person-centered care theory of Kitwood [20]. The "5A model" consists of the following steps: (1) assessing the state of behavior, beliefs, and motivation; (2) advising based upon personal health risks; (3) agreeing on a realistic set of goals; (4) assisting in anticipating barriers and developing a specific action plan; and (5) arranging follow-up [19,21,22].

There are 6 videos about different types of behavior changes that occur frequently (dependent behavior, aggressive behavior, suspicious behavior, apathy or indifference, nighttime restlessness, and masking behavior). Family caregivers can choose the number of videos they watch and the accompanying assignments that they do themselves, depending on their own needs and the behavior changes that occur in their relative with dementia. The videos (as well as the e-bulletins mentioned below) were developed by the Trimbos Institute, of which 2 of the developers are involved in the present study (BMW, IvA), in close cooperation with the Dutch Alzheimer's society, other dementia experts, and family caregivers of people with dementia. As a first step in the development trajectory, a desk search was performed to gain insight into what is known in the literature about how family caregivers perceive different types of behavior changes in their relative with dementia and the theory of person-centered care [20]. Experts also provided input for the components of the videos (eg, principles of cognitive behavioral therapy [CBT], modeling, persuasive communication, and active learning). At several stages in the development trajectory, video scripts and pilot videos were tested by family caregivers.

The behavior changes covered in the bulletins are the same as in the videos. The e-bulletins involve assignments to help caregivers translate the generic information to their own situation and to reflect on possible causes of the behavior changes, how they want to influence the behavior, and how they want to cope with it. The e-bulletins were tested in conjunction with the testing of the videos and they also have the same theoretical base as the videos.

Medium Self-Management Support Intervention

The medium self-management support intervention consists only of the online videos and e-bulletins as described above.

Minor Self-Management Support Intervention

The minor self-management support intervention consists only of the e-bulletins, the same as those in the major and medium support interventions.

Measurement Procedures

Measurements will be performed in the RCT at 3 time points: baseline assessment (T0), which is just before the family care intervention arms start; the assessment 6 weeks after the baseline (T1); and the assessment 12 weeks after the baseline (T2). Measurements will be based on self-reporting by the family caregiver and will be administered through the Internet. Up to

2 email reminders will be sent (if necessary) 1 and 2 weeks after the measurement time point to remind participants to complete the questionnaires.

Primary Outcome

The primary outcome in the RCT is self-efficacy, measured by the Trust in Own Abilities (TOA) instrument, a Dutch language questionnaire to be completed by family caregivers of the person with dementia [23]. The questionnaire has been used before to measure self-efficacy in caregivers of people with dementia living at home [24]. The TOA contains 32 items (alpha .97) divided into 3 subscales: resilience (15 items, alpha .94), solution orientation (8 items, alpha .90), and proactive competence (9 items, alpha .81). Items are measured on a 5-point Likert scale, ranging from 0 (not at all) to 4 (very good). A higher score is associated with higher perceived competence in taking care of the person with dementia [24].

Secondary Outcomes

The secondary outcome will be the presence and number of behavior and mood problems, assessed with the Dutch version of the Revised Memory and Behavioral Problem Checklist (RMBPC) [25,26]. Family caregivers have to rate the frequency of the occurrence of a specific behavior or mood problem on a scale from 0 (never) to 4 (always) where 1 is seldom, 2 regularly, and 3 is often. The total number of behavior and mood problems (0 to 24) will be calculated as well as the mean overall score. The RMBPC can be divided into scales for depression (9 items), disruptive behavior (8 items), and memory-related problems (7 items).

Another secondary outcome is the positive and negative aspects of the family relationship between the family caregiver and the person with dementia and they will be measured by the Dyadic Relationship Scale (DRS). The family caregiver version includes 11 items in 2 subscales: dyadic strain and positive dyadic interaction. Family caregivers have to rate the quality of the relationship using 4 answer categories: 1 (strongly disagree), 2 (disagree), 3 (agree), and 4 (strongly agree) [27].

Analyses of Effects

The quantitative data from the RCT will be analyzed using SPSS software (Statistics 22). Baseline characteristics will be described for each arm using proportions for dichotomous variables and means (SD) or medians (IQR) for continuous variables. In the primary analysis, primary and secondary outcomes will be compared between the 3 different groups using mixed-models analysis. All mixed model analysis will be adjusted for baseline differences between the groups.

All randomized caregivers who completed the follow-up will be included in this analysis (modified intention-to-treat). The first 9 caregivers, who are in the learning-curve block, will not be included in the primary analysis. We will use sensitivity analyses to evaluate the effect of missing data and of the prior inclusion of key baseline variables.

Process Evaluation

Alongside the RCT, a process evaluation will be conducted. Mixed-methods and sources will be used for this. Firstly, evaluation questions will be included in the T2 survey questionnaire (12 weeks after the baseline). The number of evaluation questions varies between 5 and 11 depending on which of the 3 intervention arms the family caregiver is in. The evaluation questions are based on earlier research about the perceived feasibility and usability of interventions and satisfaction with the interventions [28,29].

Secondly, semi-structured interviews will be conducted with a purposive sample of about 15 participant family caregivers (5 participants in each intervention arm). The participants will be purposively recruited to achieve a spread in the intervention arms and background characteristics (eg, sex, age, and living with or separately from the relative with dementia). Topics will include family caregivers' satisfaction with and the perceived feasibility and usability of the self-management support interventions. The interviews will be conducted by telephone by 1 of the members of the research team (IvA) and will be audio-recorded.

Thirdly, usability in the sense of actual usage of the different elements of the online self-management support intervention will be measured by analyzing the clicks on links and how long the family caregivers spent watching the videos, divided into the following categories: (1) started video, (2) played video (25%), (3) played video (50%), (4) played video (75%), and (5) completed video. These data will be collected with Google Analytics. All participating family caregivers will be given a unique code that is known only by the research team.

To collect data on actual use of the personal email contacts, nurses will be asked to complete a registration form on the number of personal email contacts per family caregiver and time spent on giving feedback to the family caregiver.

Fourthly, the content of the email contacts between the family caregivers and the nurses will be analyzed qualitatively. The email contacts will be analyzed from 3 angles: with a focus on nurses' questions and responses, with a focus on family caregivers' questions and responses, and with a focus on the interactions between the two. The focus on the nurses will be on how they delivered the self-management support as defined by the intervention protocol based on the "5A model" (assess, advise, agree, assist, and arrange). The responses by the family caregivers in the email contacts will be analyzed to get information on the uptake of the intervention and how they integrated the personalized advice from the nurse in their daily lives.

The data from the structured evaluation questions in the T2 survey questionnaire, data on actual usage from Google Analytics, and registration data on the number of personal email contacts will be analyzed descriptively using SPSS software. The semi-open interviews and the content of the email contacts will be analyzed qualitatively using the principles of thematic analyses [30]. This qualitative method was chosen because it is a useful and flexible method for identifying relevant themes within qualitative data. It consists of the following steps: (1) familiarizing yourself with the data, (2) generating initial codes, (3) searching for themes, (4) reviewing themes, (5) defining and naming themes, and (6) reporting [30]. The interview transcripts will be analyzed by 2 researchers (JGH and IvA) independently. Coding and interpretation of the codes will be

discussed by the researchers until consensus is reached. In addition, other authors will comment on the interim analyses of the interviews.

Ethical Procedures

The study protocol was approved by the Medical Ethics Committee of the VU University Medical Center (reference 2016.559).

Informed consent will be asked from all participants via an online informed consent form, which the family caregiver can use to give consent for participation. Consent from the family caregivers and the nurses will be explicitly requested in the informed consent for the analysis of the content of the email contact between the family caregivers and the nurses.

Only members of the research team (the co-authors) will have access to the data. Agreements on how to share, archive, and store data will be signed by the organizations that will be collecting the data.

Results

Enrollment of participants began in March 2017. Data collection was complete in August 2017. The study results will be reported in early 2018.

Discussion

This study will contribute to the growing body of knowledge about online support in dementia care. This is important since future generations will increasingly use the Internet, which will also affect the extent in which family caregivers will be open to receiving online self-management support. However, we also expect that if online support is tailored and involves personal email contacts with a specialized nurse, this will be more effective and more satisfying for the family caregiver than if only online videos or e-bulletins are provided. The study results will be used to inform care professionals and family caregivers about which forms of online support intervention are most effective and best match family caregivers' needs.

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Conflicts of Interest

None declared.

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Abbreviations

DRS: Dyadic Relationship Scale
e-bulletin: electronic bulletin
RCT: randomized controlled trial
RMBPC: Revised Memory and Behavioral Problem Checklist
TOA: Trust in Own Abilities

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Protocol

Providing Home-Based HIV Testing and Counseling for Transgender Youth (Project Moxie): Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Transgender and gender nonconforming people experience some of the highest human immunodeficiency virus (HIV) rates in the United States, and experience many structural and behavioral barriers that may limit their engagement in HIV testing, prevention, and care. Evidence suggests that transgender and gender nonconforming youth (TY) are especially vulnerable to acquiring HIV, yet there is little research on TY and few services are targeted towards HIV testing, prevention, and care for this population. Telehealth presents an opportunity to mitigate some structural barriers that TY experience in accessing HIV testing, allowing TY to engage in HIV testing and counseling in a safe and nonjudgmental space of their choosing. Project Moxie is an HIV prevention intervention that pairs the use of HIV self-testing with remote video-based counseling and support from a trained, gender-affirming counselor. This study aims to offer a more positive HIV testing and counseling experience, with the goal of improving HIV testing frequency.

Objective: Project Moxie involves a pilot randomized controlled trial (RCT) of 200 TY aged 15-24 years, who are randomized on a 1:1 basis to control or intervention arms. The aim is to examine whether the addition of counseling provided via telehealth, coupled with home-based HIV testing, can create gains in routine HIV testing among TY over a six-month follow-up period.

Methods: This study implements a prospective pilot RCT of 200 TY recruited online. Participants in the control arm will receive one HIV self-testing kit and will be asked to report their results via the study's website. Participants in the experimental arm will receive one HIV self-testing kit and will test with a remotely-located counselor during a prescheduled video-counseling session. Participants are assessed at baseline, and at three and six months posttesting.

Results: Project Moxie was launched in June 2017 and recruitment is ongoing. As of August 21, 2017, the study had enrolled 130 eligible participants.

Conclusions: Combining home-based HIV testing and video-based counseling allows TY, an often stigmatized and marginalized population, to test for HIV in a safe and nonjudgmental setting of their choosing. This approach creates an opportunity to reduce the high rate of HIV among TY through engagement in care, support, and linkage to the HIV treatment cascade for those who test positive.

Trial Registration: ClinicalTrials.gov NCT03185975; https://clinicaltrials.gov/ct2/show/NCT03185975 (Archived by WebCite at http://www.webcitation.org/6vIjHJ93s)

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KEYWORDS

transgender persons; HIV; telemedicine

Introduction

Evidence increasingly suggests a high prevalence of human immunodeficiency virus (HIV) infections among transgender and gender nonconforming individuals in the United States [1]. Recent studies, drawn largely from samples of transgender women, suggest the prevalence of HIV in this population is at least as high as that experienced by gay, bisexual, and other men who have sex with men (MSM) [2-4]. A 2013 report found that the estimated percentage of transgender women living with HIV in the United States was 22% [4], and among the 3.3 million HIV testing events reported to the Centers for Disease Control and Prevention (CDC) in 2013, the percentage of transgender people who received a new HIV diagnosis was more than three times the national average [1]. Transgender women of color and those under 25 years of age are disproportionately affected by the HIV epidemic [5,6].

Much of what is known about HIV risk behaviors among transgender and gender nonconforming people has been derived from samples of transgender women [1]. The high rate of HIV in this population has been associated with a high prevalence of substance abuse, commercial sex work, condomless anal intercourse, and a lack of knowledge regarding HIV transmission [5,7-10]. While data on other transgender and gender nonconforming populations is sorely lacking, many of the risk factors for HIV seen in transgender women are shared by other groups of transgender and gender nonconforming people, and the prevalence of HIV is thought to be similar across transgender and gender nonconforming populations [3]. While transgender and gender nonconforming youth (TY) are even more underrepresented in the literature, available research from a sample of trans-feminine youth shows that this population experiences multiple forms of discrimination and harassment, significantly increasing the risk of HIV transmission [11,12]. A study of 51 ethnic-minority, female-identifying TY showed higher rates of HIV compared to other racial/ethnic groups, with 41% experiencing difficulty accessing health care, 59% reporting engaging in transactional sex, and 63% reporting difficulty finding employment [9].

Telehealth uses short message service (SMS) messaging, teleconferencing and videoconferencing platforms, social media, and smartphone apps compliant with the Health Information Portability and Accountability Act (HIPAA) to increase access to health care [13]. Given the multiple barriers to accessing HIV prevention and care experienced by transgender and gender nonconforming people, telehealth may be a useful platform for delivering services directly to these populations. Due to high rates of technology use among youth [14], telehealth may be especially useful for addressing the discrimination and harassment TY encounter while attempting to access health care resources [15,16]. Telehealth may also provide an entry point to the health care system in places where no gender-affirming providers or services exist.

Telehealth has already been adapted to provide HIV care services to MSM residing in areas where stigma and minimal lesbian, gay, bisexual, transgender (LGBT)-friendly health care providers exist [17]. SMS-based telehealth efforts have also been implemented to connect MSM in metropolitan Kansas City with an HIV testing counselor to increase the dissemination of evidence-based HIV/sexually transmitted infection (STI) prevention information [18]. Telehealth-based interventions have also been used among rural HIV-positive veterans in the United States, wherein they participated in private teleconferences with HIV specialists [19]. This intervention was shown to increase the veterans' perceptions of the quality of care provided, and was considered a step towards reducing HIV risk behaviors such as condomless intercourse and multiple sexual partners [19]. While telehealth-based interventions may reduce the stigma associated with in-person appointments by allowing rural MSM and HIV-positive veterans to access services in a place where they feel comfortable, research has not focused on the use of telehealth to provide HIV prevention resources to other marginalized populations, such as TY.

Another important limitation of the current telehealth literature concerns its use as an information dissemination and case management tool. Few studies use this technology for actual clinical care, such as HIV testing. With approval by the US Food and Drug Administration in 2011, high quality (sensitivity 93.64%, 95% CI 82.46-98.66; specificity 99.87%, 95% CI 99.28-100.00 [20]), home-based HIV testing is now available commercially in all 50 states [21]. However, critiques of home-based HIV testing include difficulty interpreting the results, a lack of posttest counseling for the adoption of safer HIV prevention methods, and a lack of proper linkage to care [22]. Adding online counseling through video-chat software to home-based HIV testing has the potential to mitigate these concerns. Through telehealth-delivered counseling, individuals can receive tailored, convenient, and confidential support that due to stigma, discrimination, and/or lack of locally-available services, may not otherwise be received. While there are few telehealth-based HIV prevention interventions published in the literature, results from prior studies show increased knowledge, self-efficacy, and motivation towards effective HIV prevention methods [23-26].

This paper describes the protocol for the first study to combine telehealth and home-based HIV testing for comprehensive, gender-affirming HIV testing and counseling for TY. In this study, approximately 200 TY aged 15-24 years will be randomized into either a control group that receives an HIV self-testing kit or an intervention group that receives an HIV self-testing kit as well as a video-chat counseling session provided by a trained HIV counselor. The main outcome of this study is the frequency of HIV testing in the six months following initial testing. The study aims to examine whether the receipt of an HIV self-testing kit plus a video-chat-delivered counseling session can create changes in HIV testing behavior, sexual risk-behaviors, and linkage to care for newly-diagnosed HIV-positive TY. If successful, this low-cost intervention has the potential to shape the delivery of HIV prevention and care services to this population, who are currently overlooked in HIV programming, research, and prevention efforts.

Methods

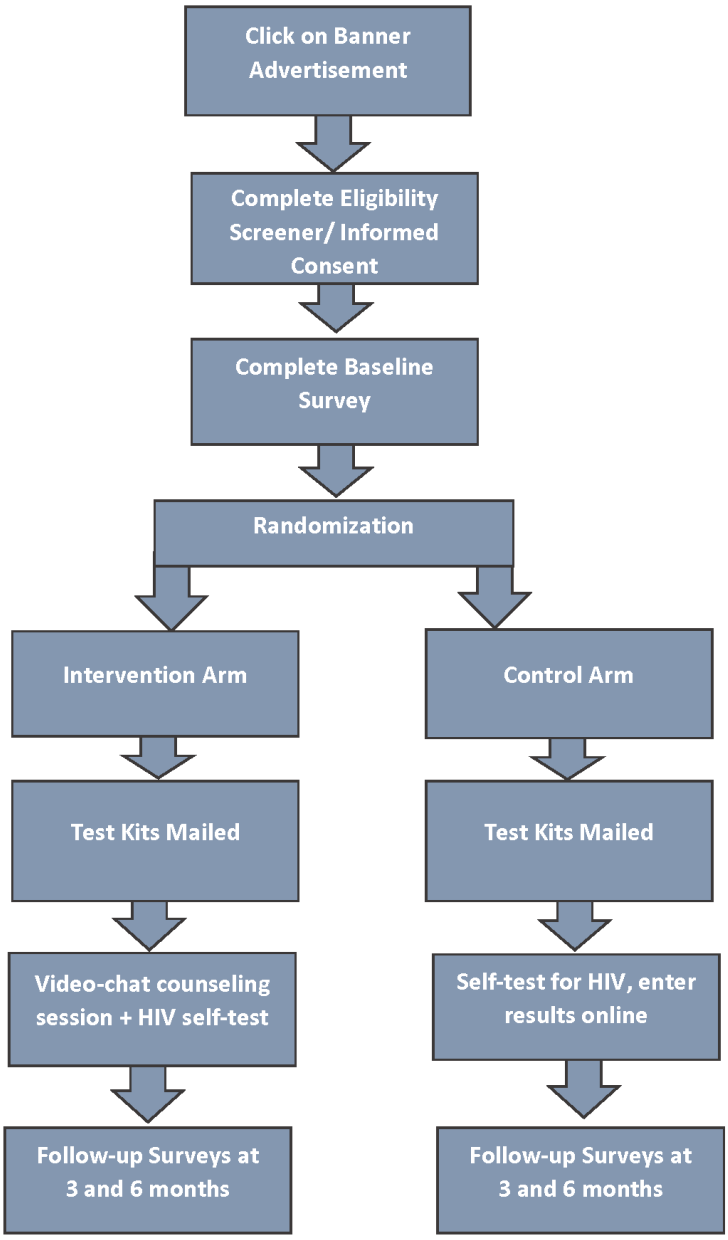
Study Overview

This study is a pilot randomized controlled trial (RCT) of 200 self-identified TY aged 15-24 years, recruited via a range of social media platforms. Participants will be randomized to one of two study arms. TY in the control arm will receive one HIV self-testing kit by mail and will be asked to report their results via a study website. TY in the experimental arm will also receive one HIV self-testing kit via mail, and will conduct this test under the supervision of a remotely-located counselor during a prescheduled video-chat session. Participants in both arms will complete a baseline survey upon recruitment, with repeat surveys at three and six months posttesting (see Figure 1). Participants will receive email and SMS reminders to log into the study website to complete follow-up surveys. The primary outcome for this study is routine HIV testing during the follow-up period. Secondary outcomes include sexual risk-taking behaviors, intervention acceptability, and linkage to care for those who test positive for HIV.

Participants

Eligible participants will: (1) be aged 15-24 years; (2) have not tested for HIV in the last 12 months; (3) reside in the United States; (4) be willing to have HIV test kits delivered to an address they provide, (5) self-identify as noncis-gender; and (6) have access to a computer, smartphone, or tablet that can support the video-chat software VSee [27], which is an encrypted program compliant with the privacy requirements of the HIPAA.

Figure 1. Study flow diagram.



Recruitment

Participants will be recruited from across the United States via advertisements placed on social media platforms (eg, Facebook, Instagram, and advocacy groups/sites aimed specifically at TY, such as Transgender Alliance and Affirming Transgender Rights; see Figure 2). Online dating apps with transgender users (ie, Scruff) will also be used. Advertisements will include depictions of young people from a variety of racial and ethnic groups to encourage inclusivity and the participation of TY from a variety of backgrounds. Information about the study will also be shared via transgender media personalities' social media accounts.

When a potential participant clicks on an advertisement, they will be taken to a page containing basic study information, including a short description of study activities. If the individual expresses interest in participating in the study, they will be directed to the study consent form. For participants aged 15-17 years, consent will only be obtained from the participant acting as an emancipated minor. Due to the sensitive nature of the study topic and the stigma and discrimination TY may face from their parents or guardians, requiring parental consent may endanger the safety and wellbeing of the participant. Waiving parental consent allows those who have not fully disclosed their gender identity, or whose guardians are not accepting, to participate in the study.

Study Procedure

After providing consent electronically, participants will be directed to a short eligibility screener. If eligible, a potential participant will register for the study by providing their contact information. This information includes an email address, mobile phone number, physical mailing address, and preferred choice of name and pronouns. It is important to note that many TY have unstable housing or may not feel comfortable having mail, however discreet, sent to their home address. For this reason, the registration form will ask for a physical address to which the participant feels safe and comfortable receiving mail. As soon as the consent form, screening questionnaire, and site registration are complete, the participant will receive an email with instructions on completing the baseline survey. After completing the baseline survey, each participant will be randomized to either the control arm (HIV self-testing only) or intervention arm (video-based counseling in conjunction with HIV self-testing), using a 1:1 treatment allocation. The treatment assignments will be generated with the use of a pseudo-random number generator, which uses permutated blocks to ensure balance in the number of participants assigned to each arm. The randomization process will generate one of two emails to study participants, indicating whether they will be receiving HIV self-testing or video-based counseling plus HIV self-testing.

Figure 2. Sample online advertisement.

Control Arm

TY in the control arm will receive one home-based HIV self-testing kit delivered in discreet packaging. In addition to an oral fluid test kit (OraQuick), the package will contain condoms, water-based lubricant packets, and one pair of ear buds. All OraQuick tests will be assigned a specific identification (ID) number that will link to the participant's study ID number. Upon taking the test, participants will be directed to enter their results on the study website. For those who report a positive result, a message will automatically be sent to the study coordinator. Study staff will then call the participant to offer information regarding places where the participant may acquire a confirmatory HIV test, as well as HIV care services and counseling in their local area or another area of their choosing.

Intervention Arm

The intervention arm is a combination of HIV self-testing and HIV test counseling offered remotely via a HIPAA-compliant video-chat session. Participants in the intervention arm also receive one OraQuick test, condoms, lubricant, and earbuds via mail, but will be informed to leave their package *unopened* until directed by the counselor during the video-chat session. Participants will be instructed via email on how to download the VSee software prior to the video-chat session. VSee is available as downloadable software for Windows and Macintosh and as an app in the iOS and Android marketplaces [27]. This software allows participants to log into the video-chat from a desktop, laptop, tablet, or smartphone. Both the software and app versions of VSee contain voice, video, and screen-sharing capabilities to provide a fully-functional counseling session across platforms and devices. VSee provides high-quality video at speeds as low as 50 kilobits per second, allowing full functionality in areas without access to broadband or high-speed cellular data networks [27]. The one-time counseling session lasts approximately 30-45 minutes and consists of two consecutive phases.

Phase one of the counseling session will use elements of motivational interviewing to ascertain reasons (eg, structural, lack of information/misinformation on HIV testing) why the participant has not tested for HIV in the past 12 months. The counselors will also ask about some of the participant's recent sexual behaviors (eg, number of partners, use of condoms, sexual activities) to establish those that may pose a risk for acquiring HIV. The answers to these questions will form the basis for phase two. Counselors will attempt to provide solutions to mitigate each of the participant's concerns regarding HIV testing. For structural concerns such as lack of transportation or cost of testing, the counselor might talk about locating local HIV testing services, retailers that sell HIV self-testing kits, and options for free HIV testing in their local area. If the participant reports not testing due to a lack of knowledge of where to test or fear of being recognized at local testing sites, the counselor will assist the participant in finding testing options in nonlocal gender-affirming spaces, and help establish a transportation plan. For participants who report a lack of information or misinformation on the need for HIV testing, the counselor will talk through risk factors for HIV transmission and the CDC recommendations for testing specific to TY. The screen-sharing function in VSee will allow the counselor to share online resources and instruct the participant on their use (eg, how to navigate AIDSVu.com or local health department websites). For those who report fear of stigma or discrimination, the counselor will provide advice on their rights as a patient, including their right to confidentiality, respect, and privacy. The counselor may also share the Gay and Lesbian Medical Association resource list with the participant, which includes *10 Things Transgender Persons Should Discuss with their Health Care Providers* [28]. Through role playing with the counselor, the participant will practice talking about sex and HIV with a health care provider. The counselor will help the participant formulate and practice specific talking points to use with their provider. The counseling will place emphasis on providing the participant with the skills necessary to routinely test for HIV by addressing individual barriers to testing, and giving each participant a supportive and affirming HIV testing experience.

Phase two of the session will consist of testing for HIV. Prior to the test, counselors will offer standard content for risk elicitation and identification of safer sex goal behaviors. The participant, directed by the counselor, will conduct their own test and read their own results. They will then show the counselor their test result for confirmation. Based on the results of the test and the information gathered in phase one, the counselor will assist the participant in developing a prevention or care plan to reduce the risk of acquiring or transmitting HIV (eg, number of sexual partners, frequency of unprotected intercourse). The counselor will describe the behavioral and biomedical interventions appropriate for each participant, such as condom use, partner reduction, decreasing drug or alcohol use, and/or preexposure prophylaxis (PrEP). At the end of the video-chat session, participants who show a positive result will be counseled on the need for timely confirmatory testing and linkage to care. The counselor will arrange a time within one week of the initial session to conduct a second video-chat session. During the second session, the counselor will determine other resources from which the participant may benefit, such as medical case management, mental health care, and/or more comprehensive psychological counseling and services. TY who test positive will also be directly linked to medical care in the second session by connecting them with a provider in their local area or another area designated by the participant. Study staff will follow up on the next business day to ensure that contact was made with the participant's desired facility. The participant will be contacted at least three more times: (1) to confirm an appointment was scheduled, (2) to confirm that the appointment was attended, and (3) to report confirmatory test results.

Counselor Training

Counselors will be trained to use motivational interviewing during a two-day training session. The training will involve didactic presentations on the history, science, and spirit of motivational interviewing, as well as role plays with other counselors acting as study participants. The counseling session protocol was developed with the input of transgender-identified staff members and community members. All counselors will be trained in HIV testing and counseling, and receive specific

training on the importance of gender affirmation and working with TY prior to delivering the intervention. Counselors who demonstrate proficiency via audiotaped role plays reviewed by study staff will be cleared to deliver remote counseling to participants. To examine protocol fidelity, all sessions will be audio-taped and research assistants will code and assess a random sample of sessions each month using the *Motivational Interviewing Treatment Integrity* (MITI-4) coding scheme [29-32], and qualitatively assess empathy and motivational interviewing-adherent and nonadherent behaviors. Counselors identified as having treatment drift will receive booster trainings as necessary.

Measures

Measures will be collected via the baseline, three-month, and six-month online surveys. All measures included in the baseline and follow-up questionnaires were included after a review of the current literature on TY.

Outcomes

The primary outcome for this study is routine HIV testing, defined as testing at least once during the follow-up period (ie, every 3-6 months) based on the HIV risk profile of the participant. Secondary outcomes consist of sexual risk-taking behaviors, intervention acceptability at the final survey, and linkage to HIV care (for those who report a positive result at baseline or during the course of the intervention). Key covariates include measures of transphobia and social marginalization.

Demographics and HIV Knowledge and Testing History

The demographics section includes measures of age, education, race, ethnicity, sexual orientation, employment, and state of residence. Both the respondent's sex assigned at birth and current gender identity will be collected. Previous literature on the sexual health of transgender individuals has been criticized for not using discrete categories for trans-masculine/transmale and trans-feminine/transfemale [33]. For this reason, current gender identity will include options for male, female, trans-masculine/male, trans-feminine/female, as well as categories for genderqueer/gender nonconforming, agender/genderfluid individuals, and a participant-driven response option. Items used in previous studies of LGBT persons will measure knowledge regarding the transmission and prevention of HIV [33,34], and knowledge and use of PrEP [34], at baseline and at each follow-up point.

HIV Testing

History of HIV testing, including measures of frequency, place of testing, method of testing, and linkage to care (if HIV-positive), will also be collected at baseline. Follow-up surveys will repeat the questions from the baseline and will also ask questions regarding HIV testing since the last survey. These parameters include location of test (eg, home, Acquired Immunodeficiency Syndrome Service Organization, Department of Public Health, or physician), test result, care received (specifically for HIV-positive participants), and reason for testing (ie, routine care versus episodic exposure).

Transphobia

Transgender persons face high levels of stigma and discrimination in the United States [12,35-37]. Dimensions of stigma and discrimination among participants will be measured to better understand their associations with testing behaviors among TY. Transphobia will be assessed using subscales from the Gender Minority Stress and Resilience Scale (GMSRS) [38]. Consisting of eight psychometrically-validated subscales, this measure was conceptualized as an assessment of potential facilitators and barriers to engaging in routine HIV testing, and was validated in a sample of 1414 transgender and gender nonconforming persons in the United States.

The *Gender-Related Rejection* and *Gender-Related Victimization* subscales of the GMSRS measure instances of enacted stigma experienced by participants, while the eight-item *Shame* subscale of the *Transgender Identity Scale* [39] will be used to assess internalized transphobia. All three scales use five-point Likert-type questions. Additional measures will also be used to assess the relationship between experiences and/or feelings of transphobia and health outcomes. These measures include the *Affirmation of Gender* scale [38] and the *Self-Admiration* GMSRS subscale [39]. Also using five-point Likert-type response options, the first measures how readily the respondent feels accepted by others in their current gender identity while the second measures the pride one feels in being transgender or gender nonconforming.

Social Marginalization

Wilson et al [40] conceptualized transgender social marginalization as having three dimensions: homelessness, incarceration, and participating in commercial sex work. To more fully understand how these dimensions may be associated with routine HIV testing behaviors, participants will be asked about lifetime experiences of homelessness. Participants who have experienced homelessness will also answer whether or not they have been homeless in the past six months. Recent (<12 months) and lifetime history of incarceration, and recent (<3 months) participation in commercial sex work will be assessed by items from the *National Transgender Discrimination Survey* [41]. Commercial sex work is defined in this study as trading sexual activity or favors for food, money, a place to sleep, drugs, or other material goods.

Sexual Behaviors

Unprotected sexual intercourse remains the most common route of transmission for HIV in the United States [1]. However, according to the CDC, less than half of transgender men who received an HIV diagnosis in 2016 had any identified or reported sexual risk behaviors [1]. To collect more data on participants' sexual risk behaviors, behavioral measures adapted from the National HIV Behavioral Surveillance behavioral inventory (and previously used with thousands of MSM by the research team [42,43]) will be used to collect information on sexual behaviors in the past three months. Participants will be asked to estimate the number of anal (and vaginal, if applicable) intercourse partners, as well as condom use or nonuse at each encounter, and the number of times they were the insertive (if applicable) versus receptive partner. The disclosure of HIV

status and reported serostatus, or lack thereof, for each partner will also be assessed.

Intervention Acceptability and Satisfaction

This is the first study to pair telehealth with HIV self-testing in this population. Understanding how to improve the acceptability and satisfaction of this modality will benefit future studies. TY will report data on the acceptability of the experimental arm at the end of the follow-up period. Two different assessments will be used to measure acceptability: (1) the Self-Evaluation Form (SEF) [44] and (2) the Client Satisfaction Questionnaire (CSQ-8) [45]. The SEF is a brief 13-item questionnaire that elicits information regarding the participant's experience with the intervention (ie, was the intervention interesting, was it relevant to their life). The CSQ-8 will be used to assess satisfaction with the intervention. The SEF and CSQ-8 will together take approximately 10 minutes to complete. Acceptability of the technology used in the intervention will also be assessed using a survey based on the Unified Theory of Acceptance and Use of Technology , which posits that an individual's acceptance of a technology is a function of performance, effort, social influence, and facilitating conditions [46]. Technology usage will also be used as a proxy for acceptability, with server logs providing records of user sessions, session length, pages visited, and functions utilized.

Linkage to Care

It is important to introduce participants whose self-tests are positive to the HIV treatment cascade and continue following-up on their HIV testing frequency, sexual risk behaviors, and experiences with HIV stigma and transphobia. Per the recent recommendations of the Institute of Medicine [47], indicators of linkage to care will include: (1) attending at least one clinical care appointment, (2) having at least one CD4 test performed, and (3) having at least one viral load test performed within three months of HIV diagnosis [32,48].

Statistical Analysis

The primary outcome will be the proportion of TY who tested for HIV at least once in the six-month follow-up period. Descriptive statistics of participant characteristics will be presented for all participants and also by study arm. These results will be compared using student t-tests or Wilcoxon rank sum tests for continuous variables, and Chi-square tests for categorical variables. The analysis for each outcome measure is described in detail below.

HIV Testing

Analyses will be conducted using logistic regression. The proportion of participants who obtain at least one HIV test within the follow-up period will be calculated for each study arm, along with corresponding 95% confidence intervals. First, the regression model will be fit using study arm only. A second model will control for baseline characteristics, as well as self-reported stigma and discrimination to measure their roles in mediating the outcome.

Sexual Risk-Taking

Sexual risk behavior will be defined as any unprotected anal or vaginal intercourse that occurs during the follow-up period with a person who is known by the participant to be HIV-positive, or has an unknown serostatus. The incidence of at-risk sex acts will be calculated as an incidence density, with the numerator being number of individual at-risk sex acts, and the denominator being person-years of follow-up time. Comparisons of the incidence of unprotected sex will be made by comparing incidence densities across arms. Incidence rates per person-year of follow-up will be estimated and compared using methods based on the Poisson distribution and using the generalized estimating equation (GEE) approach. Key covariates include demographic characteristics, previous HIV testing history, and reported stigmas and transphobia. Period incidence rates (three-month incidence density rates) of at-risk sex will be estimated by performing a GEE Poisson regression analysis of the trimonthly counts, implemented using SAS PROC GENMOD [49]. GEE models will control for demographic characteristics, baseline HIV testing history, and stigma, and will also be used to examine interactions between forms of stigma (HIV and transphobia) and sexual risk-taking.

Linkage to Care

The percentage of newly-identified HIV-positive participants who attend a comprehensive HIV care visit with a health care provider within three months of diagnosis will be tested for significance across the two study arms using logistic regression analysis. Demographic characteristics and self-reported stigma and discrimination will be controlled in these analyses.

Incentives

All participants will receive US $30 for completion of the baseline survey and an additional US $30 after completing each of the follow-up surveys. Incentives will be given via email in the form of gift cards to an online retailer, such as Amazon.

Sample Size

The research team proposes to enroll and maintain a sample of 200 TY aged 15-24 years. In order to achieve this target, recruitment efforts will continue until approximately 250 TY are enrolled. Allowing for 20% loss to follow-up, this approach will produce a sample of 200 TY who are expected to complete the prospective pilot RCT. As a comparison, an ongoing RCT of couples' HIV counseling and testing in MSM [44] has a retention rate of 90-95%, making a 20% loss-to-follow-up a generous allowance. The sample size is calculated based on the detection of significant changes in each of the outcomes between the control and intervention groups. If data are pooled across participants' gender identities, the study will have 81%, 92%, and 99% statistical power to observe differences of 10%, 12%, and 15% in the primary outcomes, respectively.

Trial Registration, Ethics, Consent, and Institutional Board Approval

The Institutional Review Board of the University of Michigan has approved this study (HUM00102906). The study has also been registered on ClincalTrials.gov (NCT03185975). The samples will be reflective of the racial and ethnic diversity of the United States and are deemed to pose no more than minimal risk to the participants.

Results

Project Moxie began recruitment on June 19, 2017 and has enrolled 130 participants as of August 21, 2017. Self-testing kits have been mailed to a total of 71 participants. Video-chat sessions for 12 participants randomized to the experimental arm have been completed and 58 participants from the control arm have entered their test results into the study database.

Discussion

Telehealth-based HIV counseling provides TY the opportunity to test for HIV in a comfortable and safe space, as well as problem-solve issues related to testing and risk behavior that are specific to their life experiences. This approach also provides a point of care to TY residing in areas where gender-affirming health care may be scarce, and provides a space free of the discrimination and harassment TY often encounter while trying to access health care resources.

A potential limitation is the protocol's reliance on existing health care resources for linkage to care and follow-up. TY may participate in Project Moxie due to a lack of locally-available resources that are accepting and gender-affirming. However, after their initial session, those who test positive and/or require additional services may find limited options in their local area and may have difficulty entering into the continuum of care. The current price of self-test kits (approximately US $30-40) may be prohibitive for many TY and could be a barrier to routine testing in areas without gender-affirming or subsidized HIV testing services.

Despite these limitations, pairing HIV testing with counseling and linkage to care is an innovative approach to increasing access to sexual health care. Using telehealth to link high-risk TY to HIV testing and care has the potential to reduce the high rate of HIV and STI transmission among this high-risk and often-marginalized population.

Conflicts of Interest

None declared.

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Abbreviations

CDC: Centers for Disease Control and Prevention
CSQ-8: Client Satisfaction Questionnaire
GEE: generalized estimating equation
GMSRS: Gender Minority Stress and Resilience Scale
HIPAA: Health Information Portability and Accountability Act
HIV: human immunodeficiency virus
ID: identification
LGBT: lesbian, gay, bisexual, transgender
MSM: men who have sex with men
PrEP: preexposure prophylaxis
RCT: randomized controlled trial

SEF: Self-Evaluation Form
SMS: short message service
STI: sexually transmitted infection
TY: transgender and gender nonconforming youth

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Original Paper

Recruiting Women to a Mobile Health Smoking Cessation Trial: Low- and No-Cost Strategies

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Abstract

Background: Successful recruitment of participants to mobile health (mHealth) studies presents unique challenges over in-person studies. It is important to identify recruitment strategies that maximize the limited recruitment resources available to researchers.

Objective: The objective of this study was to describe a case study of a unique recruitment process used in a recent mHealth software app designed to increase smoking cessation among weight-concerned women smokers. The See Me Smoke-Free app was deployed to the Google Play Store (Alphabet, Inc., Google, LLC), where potential participants could download the app and enroll in the study. Users were invited in-app to participate in the study, with no in-person contact. The recruitment activities relied primarily on earned (free) and social media.

Methods: To determine the relationship between recruitment activities and participant enrollment, the researchers explored trends in earned and social media activity in relation to app installations, examined social media messaging in relation to reach or impressions, and described app users' self-reported referral source. The researchers collected and descriptively analyzed data regarding recruitment activities, social media audience, and app use during the 18-week recruitment period (March 30, 2015-July 31, 2015). Data were collected and aggregated from internal staff activity tracking documents and from Web-based data analytics software such as SumAll, Facebook Insights (Facebook, Inc.), and Google Analytics (Alphabet, Inc., Google, LLC).

Results: Media coverage was documented across 75 publications and radio or television broadcasts, 35 of which were local, 39 national, and 1 international. The research team made 30 Facebook posts and 49 tweets, yielding 1821 reaches and 6336 impressions, respectively. From March 30, 2015 to July 31, 2015, 289 unique users downloaded the app, and 151 participants enrolled in the study.

Conclusions: Research identifying effective online recruitment methods for mHealth studies remains minimal, and findings are inconsistent. We demonstrated how earned media can be leveraged to recruit women to an mHealth smoking cessation trial at low cost. Using earned media and leveraging social media allowed us to enroll 3 times the number of participants that we anticipated enrolling. The cost of earned media resides in the staff time required to manage it, particularly the regular interaction with social media. We recommend communication and cooperation with university public affairs and social media offices, as well as affiliate programs in journalism and communications, so that earned media can be used as a recruitment strategy for mHealth behavior change interventions. However, press releases are not always picked up by the media and should not be considered as a stand-alone method of recruitment. Careful consideration of an intervention's broad appeal and how that translates

into potential media interest is needed when including earned media as part of a comprehensive recruitment plan for mHealth research.

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KEYWORDS

smoking cessation; mobile applications; social media; women; mHealth

Introduction

Background

Since the introduction of the iPhone (Apple, Inc.) in 2007, integration of mobile and wireless technologies with everyday life has become ubiquitous, with broad reaching implications for health and health care. Tools and resources of varying quality for disease prevention and management previously limited by geography, cost, and time are now widely available and accessible via the Internet to the majority of individuals who seek these services. At the same time, an evidence base supporting the efficacy of mobile and wireless health behavior change interventions (mobile health, mHealth) has grown substantially as the field's methodology and rigor continues to advance. However, foremost among remaining challenges is determining which mHealth intervention approaches work for specific conditions and outcomes. When, how, and for whom these approaches work best must also be elucidated. Critical to answering these questions is the ability of researchers to successfully recruit an adequate number of participants to mHealth trials.

There is a growing body of literature outlining best practices for participant recruitment [1,2], including use of social media. [3,4]. Nevertheless, such methods may not be entirely applicable to mHealth intervention studies. There are advantages and disadvantages when recruiting nationally for an mHealth study. The advantages include a much larger pool from which to draw, but the disadvantages include the potential for lack of contacts in the target community and no face-to-face interaction during which to build rapport and accountability. In addition, intervention studies may not be able to rely on services such as mTurk because of the inclusion or exclusion criteria, length of commitment, and other requirements for participating in an intervention, or depend on FindParticipants because of cost. Limited empirical data are available to inform approaches to recruiting participants to mHealth trials. Our own experience in conducting an mHealth trial highlighted several challenges in recruitment, including low return on investment of paid advertising [5]. Yet, recent polls show that large sectors of the population are actively using Web-based health resources [6] and wider demographics are seeking and connecting to social media communities, both of which hold promise for overcoming recruitment challenges in mHealth research [7].

Our systematic review of methods used to recruit participants to mHealth and Web-based interventions [8] identified several promising recruitment strategies specific to Web-based and mHealth studies, including search engine advertising, Web-based classifieds, paid advertising, and news stories (earned or free media) posted on social media. Eight out of 12 studies included in that review used some combination of social media, search term queries on multiple search engines, and health-focused websites to reach potential participants, whereas the remaining four studies used a combination of Web-based and traditional methods [8]. Each study targeted a specific population, and no two studies used identical recruitment methods. In addition, the recruitment periods and costs for each study varied widely. Therefore, we could not identify which strategy or combination of strategies were most effective or cost-effective [8]. Studies did not distinguish between participant yields from paid advertising versus other promotional efforts (ie, earned media). Given that researchers must decide how to invest limited recruitment resources, it is important to describe different methods of recruitment and their potential costs.

The authors conducted a study of the See Me Smoke-Free (SMSF) mHealth app to develop and evaluate the feasibility of the app designed to increase smoking cessation among women. SMSF specifically targeted women smokers because they face particular challenges when quitting [9]. Women gain an average of 9 pounds when quitting smoking [10-12], and weight gain is identified as a major reason for subsequent relapse [13]. In addition, women are disproportionately burdened by the health effects of smoking, with greater risks of cancer and coronary heart disease as compared with men [14,15].

The SMSF study was a within-subjects, pre- or posttest trial to develop and evaluate the feasibility of delivering a guided imagery intervention via a mobile phone mHealth app [16]. Study outcomes included feasibility of recruiting participants, retaining participants at the 30- and 90-day assessments, and adherence to the intervention [17]. We also explored the association between the use of the SMSF app and multiple health behaviors, including smoking cessation, healthy eating, increased physical activity, and improved body image [17]. The mHealth app was deployed to the Google Play Store. After download and completion of the user profile, users were invited to participate in a research study and consented within the app. Eligible participants were female, aged 18 years or older, spoke English, were US residents (to receive study incentives), smoked cigarettes in the past 30 days, and owned an Android (Alphabet, Inc., Google, LLC) phone (as the app was developed only for that platform). The intervention engaged participants in smoking cessation and behavior change using daily audio-guided mental imagery sessions initiated by the participant during scheduled sessions or when she felt an urge to smoke. The app included tracking and goal-setting features related to the number of tobacco-free days, servings of fruits and vegetables consumed, minutes spent engaged in physical activity, mood, and money saved by not smoking. SMSF also included links to additional information and resources, including a smoker's quitline [9,16]. Participants were expected to use the app for most days during 1 month and to complete a survey at baseline, 30 days, and 90

days for which they were compensated a total of US $50. The University of Arizona's institutional review board (IRB) deemed this research project to be exempt from oversight.

Objectives

As part of this study, the research team developed a recruitment plan based on their literature review and previous experiences recruiting for electronic health or mHealth interventions. The plan included a stepwise approach to recruitment, starting with publicity through earned or social media and tobacco treatment contacts and then moving to paid advertising. First, the team partnered with the University of Arizona's Office of Public Relations to issue a press release about the study. The resulting media exposure presented a unique opportunity to refocus our recruitment efforts to capitalize on this free media and leverage social media to recruit the target sample of 50 self-identified women smokers. Our sample size was determined to be sufficient to measure our feasibility goals (eg, achievement of our recruitment, enrollment, retention, and adherence), with a standard error of <7%, and to gather preliminary consumer satisfaction data [18]. In addition, with 50 participants and a significance level of .05, we had .80 power to detect change of d=0.66 (a medium effect size) in our cessation, diet, and physical activity outcomes. The purpose of this study was to describe this case study example, including our free media and social media recruitment efforts, and our results.

Methods

Overview

We present a case study describing the recruitment strategies used and results of these activities during our feasibility and acceptability study of the SMSF mHealth app. The feasibility study was conducted from January 2014 to December 2015. Recruitment of participants to the SMSF study occurred from March 30, 2015 to July 31, 2015, and analysis of the recruitment methods occurred from June 2016 to December 2016. Variables of interest included the number and timing of press releases and media mentions, Facebook reach, and Twitter (Twitter, Inc.) impressions. KA worked with JG to establish outcomes for the evaluation, which included descriptive analyses to explore trends in earned and social media activity in relation to app installations, examine social media messaging in relation to reach or impressions, and describe app users' self-reported referral source. Data were collected from a variety of sources and assembled by KA to examine frequencies by date and content. The research assistant and KA tracked all study team posts to social media by date, frequency, content, and location. Press release distribution was tracked by date, media outlet, and content by the Office of Public Affairs (OPA). Media mention data by media outlet were sent from the OPA to the research assistant, who retrieved the coverage and entered the publication date, URL, content, and audience (local or national) into a spreadsheet. Twitter impressions were pulled from SumAll, a free software that tracks social media accounts, to examine frequencies and identify tweets yielding high impression data. Although the team managed a number of social media accounts, including Google+ and Pinterest, at the time, SumAll provided metrics for Facebook and Twitter only. KA pulled data regarding posts' reach from Facebook Insights, examined frequencies, and identified specific posts with particularly high reach data. SMSF installation data were pulled from Google Analytics by date.

Recruitment Activities and Timeline

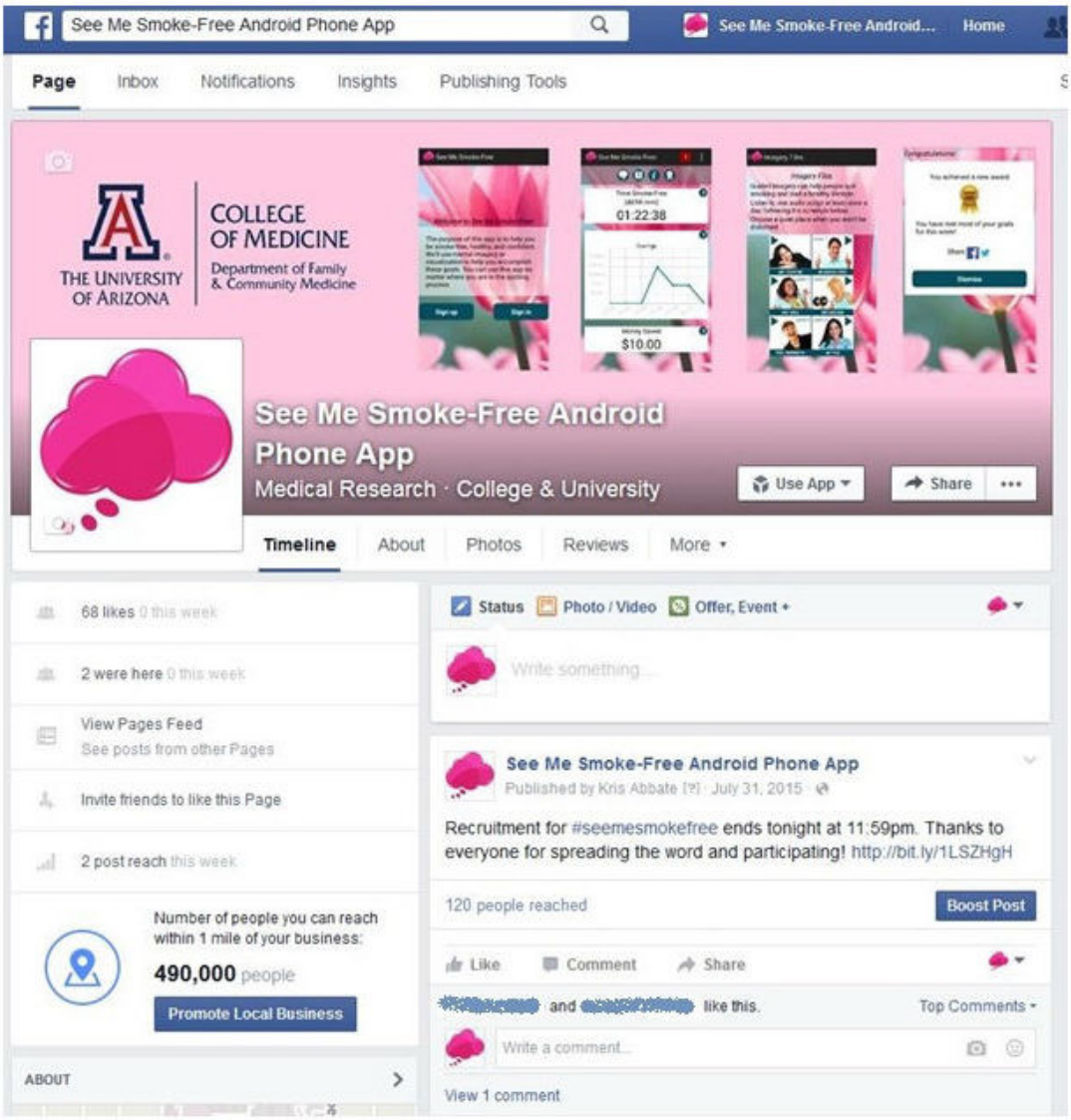
During our previous mHealth study [5], we employed a recruitment strategy in which potential participants were invited to visit the research website to learn more about the study and if interested, enroll. Participants would then complete eligibility screening, informed consent, and the Web-based baseline survey. Once completed, they would receive an email with a link to download the app. This process was cumbersome and resulted in loss of participants before they downloaded the app. After several months, we changed our recruitment process so that the app was deployed to the App Store (the app was developed only for the iPhone operating system [iOS]) and recruited participants from within the app. This streamlined process resulted in a much higher conversion rate of potential participants to enrolled participants [5]. On the basis of this experience, we opted for the latter recruitment process in the SMSF study, and we deployed the SMSF app to the Google Play Store [19]. All recruitment activities occurred within the app after interested respondents downloaded it. After completing the SMSF profile, the app displayed a notification inviting the participant to enroll in the study (yes, no, and maybe). If the user selected "maybe," she received a notification with more study description and another yes or no invitation. If the user answered "no," she was returned to the SMSF home screen. If the user selected "yes," she was taken to the in-app eligibility screener. If the user was not eligible, she was returned to the home screen. Eligible users began the in-app consent and baseline survey process. Additional details regarding enrollment can be found in the SMSF outcome paper [17].

Release of the app on the Google Play Store marked the beginning of the recruitment period (March 30, 2015). Learning from our previous experience with the high cost of Facebook and Google advertising for study recruitment [5], we had planned a multi-tiered recruitment strategy, including recruitment flyers in health care settings and cessation programs, soliciting volunteers on Craigslist, postings on social media sites, and paid Facebook advertising. As a first step, we worked with the University of Arizona Health Sciences' Public Affairs Office to disseminate a press release about the study to the media and prominent members of the Arizona health care community. The purpose of the press release was to provide general information about the SMSF app and build credibility for the project that could be leveraged for other recruitment activities. The press release directed the reader to the Google Play Store or the project website which also linked directly to the Google Play Store (a copy of the press release is included in Multimedia Appendix 1). The first press release was sent to 191 local and Arizona media contacts (eg, *Arizona Daily Star* and *Cronkite News*). One week later, the app was released on the Play Store. Research team members also posted study information to 15 local digital media outlets with free classified listings.

The next phase of media releases described the SMSF app's features, highlighted the app's purpose, and focused on drawing women from throughout the United States—particularly from states with high smoking rates—to use the SMSF app. The second media release (April 28, 2015) targeted 17 publications that regularly feature articles on women's health (eg, *Cosmopolitan* and *Harvard Women's Health Watch*) and 66 outlets in US states with the highest smoking rates (eg, *The Columbus Dispatch* and *Lexington Herald Leader*). A study coinvestigator (PG) at West Virginia University (WVU) arranged for a third media release from his university's Public Relations Office (May 12, 2015), which like the previous two project press releases described the SMSF app's function and purpose but also highlighted his involvement as WVU faculty.

The research team disseminated earned media mentions (Web or printed references to SMSF not published by the study team) resulting from the press releases using the University of Arizona Facebook Family and Community Medicine (FCM) Tobacco Research Program and Twitter account, the SMSF Study Facebook page (Figure 1), and the study website connecting with broader social media campaigns on tobacco cessation whenever possible. The SMSF study team also identified and posted news articles and research studies about tobacco cessation on the study's Facebook page to supplement social media outreach. For instance, the team posted a link to a study titled *Smoking and survival after breast cancer diagnosis in Japanese women: A prospective cohort study* to the SMSF Facebook page, accompanied by the caption, "More evidence that #smoking significantly increases #women's risk of #breastcancer. (bitly link to article) #seemesmokefree helps women quit smoking, while also maintaining body weight and overall health (bitly link to SMSF website)." All of these posts leveraged media coverage of SMSF or related health issues by sharing the news in posts that directed the reader to the Google Play Store to learn more about and download the SMSF app. The vast majority of these efforts were performed by Mr Abbate, a medical student worker on the project, who spent on average 5 hours per week for 12 weeks on recruitment activities, including postings on social media. The total cost for his recruitment efforts was US $825 (60 hours @ US $13.75/hour [salary plus fringe]). During the remaining 4 weeks of recruitment, the research specialist performed these activities for a cost of approximately US $425 (20 hours @ US $21.25/hour [salary plus fringe]). Therefore, the total cost for these recruitment activities was US $1250 or US $8.28 per enrolled participant (N=151) and after accounting for participant attrition that occurred during the 3-month study period, US $17.12 per retained participant (N=73).

Figure 1. See Me Smoke-Free app Facebook profile page.



The use of hashtags with Facebook and Twitter postings ensured that these communications were included in search results of other postings focused on cessation or related topics. Posts that included more general hashtags (eg, #women) appeared to a large number of users searching social media for posts targeting women. Using a more health-specific hashtag with high relevance to women (eg, #breastcancer) was intended to further increase the likelihood that that SMSF posts appeared in the search results of users who were interested in health and inclined to participate in a research study. The research team also used hashtags associated with relevant and trending topics (eg, #NWHW indicated the established national campaign, National Women's Health Week) that had the potential to be seen by large numbers of interested users. In this study, we used the hashtag #seemesmokefree to promote the study, which allowed researchers to easily follow SMSF-related postings and potential participants to follow the project and receive updates.

Finally, the research team also posted content to several private smoking cessation support groups on Facebook after receiving moderator approval. These groups had memberships ranging from 616 to 10,515 people (as of 28 July, 2015). All social media posts used IRB-approved language to describe the study and included a link to the SMSF study Web page.

Data Capture and Analytics

Facebook reach (number of people whose Facebook feed contained SMSF content either in Facebook News Feed or in the right column ad area) and Twitter impressions (number of user feeds in which tweets and retweets appeared) data were used to document social media–related recruitment activity during recruitment. Google Analytics data were used to determine the number of daily page visits to the SMSF website and to document new app users—these data were exported and tabulated by date. Frequency and type (local, national, or international) of earned media coverage was monitored through personal contact with media outlets, especially Arizona State University's Cronkite News Service and the Arizona Health Sciences' Public Affairs Office, and automatically, using Google alerts. Finally, respondents who downloaded the app and opted to participate in the study (here defined as participants) answered several screening questions to determine their eligibility; among these questions was an optional multiple-choice item asking

respondents to report how they learned about the SMSF study (ie, Facebook, Twitter, Pinterest, Google/+, Google Play Store, email, radio or television, newspaper, health care provider, friends or family, or other). Deidentified data were also collected on individuals who were confirmed app users but either did not qualify or opted out of the SMSF feasibility study (here defined as nonparticipants). All of these data were collected using the in-app questionnaire tool and tabulated.

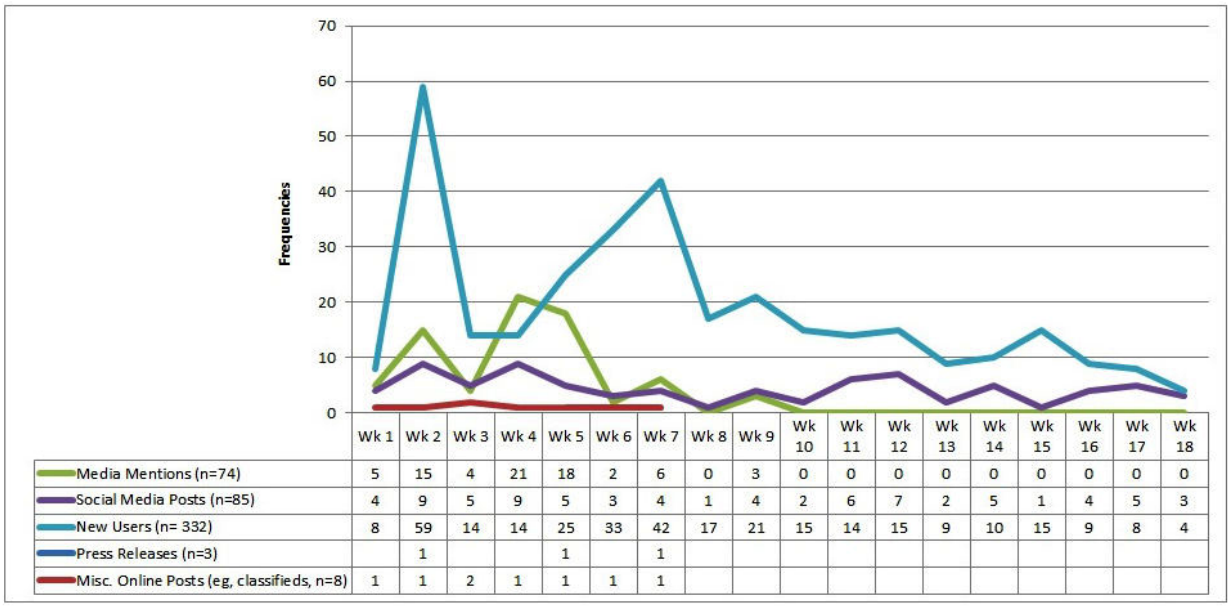
Results

Media Mentions and Articles

Three press releases resulted in earned media mentions, including full-length printed or Web articles and broadcast pieces in 74 outlets: 34 local, 39 national, and 1 international. A summary of study recruitment activities relative to weekly recruitment outcomes is presented in Figure 2.

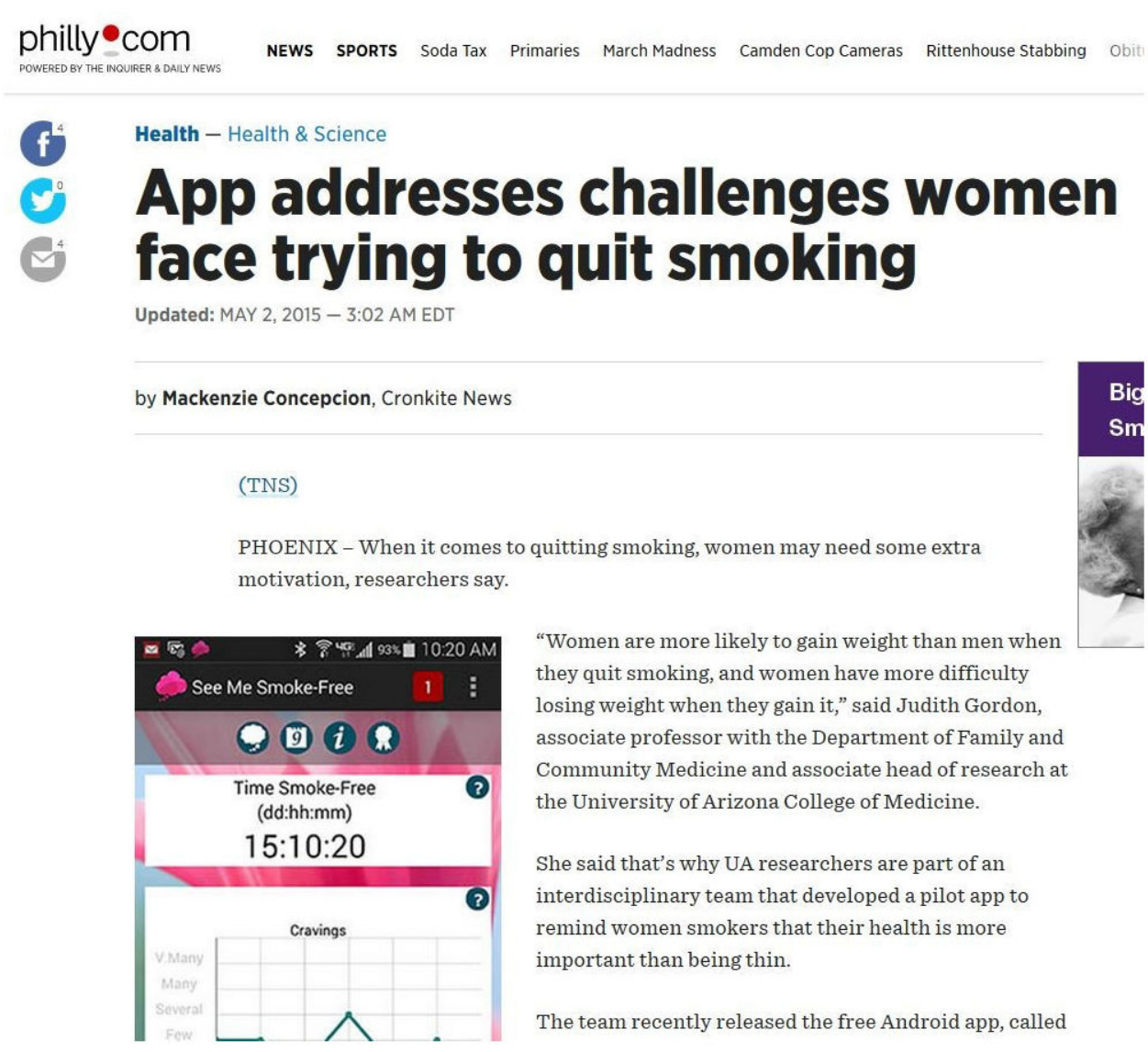
Media mentions included coverage by the Cronkite News - Phoenix Bureau, which distributed the story about SMFS nationwide through the Tribune News Service. This led to additional stories in the *Philadelphia Inquirer*, *Chicago Tribune*, *The Kansas City Star*, the *Idaho Statesman*, *The Modesto Bee*, and many others. After the initial press release, earned media mentions steadily accrued, beginning with a single mention on March 30 and concluding on May 27, with stories in two national publications. The most earned media mentions occurred on April 20 (10 local media outlets picked up one release) and April 28 (12 national outlets carried stories about the study). From April 1 to April 28 (weeks 1-5), 30 local media outlets and 15 national media outlets shared posts regarding the SMSF study.

Figure 2. Recruitment activities and new users, March 30, 2015 to July 31, 2015.



	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15	Wk 16	Wk 17	Wk 18
Media Mentions (n=74)	5	15	4	21	18	2	6	0	3	0	0	0	0	0	0	0	0	0
Social Media Posts (n=85)	4	9	5	9	5	3	4	1	4	2	6	7	2	5	1	4	5	3
New Users (n= 332)	8	59	14	14	25	33	42	17	21	15	14	15	9	10	15	9	8	4
Press Releases (n=3)		1			1		1											
Misc. Online Posts (eg, classifieds, n=8)	1	1	2	1	1	1	1											

Figure 3. Article header screenshot.



Recruitment of participants occurred daily beginning on March 30 (week 1) until recruitment ended on July 31 (week 18). The most successful single days for recruitment occurred on April 9 (33 new users), May 11 (10 new users), and May 13 (12 new users).

As demonstrated in Figure 3, cross-platform sharing via email, Facebook, or Twitter expanded potential reach of Web-based coverage. The story, "App addresses challenges women face trying to quit smoking," was shared 4 times each on Facebook and email. At the conclusion of recruitment, the SMSF Facebook page had 57 members, whereas the FCM Tobacco Twitter account had 200 followers. Because both accounts were public, posts could be viewed and accessed by users that were not direct followers, primarily through retweets, posts to third party groups, and social media platform search results.

Social Media

During the recruitment period, the research team made 30 Facebook posts and 49 tweets, yielding 1821 reaches and 6336 impressions, respectively. This did not include posts made to three third-party private smoking cessation Facebook groups (one per group) whose respondent yields could not be documented. Four Facebook posts attained a reach of 100 or more each (see Table 1). All four posts were linked to earned media. Five Twitter posts resulted in at least 200 impressions each (as displayed in Table 2). Tweets using popular or woman-specific hashtags (eg, #NWHW, #women, and #healthyliving) and tagging popular accounts (eg, @Philadelphiagov and @cronkitenews) led to a greater number of impressions. Facebook posts were more detailed because they had no character limit, whereas tweets needed to be limited to 140 characters.

Table 1. Facebook post reach.

Description of Hook	Content	Reach
Link to a YouTube clip of a Cronkite News segment that included an interview with the study principal investigator	The interview link was accompanied by the following quote: "Among the challenges for women who want to stop smoking: they gain more weight on average when trying to quit. An app developed by University of Arizona researchers uses inspirational messages and other means to keep women committed to kicking the habit."	April 22, 2015: 313 people reached
Link to a news segment that described the app on a local radio station (Mix 96.9, KFYI)	The segment was accompanied by the following caption: *"See Me Smoke Free* uses guided imagery, a technique that's been used in sports and other disciplines for years. Motivational messages, a tracker of how long you've been smoke free, and other tools are available."	May 4, 2015: 440 people reached
Link to an arkansasonline article	The article was posted with the following quote from the study principal investigator: "Most people smoke as a response to stress, and guided imagery may also help smokers quit by helping them relax. I'm not aware of any other app that's used guided imagery to deal with the issue of stress related to smoking."	November 5, 2015: 116 people reached
Link to a Maine News Online article	The article link was posted with a note that included an embedded link to the *See Me Smoke Free* Facebook page: "More coverage of the See Me Smoke-Free Android Phone App."	May 27, 2015: 102 people reached

Table 2. Twitter post impressions.

Description of Hook	Content	Reach
Links to Cronkite News' coverage of SMSF[a] while tagging @cronkitenews	Arizona State University's @cronkitenews covers See Me #smokefree app: *link*. #quitsmoking #healthyliving #news	April 21, 2015: 294 people reached
Links to SMSF study page in association with "NIH In Your State" campaign	NIH[b]-funded smoking cessation research in the @UofA Department of Family and Community Medicine *link* #NIHinYourState	May 6, 2015: 654 people reached
Links to the West Virginia University news article about SMSF collaboration with University of Arizona in association with National Women's Health Week campaign	WVU's Giacobbi collaborates with @UofA experts to launch "See Me Smoke-Free" app *link* #Android #NWHW #mHealth #smokefree	May 13, 2015: 225 people reached
Links to article about SMSF by local West Virginia TV affiliate WBOY	New #Android #App for #Women Aids #SmokeFree Quest	May 26, 2015, 205 people reached
Link to article about all time low smoking rates. Tags City of Philadelphia. Suggests mhealth, including SMSF may lower rates further	US cities such as @PhiladelphiaGov has all time low smoking rate. Can #mhealth #apps help this trend? *link* #seemesmokefree	June 29, 2015, 233 people reached

[a]SMSF: See Me Smoke-Free.

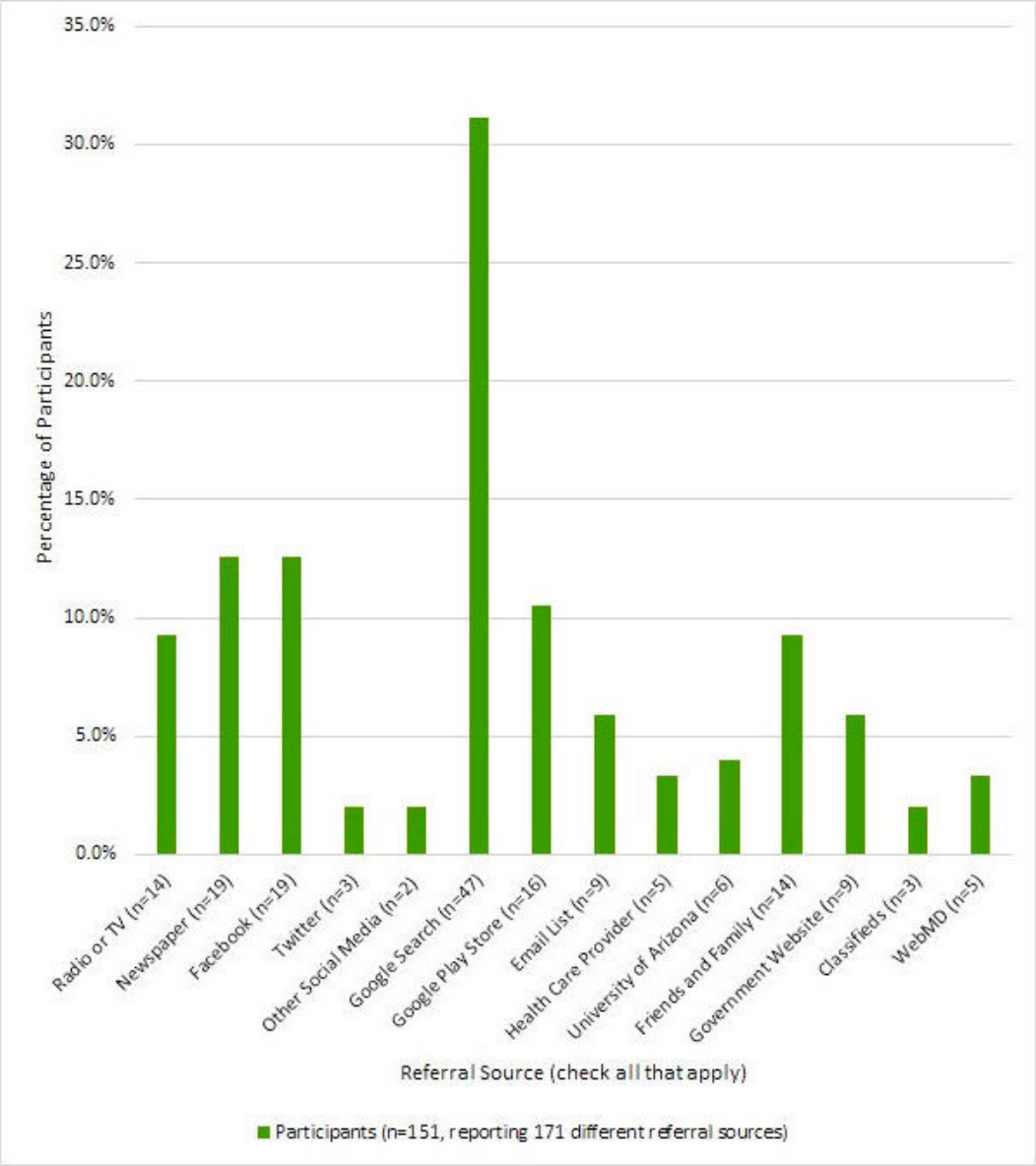
[b]NIH: National Institutes of Health.

Referral Resources and Participant Demographics

SMSF app downloads yielded 289 users (defined as unique installations of the app) and 151 participants. Of the participants, 151 (100.0%) shared where they had heard about the SMSF through an in-app questionnaire. The participants reported a total of 171 referral resources across 14 categories (eg, radio or TV, newspaper, Facebook, and Twitter; Figure 4). Many participants reported learning about the study through multiple sources, with Google Search being the most endorsed referral source at 31.1% (47/151) followed by newspaper and Facebook at 12.6% (19/151) each.

As per the eligibility requirements, all participants were female. Participants were, on average, 39.1 (standard deviation 13.1) years of age, 72.5% (109/151) white, 65.7% (99/151) completed at least some college education, 57.5% (87/151) single, and 71.2% (108/151) "very dependent" on nicotine [17].

Figure 4. How participants became aware of the study.



Discussion

Conclusions

No-cost recruitment efforts, via social media and in coordination with university public affairs offices that distributed press releases to media outlets, proved sufficient to secure adequate participant counts for the SMSF feasibility study. We were able to recruit 151 participants. We retained 73 participants throughout the study, and our baseline analyses indicated that there were no differences among those who remained in the study and those who dropped or withdrew. A more detailed discussion of retention can be found in the report of our feasibility outcomes [17]. Earned and social media approaches to recruitment have the potential to ensure socioeconomic, racial, and ethnic diversity in a study sample; however, certain populations may be less likely to use social media or to access Internet-based health news, although they are potential consumers of mHealth apps [20,21]. Our sample was representative of our target audience—US women smokers who use mHealth apps [22]—and was similar to other populations who use mHealth apps. Several studies have shown that mHealth users are predominantly white and have a relatively high level of education [23-26]. In addition, in the United States, mHealth users are primarily female [22-26]. Therefore, our sample appears to be representative of the population of women smokers who are most likely to use the SMSF program [6,26]. Future research is warranted to determine factors associated with lack of mHealth use and to elucidate strategies to attract more diverse populations to use mHealth apps.

Social media is increasingly a method by which to recruit research study participants, including studies focused on smoking cessation [27]. Unlike our study, which relied exclusively on earned media posts to social media, the majority of social media–based recruitment to date has relied upon targeted paid advertisements developed by the investigator and

distributed by social networking companies through their marketing services [28,29].

The majority of our study participants reported learning of the SMSF app through a Google search, Facebook, or a newspaper. Nonparticipants indicated they learned of the SMSF app through TV, radio, or newspaper stories. Although we were not able to test for differences, these contrasting findings may suggest that our participants were actively seeking out methods for smoking cessation using Google and Facebook search engines, smoking-related stories or research, or joining a Facebook cessation group. It is also possible that Internet-savvy individuals were more likely to participate in a mobile app–based study. The fact that many participants reported hearing about the app through multiple sources not only indicates that information was disseminated through multiple channels but also that these channels are intertwined. For example, a hypothetical participant's Google search may have yielded the SMSF Facebook page through which the participant accessed an earned media story.

The accumulation of app-related media mentions during the month of April did not result in a corresponding increase in users. This delay in app download and enrollment may have resulted from users feeling more comfortable joining a study when a specific media outlet or an accumulation of stories in multiple outlets contributed to credibility and legitimacy, or the fact that information about the app became widely available across multiple media outlets. This interpretation is supported by the number of users who reported hearing about the study from multiple platforms and media sources. The initial delay may also represent a period during which word-of-mouth sharing (from friend to friend, family member to family member, doctor to patient, etc) occurred. Although third-party sharing (eg, through an article, email, or social media sharing mechanisms) was beyond our ability to track, this may also explain steady accumulation of users even when new media mentions began to taper. Web publications and Web-based versions of radio and television broadcasts can be available indefinitely and accessed through a variety of methods (Internet search engine, direct referral, publication home page, etc). Social media posts advertising the end of recruitment may be responsible for a relative increase in new users during the second to last week of recruitment.

As recruitment progressed, we observed a decrease in the number of posts that received large numbers of reach and impressions on Facebook and Twitter. Facebook's algorithms are designed to favor posts from major publishers while limiting meme-like posts, which would result in well-known content providers' information to be displayed more frequently [29]. This suggests that content generated from mainstream media (ie, earned media stories), which is then shared via social media, has a greater chance of appearing in Facebook news feeds than organic posts by researchers to a study Facebook site. Additionally, the Facebook algorithms identify when fewer users engage with posts, and subsequent posts have less reach. Facebook encourages marketers to buy advertisements rather than relying on free posts [29]; indeed, Facebook posted a suggested advertisement layout to our study's page moderator's personal feed and recommended that the SMSF page would benefit from paid advertising. This also suggested that Facebook algorithms are not based on marketing intent (eg, recruitment to a research study vs advertisements for a commercial product or opportunity).

A frequent and unsubstantiated assertion in mHealth research is that online recruitment is more cost-effective than traditional approaches. However, as we experienced in our study, limited face-to-face interaction with respondents has the potential to slow or bias the recruitment process, and additional screening steps must be taken to ensure respondents are not bots or sham subjects whose study profiles were created solely for material gain. In a previous 3-month mobile app feasibility study that involved very little staff interaction with participants, we discovered sham subjects (eg, the same person signing up multiple times with different usernames and email addresses) when a research assistant attempted to reach participants by phone [5]. In the study described here, careful monitoring of participants' study activities combined with phone and email communications with nonadherent participants enabled the research team to identify sham participants and drop them from the study. Building rapport and identifying and winnowing out sham subjects requires dedicated staff time and has implications for project budgets. Even when direct costs are not significant (eg, recruitment conducted using earned media), the distribution of earned media through websites, social media platforms, and email or texting necessitates staff time to manage inquiries and curate social media activity. At US $17.12 per participant (N=73), our cost was less than the US $43.29 per participant cost reported by Gilligan et al who used an earned and social media approach to recruit one-time survey completers [30]. Studies recruiting one-time survey completers via Facebook advertising have per-participant costs ranging from approximately US $4.00 [27,30] to US $25.00 [31,32], whereas research projects that require more participant time investment report higher Facebook advertising per-participant costs, up to approximately US $697 [33].

Although Facebook reach and Twitter impressions allow estimates of number of people who accessed pages or relevant posts, it was not possible to determine how many of those views represented our target demographic. With respect to Twitter and Facebook posts, it was also not possible to know whether posts were read, even when their presence was confirmed in potential subjects' news feeds. Additionally, on at least one occasion, information was copied directly from an SMSF recruitment post and tweeted without attribution to the @FCMTobacco account, making it impossible to track how many Twitter users the information reached using Twitter's analytics.

A large proportion of Web traffic involves the transfer of deidentified or encrypted data, which does not allow repeat impressions, reaches, and visits to be distinguished from new ones. Furthermore, self-report remains the only method of tracking certain referrals (eg, word-of-mouth and email and text message [short message service, SMS]–based referrals) and does not allow us to determine with any great degree of accuracy how respondents learned about the study. For example, respondents might have learned of the opportunity to participate through an earned media story on the radio but followed up

with a Web search that brought them to the Google Play Store and allowed them to download the study app. It is possible that this respondent would self-report their recruitment as either "media story" or "Web search," and both would be accurate. It is the nature of Web-based communication that information is disseminated and accessed in many different ways—ultimately all through a Web page or app—and that multiple strategies complement one another. In our study, earned media posted on social media were synergistic strategies that allowed us to earn credibility via a third party, which ultimately helped extend our reach in social media. Working with university public relations can further help position study-related stories and optimize the tone of the story for maximum appeal to a lay audience. However, we have attempted to use this strategy in other studies with less success. For example, a press release issued for an earlier study was not picked up by the media, and we had to rely on paid advertising for the majority of enrolled participants [5].

Lessons Learned

Research regarding online recruitment methods for mHealth studies remains minimal, and findings are inconsistent. We demonstrated how earned media can be leveraged to recruit women to an mHealth smoking cessation trial at a low cost. The cost of earned media resides in the staff time required to manage it, particularly the regular interaction with social media. We recommend communication and cooperation with university public affairs and social media offices, as well as affiliate programs in journalism and communications, so that earned media can be used as a recruitment strategy for mHealth behavior change interventions. However, press releases are not always picked up by the media and should not be considered as a stand-alone method of recruitment. Careful consideration of an intervention's broad appeal and how that translates into potential media interest is needed when including earned media as part of a comprehensive recruitment plan for mHealth research.

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Authors' Contributions

KA, JA, JSG (senior author), and MDH contributed equally to the writing of this manuscript. PG reviewed and edited the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

See Me Smoke-Free press release 4-21-2015.

[PDF File (Adobe PDF File), 807KB - resprot_v6i11e219_app1.pdf]

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Abbreviations

FCM: Family and Community Medicine
IRB: institutional review board
mHealth: mobile health
NIH: National Institutes of Health
OPA: Office of Public Affairs
SMSF: See Me Smoke-Free
WVU: West Virginia University

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Protocol

Behavioral Interventions to Prevent or Delay Dementia: Protocol for a Randomized Comparative Effectiveness Study

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Abstract

Background: Currently, people at risk for dementia and their caregivers are confronted with confusing choices about what behavioral interventions are most effective.

Objective: The objective of this study is to determine which empirically supported behavioral interventions most impact the outcomes highly valued by patients with mild cognitive impairment and their partners.

Methods: This protocol describes a comparative effectiveness trial targeting 300 participants with mild cognitive impairment and their study partners. The trial is being conducted at the Mayo Clinic campuses in Arizona, Florida, Minnesota, and the University of Washington in Seattle. The study examines the contribution of five behavioral interventions (yoga, memory compensation training, computerized cognitive training, support groups, and wellness education) on primary outcomes of participant and partner quality of life and self-efficacy. In this unique 10-day multicomponent intervention, groups of couples were randomized to have one of the five interventions withheld while receiving the other four. Although the longitudinal follow-up is still under way, enrollment results are available and reported.

Results: In total, 272 couples have been enrolled in the trial and follow-up visits continue. Outcomes will be assessed at the end-of-intervention and 6-, 12-, and 18-month follow-ups. We anticipate reporting on our primary and secondary outcomes across time points in the next 2 years.

Conclusions: This paper describes the protocol for a randomized comparative effectiveness study of behavioral interventions to prevent or delay dementia. We describe of the rationale, design, power analysis, and analysis plan. Also because enrollment is complete and we are in follow-up phases of the study, we have included enrollment data from the trial.

Trial Registration: ClinicalTrials.gov NCT02265757; http://clinicaltrials.gov/ctsshow/ NCT02265757 (Archived by WebCite at http://www.webcitation.org/6ueRfwSYv)

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KEYWORDS

cognition disorders; dementia; secondary prevention; behavioral research

Introduction

Scope of the Problem

Alzheimer disease (AD) is the most common cause of dementia. An estimated 5.5 million Americans had AD in 2016, including 454,000 people receiving a new diagnosis of AD every year [1,2]. Roughly 16% of women and 11% of men aged 71 and older have AD. Unless dementia risk can be reduced, it is estimated that by 2050, the number of Americans with AD will triple, exceeding 13 million [1]. Worldwide projections are, for the number of people with AD, to rise from 26.6 million in 2006 to 107 million in 2050 [3]. The cognitive, emotional, behavioral, and functional impact of AD and related dementias is devastating. The majority of people with dementia (75%) live at home where they receive 83% of their care from informal caregivers—unpaid individuals such as family members, friends, and neighbors [1] **.** These caregivers provide valuable services, often at great economic, health, and psychological cost to themselves. Hurd et al [4] estimate the average annual cost of dementia care to be US $56,290, of which more than half is in unpaid care. In 2016, over 18 billion hours of unpaid care were estimated to have been provided by roughly 15.9 million caregivers, translating to nearly US $230 billion in a single year. The stress of caregiving is reflected in 8% higher costs for caregivers' health compared with noncaregivers [1]. In the later stages, nursing home placement is almost inevitable [5], and those not already qualifying for Medicaid will pay an average of US $81,000 per year for such care [6].

Early Detection Engenders Secondary Prevention

Dementia prevention through early intervention of risk is now possible. For example, AD has a decade-long predementia phase (ie, a prodrome) that includes reliably identifiable epochs preceding the manifestation of the full syndrome of dementia [7,8]. This understanding has led to new consensus diagnosis criteria for AD that recognizes a prodromal period called mild cognitive impairment (MCI) due to AD [9]. Approximately 15% to 20% of people aged 65 or older have MCI, and it is estimated that 32% to 38% of individuals with MCI develop Alzheimer dementia in 5 years [10]. This concept of MCI fits neatly within a public health framework [11] that identifies three forms of prevention: (1) primary prevention involving interventions to the entire population to reduce risk, (2) secondary prevention involving interventions targeting those at higher risk for a condition, and (3) tertiary prevention involving interventions given to those with disease to mitigate morbidity, such as providing cardiac rehabilitation to reduce the functional impact of heart attack. Nearly all primary prevention models for dementia involve behavioral interventions that improve overall health. For example, it was recently noted that a combined 25% reduction in midlife diabetes, obesity, hypertension, and physical and cognitive inactivity could potentially alleviate 500,000 cases of dementia [12]. Importantly, the emergence of the concept and diagnosis of MCI as a risk state for dementia creates the opportunity for secondary prevention models aimed at delaying (or ideally preventing) progression to dementia. The same interventions proposed for primary prevention show promise as secondary prevention interventions [13]. Moreover, behavioral interventions are growing in popularity and demand by patients with MCI.

Unfortunately, clinical trials with medications for MCI have been uniformly disappointing [14]. However, behavioral interventions involving physical [15] and mental [16] exercise, social engagement [17], and compensation strategies [18,19] have consistently shown positive effects in efforts to delay or prevent dementia. Greater use of behavioral strategies can lessen medication, health care, and long-term care utilization [20]. It is not clear whether these interventions impact the biology of the dementia, but they appear to at least mitigate the functional symptoms it produces, given the above findings. To date, these studies have largely looked at single behavioral interventions. However, dementia is a disorder where multicomponent therapies may be essential to treatment [21].

A Multi-Modal Behavioral Intervention Program

At Mayo Clinic, we have developed a multicomponent behavioral intervention for patients diagnosed with MCI and a loved one partner called HABIT (Healthy Actions to Benefit Independence and Thinking). This intervention began with a cognitive rehabilitation component because of Mayo Clinic's long history in cognitive rehabilitation for acquired brain injury. Our study first involved modification of existing compensatory memory techniques and development of a curriculum to help patients with MCI develop procedural memory around using an external memory compensation device. After involvement in brain fitness trials by some of our principal investigators, we added cognitive exercise to the program. We had long offered stand-alone support groups to our patients and partners and developed a partner education series offered in our Alzheimer's Disease Research Center, and these offerings were eventually also folded into the program that became HABIT. Finally, we opted to add yoga to the programming for its benefit on balance and flexibility improvement and because of literature supporting the benefit of mindfulness practice (which is a feature of yoga)

on emotional health and the ease of application of the yoga techniques to individuals across a range of ability levels. Thus, over the period of approximately 3 to 4 years, beginning with cognitive rehabilitation work, HABIT evolved to include 5 components because of the individual work supporting each piece.

This study focuses on the interventions used in the HABIT program. HABIT is a 5-hour-per-day, 5-day-per-week, 2-week program representing an intensive state-of-the-art behavioral and lifestyle approach to preventing progression in MCI. The 5 components are 1 hour each of (1) daily physical exercise, (2) computer-based cognitive exercise (brain fitness), (3) patient and family education, (4) separate support groups for MCI patients and partners, and (5) memory support system compensation training. As described below, there is research to support each of these separate interventions. However, there is little in the way of comparative effectiveness research pitting each component against the other in terms of the highest value for patients and their families.

Physical Activity

Exercise interventions are being explored as a means to minimize cognitive decline in MCI. One study observed significant improvement in memory in participants who engaged in a 24-week physical exercise regimen [15]. Participants were encouraged to perform at least 150 min of moderate intensity exercise per week. Walking was most frequently recommended, but participants were free to choose other forms of exercise. However, these participants did not necessarily meet contemporary criteria for MCI.

Computer-Based Cognitive Exercise ("Brain Fitness")

In appropriately designed studies, various investigators, including the principal investigator (PI) of this study, have shown that computerized brain fitness training can improve cognitive function in normal older adults [16,22,23]. Barnes et al [24] reported no significant benefit from brain fitness training in MCI. However, the memory effect size they observed was nearly the same as that reported as significant in the larger study in cognitively normal older adults. This suggests that the Barnes and colleagues' study (and other studies) may be underpowered to see the modest beneficial effect of computer training in MCI. Other recent trials of a computer training program have suggested modest benefit on cognition and mood in patients with MCI [25]. Belleville et al [26] also reported positive outcomes for a program combining education, computer-based attention training, and internal memory compensatory training. They reported improved list-recall memory and face-name association performance, as well as improvements in subjective memory report and sense of subjective well-being. Another randomized case-control trial of a computer training program demonstrated improvements in story recall, abstract reasoning, and behavioral problems in participants with MCI [27].

Education

There is evidence that psychoeducation can bring about positive change in care partners of those with MCI [28,29]. Although most research focuses on dementia education for caregivers, a recent study in patients with MCI found that care partners were more depressed when they had less knowledge of MCI at the time of diagnosis [30]. Studies further show that greater knowledge increases feelings of competence, confidence, and less overall distress in care partners [29].

Support Groups

It is becoming apparent that social support is an important aspect of behavioral interventions. For example, research shows that patients with MCI who participate in group therapy learn acceptance of their diagnoses and what lies ahead of them, and care partners become more aware and accepting of cognitive and behavioral problems [31]. A high level of social engagement can reduce the mortality risk in individuals with MCI [32]. More recent studies are reporting similar findings—there is greater acceptance in participants and care partners undergoing group therapy versus wait-list controls [17,33]. Furthermore, a meta-analysis [33] revealed that a higher risk of AD was associated with loneliness and lower levels of social networking and physical activity.

Memory Support System Compensation Training

The Memory Support System (MSS) involves use of a portable calendar and note-taking system that includes three sections: (1) appointments, (2) "to-do" items, and (3) a notes section. MSS trainers provide persons with MCI and a care partner training sessions following a structured curriculum of orientation, modeling, practice, and homework assignments. Standardized forms are used daily to document adherence to the process by the trainers as well as to note individuals' progress. The MCI state is the ideal target for this intervention as people demonstrating MCI typically have "cognitive reserve" in the form of preserved procedural memory even in the face of clinically significant declarative memory impairments [34]. We have specifically studied this strategy and found significant effect sizes on memory-based everyday functions at training end (d=1.0), 2-month follow-up (d=.88), and 6-month follow-up (d=.56) compared with no-treatment controls [18].

As detailed above, multiple kinds of behavioral interventions have shown promise for different outcomes (eg, quality of life [QoL], functioning, cognition, and self-efficacy). Thus, in the HABIT program and in this trial, we opted to measure all of these outcomes, given that individual studies suggest different interventions may impact different outcomes.

Older adults and especially those with cognitive impairment have unique challenges in adhering to behavioral interventions [35,36]. Yet, in our preliminary studies of various combinations of these behavioral interventions, we have found reasonable enrollment, adherence, and excellent retention of patients with MCI and their partners in this type of research [37]. Preliminary comparative effectiveness data comparing MSS with computerized training showed that the MSS is superior to computerized training on a memory-related functional outcome [38], and both MSS and computer training appeared to contribute to improved partner mood in comparison with providing no treatment [39]. The study described herein used the recruitment, intervention, and evaluation infrastructure of the clinical HABIT program to expeditiously determine which behavioral intervention outcomes related to the prevention and

delay of dementia are most important to persons with MCI and their partners.

Aims

Engage patients and care partners who have previously completed a multicomponent behavioral intervention for MCI in the prioritization of outcomes for persons diagnosed with MCI. This aim is complete and under review elsewhere.

Incorporate the results of aim 1 into a study comparing the effectiveness of each of the 5 components of the program with the other components, where the results of aim 1 provide the primary outcome for aim 2.

Demonstrate the use of a novel research design and data analysis method for the evaluation of multicomponent interventions that allows all participants to receive 80% of the intervention.

In aim 1 of this study, we surveyed patients with MCI and their partners who had previously completed the clinical HABIT program. We found these patients and partners ranked QoL and self-efficacy as the most important outcomes for the behavioral interventions to target [40].

In aim 2, we will simultaneously compare all 5 components of the full HABIT program and their respective contributions with these patient-centered outcomes. This program capitalizes on an accomplished multidisciplinary team that included neuropsychologists, dementia educators, exercise specialists, nurse practitioners, social workers, and biostatisticians integrally, as well as substantial existing infrastructure for delivering a multicomponent behavioral intervention developed during prior collaborative grant, "A Multicenter Rehabilitation Intervention for Amnestic Mild Cognitive Impairment" (R01NR012419). That program helped develop resources across the sites involved in this study, which included Mayo Clinic campuses in Minnesota, Arizona, Florida, and the University of Washington.

Methods

Participants

Participants in the comparative effectiveness trial were identified from referrals to the HABIT program that come from the neuropsychology and behavioral neurology clinics and/or Alzheimer's Disease Research Center clinical cores of each participating site. Medical history, symptom profile, physical exam, and neuropsychological testing were reviewed by the neuropsychologists. All subjects had a clinical diagnosis of amnestic MCI (either single domain or multidomain). MCI diagnosis was based on National Institute on Aging-Alzheimer Association criteria [9]. Consecutive HABIT candidates with diagnoses of amnestic MCI (single domain or multidomain) who also met our inclusion/exclusion criteria were approached for consent. The inclusion and exclusion criteria are presented in Textbox 1.

These proposed inclusion and exclusion criteria were vetted and approved by our patient and partner advisory group before the initiation of the study.

Our target was to enroll 300 participants by having each of the 4 sites enroll 75 participants in a 16-month period (5 HABIT sessions with 15 participants each at 4 sites). On the basis of our earlier research, we anticipated only a 10% attrition rate, leaving 270 complete datasets.

Randomization

Randomization by Subtraction not Addition

At the encouragement of patient and partner advisors, we undertook a nontraditional study design. Traditional randomized controlled trials (RCTs) can be thought of as "additive" trials where randomization leads to the addition of treatments beyond placebo. Participants are confronted with a significant probability of receiving placebo (no treatment). This leads many potential participants to reject participation or to withdraw if they believe they are receiving no treatment. In contrast, this proposed trial was approached as "subtractive." People were randomized to conditions involving the withholding of one of the five interventions but receiving the other four. This innovative approach to randomization involved suppression of just one of the five treatment components. Thus, all participants received at least 80% of the menu of interventions offered in this trial. Data analysis will focus on determination of which groups had the weakest outcomes as a result of missing a given intervention (see Data Analysis below).

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Clinical dementia rating (CDR) scale score ≤0.5
- A cognitively normal care partner screened with the Mini Mental State Exam (MMSE; >24) who has at least twice-weekly contact with the participant
- Either not taking or stable on nootropics for at least 3 months
- Fluent in English (expanding the program to communities of Spanish speakers will be a high priority in subsequent dissemination studies)

Exclusion criteria

- Inclusion in another clinical trial that would exclude participation; subject will be considered for participation at the end of such a trial or as appropriate
- Medically unable to participate in all arms by virtue of visual or auditory impairments or nonambulatory status

Randomization of Sessions Not People

In the HABIT program, individualized randomization posed significant risk for diffusion of treatment effects, as the group nature of HABIT permits participants to compare their experiences. There was no blinding of intervention. Thus, we randomized by session. Sessions were offered 4 times per year at each of 4 sites. Thus, in 16 months, we had the opportunity to randomize 20 HABIT sessions (5 each at the 4 sites). We employed block randomization, seeking to assure that randomization to each of the 5 arms of the study resulted in at least 60 participants per arm, and that all sites ran each arm once. All randomization was overseen by Dr Crook (the statistician) and handled by the data management center at Mayo Jacksonville. To avoid bias in enrollment, investigators were not made aware of which arm would be delivered until each session was filled. Participants were not made aware of which arm would be delivered until day 1 of their session.

Interventions

Our intervention, using the infrastructure of the HABIT program, consisted of 10 days of intervention over 2 weeks. Although the participants were given the weekend off, they were given "homework" to practice each trained component on their own. With one of the five components randomly suppressed in the existing design, each participant and care partner received 4 hours (4 components by 1 hour each) of intervention daily. As noted above, HABIT programming initiates new healthy behavioral habits that MCI patients sustain with the support of care partners cuing, which we implemented within this study.

Yoga

Participants engaged in daily 45 to 60 min of yoga. We used yoga as it is suited to the constraints of space and the different levels of baseline physical activity of our participants and partners. We used the HABIT framework, which uses an adapted Hatha Yoga practice where participants sit on chairs for some asanas (poses) and use the chair for support for balance during other standing poses and for others parts of the sequence. This adapted Hatha Yoga style is appropriate for older adults and is both beneficial and accessible for those who have limited mobility, including those with walkers or those who are in wheelchairs. HABIT yoga also incorporates breathing and meditation and cultivates an overall sense of connection and support.

Our instructors had at least 200 hours of training and were certified. The appropriately sequenced HABIT yoga practice met the American College of Sports Medicine recommendation for older adults for muscle strengthening and flexibility. The sessions used an armless sturdy chair placed on top of a sticky mat. Instructions were mirrored for the participants (the instructor faced the students and performed a posture on the left side while instructing the right side to reduce confusion). Breathing practice focused on increasing lung capacity and oxygenation. The sessions included meditation practice to support internal focus.

The HABIT yoga intervention was intended to initiate and sustain a schedule rather than a type of physical activity. Following the 10-day program, participants and partners were encouraged to maintain a schedule of 150 min of their preferred exercise per week. Post program, we consider yoga, swimming, walking, running, or formal exercise programming (water aerobics, resistance training, etc) to count equivalently toward this total. Because most clinical trials of yoga include group classes supported by home practice, we provided a customized DVD (digital video disc) as a supplement for continued use and practice after the program to those who opt to continue yoga. The DVD included sections on the following: poses, modifications, benefits, breathing, and meditation practices.

Computerized Brain Fitness Training

We used the commercially available Posit Science product BrainHQ [41] on tablets (eg, iPads). At the time of the study, this product was the latest generation of the BrainFitness auditory processing speed program studied by Smith et al [16] and Zelinski et al [23] (and included components of the Insight visual processing speed program). Participants completed 45 to 60 min of training daily in the program and were encouraged to maintain 150 min of computerized brain training per week for 18 months post program. Participants were provided a 1-year subscription to the program. Each participant's adherence and progress were tracked through the clinician portal provided by Posit Science, both during HABIT and for 12 months post program.

Wellness Education

This education program involved daily 45- to 60-min group lecture sessions with topics including the following: Introduction to the Program, Living with MCI, Changes in Roles and Relationships, Sleep Hygiene, Steps to Healthy Brain Aging, Preventing Dementia, MCI and Depression, Nutrition and Exercise, Assistive Technologies, Participating in Research, and Community Resources.

Support Groups

We conducted separate support groups with patients and partners. Group size was limited to 10 members at a maximum. The patient group was focused on reminiscence and adaptation, while the partner groups focused on building resources for coping.

Patient

The patient support group met for 45 to 60 min daily. Homework assignments were given in the *LifeBio Memory Journal* and used as a basis for reminiscence-focused group sessions the next day. Patients also accomplished emotional processing around MCI diagnosis and lifestyle impact with a goal toward acceptance and healthy dialog with partners.

Partner

The care partner support group met separately from the patient group for 45 to 60 min daily. It involved a traditional support group with no set curriculum, but the following common caregiving themes variously emerged and were addressed in these sessions including the following: Ambiguity of the Diagnosis, Denial, Disclosure to Friends and Family, Role Changes, Communication, Emotional Adjustment, Behavior Changes in Our Loved One, Safety, Driving Issues, Planning

for the Future, Caregiver Health, Manufacturing Success, Dementia and Relationships, Communication Skills, Defense Mechanisms, Dimensions of Wellness, Effects on Emotions, Family Roles, Grief and Loss, Healthy Relationships, Intimacy Needs, Introduction to Self-Help, Ongoing Care Needs, Spirituality, Stages of Change, and Thought Restructuring. Trained group facilitators enhanced emotional support, provided guidance about communication approaches, and addressed denial, as well as the process of grief and loss associated with the diagnosis of MCI in a loved one.

MSS Compensation Training

We provided each couple with MSS training 45 to 60 min daily with initial and ending adherence sessions. The curriculum is described briefly here.

Learning Phases

We utilized 3 training stages from learning theory [42]: (1) an acquisition phase in which use of the MSS is learned, (2) an application phase in which a participant is taught to apply MSS use to his/her daily life, and (3) an adaptation phase in which a participant practices incorporating the MSS into his/her daily life to make its use habitual and allow users to benefit from spared priming abilities in MCI [43].

Intervention Plan/Questions

This set of questions used in each training session was constructed to help the participants learn each training phase. These questions cover the topics to be learned in each phase of training. Participants progressed to the next training phase after demonstrating 100% accuracy on the intervention plan/questions in a stage for 2 consecutive days.

Homework

In addition to asking the intervention plan/questions, homework was given at the end of session to focus on the practice of an MSS skill.

Importance of the Care Partner

We were aware that even in cognitively intact people, 10 hours of direct training may be insufficient for the acquisition of a new procedural learning skill [44]. As such, we included a care partner in the training to help with cuing and practice outside of the therapy sessions.

Adherence

MSS adherence (ie, how well an individual utilizes all sections of their MSS calendar system) was defined as a score of 7 or greater on the adherence assessment. The adherence assessment was given on 5 occasions: on the first day of the intervention, the last day of the intervention, and 6, 12, and 18 months post HABIT. The evaluator examined MSS compliance for 2 days that are randomly selected from the prior week. Random days are selected to offset the possibility of a participant "preparing" the calendar for the evaluator's visit.

Longitudinal Outcomes and Booster Sessions

This study was originally proposed to study 6-month outcomes. However, our funding agency's reviewers recognized that in typical neurodegenerative conditions, outcomes may diverge more clearly over time. Thus, Patient Centered Outcomes Research Institute required us to use the longitudinal time points tenable with the 5-year funding period. This was ultimately 18 months of follow-up. A robust literature suggests that "booster" sessions are helpful for behavioral interventions to have long-term impact [45]. We therefore had participants return at 6 and 12 months post intervention for a 1-day booster session where they first completed all follow-up measures and then received 1-hour sessions of the 4 intervention components of their particular study arm.

Outcomes

Table 1 lists the measurement domains and measures in each domain. The table is organized according to which member of the dyad completed the measure. As previously determined in aim 1 of the study, patients' QoL was our primary outcome.

Table 1. Treatment efficacy measures proposed to the patient and partner advisory group.

Target	Cognition	Physical function	Functional status	Mood	Quality of life	Self-efficacy	Care partner burden
Participant	Cogstate	SPPE[a]		CES-D[b], AIF[c]	QoL-AD[d]	SE[e] in MCI[f,g]	
Care partner		SPPE	ECog[h], FAQ[i]	CES-D, AIF	QoL-AD	Caregiver SE	CB[j]

[a]SPPE: Short Physical Performance Examination.

[b]CES-D: Center for Epidemiological Studies Depression Scale.

[c]AIF: Anxiety Inventory Form.

[d]QoL-AD: Quality of Life-Alzheimer's Disease.

[e]SE: self-efficacy.

[f]Modified from chronic disease Self-Efficacy Scales.

[g]MCI: mild cognitive impairment.

[h]ECog: Everyday Cognition.

[i]FAQ: Functional Assessment Questionnaire.

[j]CB: care partner burden.

Cognition

We assessed the patients' cognitive function using Cogstate [46], a computerized measure of cognition. We used the Cogstate battery specifically designed for preclinical Alzheimer and MCI populations. This includes measures of simple and choice reaction time (the detection and identification tests, respectively), a test of visual memory (the One-Card Test) and a measure of working memory (One Back Test). This was completed at baseline and at 12-month follow-up.

Physical Function

We administered a timed 400-m walk and the Short Physical Performance Examination [47], which includes a timed 4-m walk, standing side by side, semitandem and full-tandem stance, and a timed arms-folded rise from seated to standing 4 times. This was completed at baseline, intervention completion, and 12-month follow-up.

Functional Status

Activities of daily living (ADL) functional status ratings based on informant assessment were obtained at baseline, intervention completion, and 6 months, 12 months, and 18 months post intervention. The Everyday Cognition (ECog) [48] was used to assess impairments in instrumental ADL. The ECog is an informant-based measure that assesses a participant's ability to perform everyday tasks in the following areas: memory, language, visuospatial abilities, planning, organization, and divided attention. It was constructed specifically to be sensitive to changes in MCI. Factor analysis supports a 7-factor structure, including one global factor and 6 domain-specific factors. The global factor is strongly correlated with CDR score, MMSE, and clinical diagnosis. In addition to the global factor, the everyday memory factor differentiates MCI from normal cognition, and the everyday language factor differentiates MCI from dementia. Test-retest reliability over an average of 29 days is good (r=.82) [48]. The ECog was modified with its author's support to assess the participant's existing functional ability at each time point rather than the original wording comparing functioning with 10 years before to better gauge change from baseline to follow-up. Additionally, in anticipation of future long-term follow-up, ADL and instrumental ADL were further assessed with the Functional Assessment Questionnaire (FAQ) at baseline, intervention completion, and 6, 12, and 18 months post intervention. The FAQ is the standard functional measure required for use throughout the Alzheimer's Disease Research Center's network and was developed for use with dementia patients but has also shown to discriminate between normal controls and those with MCI [49]. In this regard, we surmised the FAQ would prove to be more useful in measuring advanced ADL impairments than the ECog in longitudinal follow-up.

Mood

At all assessment points, both the patient with MCI and the care partner completed the Center for Epidemiological Studies Depression Scale (CES-D). In addition, both the participant with MCI and the care partner completed the Anxiety Inventory Form, a 10-item rating scale modified from the State-Trait Anxiety Inventory [50] by the Resources for Enhancing Alzheimer's Caregiver Health project [51].

Quality of Life

Both the participant and care partner completed the QoL-ADL [52]. The QoL-ADL is a 13-item measure developed for individuals with dementia that has been utilized in MCI and with care partners. Participants and care partners were asked to rate their relationships, concerns about finances, physical condition, mood, energy level, memory, aspects of daily functioning, and overall life quality on a 4-point scale.

Participant Self-Efficacy

The MCI participants completed a measure of self-efficacy at all assessment points using modified, selected items from the chronic disease Self-Efficacy Scales [53]. The entire 3-item Do Chores Scale, 2-item Social/Recreational Activities Scale, and 4 items of the 5-item Manage Disease in General Scale were utilized based on their relevance to MCI. Original scales have reported internal consistency reliability of $r \geq .82$ and test-retest reliability of $r \geq .84$ [53]. The language from the original scales was modified to be specific to those with MCI (ie, "your memory/cognitive difficulty" rather than more general references to "your health condition"). The result is the 9-item Self-Efficacy in Mild Cognitive Impairment Scale.

Care Partner Self-Efficacy

Care partners completed the caregiving competence and mastery components of the Pearlin [54] at all assessment points. The measures reflect their titles and range from 4 to 6 items.

Care partners completed the short form of the Caregiver Burden Inventory [55] at all assessment points. This measure is an assessment of degree of stress experienced by family caregivers. It includes 12 questions concerning the effect of the participant's disability on care partners' lives. It is scored as a composite measure, combining several aspects of caregivers' reactions.

Ancillary Data

Clinical Dementia Rating

Patients were given a CDR [56], which is a structured interview designed to stage dementia. In the CDR, the patient is rated on 6 dimensions: Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care; they are then assigned a global score, which is generated via an established algorithm. A global score of ≤0.5 was required for enrollment into the study. This measurement was updated at the 18-month visit to stage the patient's cognitive impairment at study completion.

Global Cognitive Function

The Dementia Rating Scale, 2nd edition [57], was administered to help determine the overall level of cognitive functioning at baseline. This was also given at the 12-month follow-up point to characterize global cognitive functioning.

The MMSE [58] is a widely used screening measure of cognitive impairment. The MMSE was given to care partners at the eligibility session to determine whether global cognitive functioning is intact. A score of 24 was required for enrollment in the study.

Participant and Care Partner Self-Compassion

The participant with MCI and the care partner completed a measure of self-compassion at all assessment points using the 12-item short form of the Self-Compassion Scale [59]. This form has high internal consistency reliability of *r*=.87 and a very high correlation *r*=.97 with the full 26-item Self-Compassion Scale [60].

Participant and Care Partner Gratitude

The participant with MCI and the care partner completed the 6-item Gratitude Questionnaire Scale [61] at all assessment points. This Likert scale also has high internal consistency reliability of *r*=.82 and a high fit index (.95) for a single-factor model and good concurrent validity [61]. Table 2 lists the timing of the efficacy and ancillary measures used in the study.

Table 2. Timing of assessment measures.

Measure	Eligibility	Baseline	Intervention completion	6-month booster	12-month booster	18-month post (mail out)
DRS-2[a]		X			X	
MMSE[b]	X					
CDR[c]	X					By phone
Cogstate		X			X	
SPPE[d]		X	X		X	
Calendar adherence		X	X	X	X	By mail
Participant CES-D[e]		X	X	X	X	By mail
Participant QoL[f]		X	X	X	X	By mail
Participant SE[g]		X	X	X	X	By mail
Participant AIF[h]		X	X	X	X	By mail
Participant SC[i]		X	X	X	X	By mail
Participant G[j]		X	X	X	X	By mail
FAQ[k]		X	X	X	X	By mail
CB[l]		X	X	X	X	By mail
ECog[m]		X	X	X	X	By mail
Partner CES-D		X	X	X	X	By mail
Partner QoL		X	X	X	X	By mail
Partner SE		X	X	X	X	By mail
Partner AIF		X	X	X	X	By mail
Partner SC		X	X	X	X	By mail
Partner G		X	X	X	X	By mail
Activity log				X	X	By mail

[a]DRS-2: Dementia Rating Scale, 2nd edition.
[b]MMSE: Mini Mental State Exam.
[c]CDR: Clinical Dementia Rating.
[d]SPPE: Short Physical Performance Examination.
[e]CES-D: Center for Epidemiological Studies Depression Scale.
[f]QoL: quality of life.
[g]SE: self-efficacy.
[h]AIF: Anxiety Inventory Form.
[i]SC: self-compassion.
[j]G: gratitude.
[k]FAQ: Functional Assessment Questionnaire.
[l]CB: care partner burden.
[m]ECog: Everyday Cognition.

Data Management

The study utilized Web-based electronic data capture in REDCap software [62] using forms previously created for use in our earlier study (Grant R01NR012419). The REDCap application uses PHP + JavaScript programming languages and a MySQL database engine. The forms were securely accessible at each site from computers or mobile devices with a Web browser. The data forms and data files are stored on a server hosted by the Mayo Clinic Center for Clinical and Translational Science (Grant UL1 RR024150).

Data Analysis

Aim 1

Data analysis for aim 1 is complete and reported elsewhere.

Aim 2

To determine the degree to which the different components of the HABIT program contribute to improvements in each of the targeted outcomes, we will utilize linear mixed effect models approach that accounts for the randomized complete block design that was employed in the assignment of treatment combinations to study sessions within each site . In these models, we will include indicators for the different treatment effects, as well as indicators for potential confounding features such as age, sex, study site, and study session. Using these analyses, we will test for improvements from baseline over follow-up by testing for the significance of interactions between the variables representing study components and those reflecting follow-up period. These tests are similar to paired *t* tests but are more flexible. For example, they allow simultaneous analysis of data from more than 2 time points, and they enable the inclusion of covariates that may differ from baseline to follow-up.

We will examine the significance of the different treatment effects both with and without adjustment for potential confounders such as gender, age, and baseline scores on the Dementia Rating Scale. We will also explore potential heterogeneity of treatment effects by assessing interactions between treatments and gender, age, and baseline Dementia Rating Scale score of the patient and relationship of the partner (spouse vs other).

Aim 3

We aim to illustrate the efficiency of our novel design and statistical analysis methods for the evaluation of multicomponent interventions. The need for multicomponent studies is so critical that the Food and Drug Administration has gone so far to issue a plan for how to ensure combination (multicomponent) trials meet its standards [63]. Typical clinical trials often contrast one treatment to another (often a placebo). In the case where multiple treatments are studied, it is possible to employ fractional factorial designs [64]. In these designs, subsets of experimental combinations are carefully selected to enable the estimation of treatment effects of interest. As these designs compare an experimental condition with no active treatments to experimental condition with only one or two treatments, we opted to pursue a different experimental approach. In this approach, we formed 5 distinct treatment group combinations by removing a single component of the 5 possible components comprising the HABIT program. As part of this proposed effort, we will assess the efficiency of this study design in comparison with 2-arm studies (ie, treatment vs control) and fractional factorial designs. In our application of this study design, we randomly assigned one of these five treatment combinations to study session, stratified by study location in such a way that imbalance is minimized. Our existing study design meets the following constraints: (1) each study site (Arizona, Florida, Minnesota, and the University of Washington) administered each candidate treatment combination once and (2) each treatment combination was given 4+ times for a total of at least 20 sessions of treatment.

Power Analysis

In aim 2, we will conduct a randomized trial to assess the ability of the different components of the HABIT program to effect change in patient QoL. As outlined above, analyses will be based on data gathered from approximately 300 individuals with amnestic MCI participating in one out of a total of 20 sessions. Randomized complete block study design was employed to assign treatment combinations within study sites. We used approaches developed for this design to estimate the power to conclude that a specific HABIT component provided benefit on the primary outcome. Data from our existing clinical sample and a matched, nonrandomized, untreated control group (collected for a different project by author JF) provided initial estimates for this simulation. We computed the expected variance of the estimated treatment effect for one HABIT component by extracting the appropriate value from the variance-covariance matrix derived from the design matrix corresponding to the allocation of treatment groups within the study. Using this, we estimated the magnitude of the effect size (difference score divided by its standard deviation) that is detectable with 80% power using a 2-sided .05 level test. The results of this effort suggest that we have 80% power to conclude that a treatment component is efficacious if it is associated with an improvement of 0.53 standard deviation units (d=0.53) while accounting for effects due to the other treatment components, study sites, and sessions within sites. We have observed differences larger than this in previous studies. For instance, we observed that training in the MSS improves ECog scores by nearly 0.9 standard deviations at first follow-up in a previous study [18]. Therefore, as we undertake the planned data analysis at study end, we will have sufficient power to detect the meaningful changes that we expect to observe.

Results

Enrollment for the trial began in September 2014 and was completed in August 2016. Figure 1 depicts our enrollment success. We screened all patients seen by our general clinical diagnostic neuropsychology services as potential candidates for the HABIT program (N=1245). Most of our patients are not candidates for HABIT because they did not meet MCI due to AD criteria (eg, they were cognitively normal after evaluation or had progressed to dementia or had cognitive impairment due to another known neurologic disorder such as epilepsy). A less common reason a patient would not be a candidate for HABIT was the absence of a study partner. Eventually we determined

that 486 of our patients seen during the study enrollment period were eligible for the trial. Of those, 272 consented to participate in study. Past research suggests the primary reasons for nonenrollment of potential participants were time and distance involved, which are required to receive the intervention [35]. Thus, in our enrollment window, we were able to enroll a little over 90% of our targeted 300 participants. However, this required the conduct of extra HABIT sessions at each Mayo site. Ultimately, Mayo Minnesota, Mayo Florida, and Mayo Arizona conducted 6 HABIT sessions each. The University of Washington, with its later start, conducted 5 sessions. Table 3 lists site by arm enrollments. Demographics for the overall enrolled sample are listed in Table 4. Longitudinal follow-up to our key time points of 6, 12, and 18 months is partially completed and is now ongoing. Follow-up time visits will continue through February 2018.

Figure 1. Recruitment and enrollment.

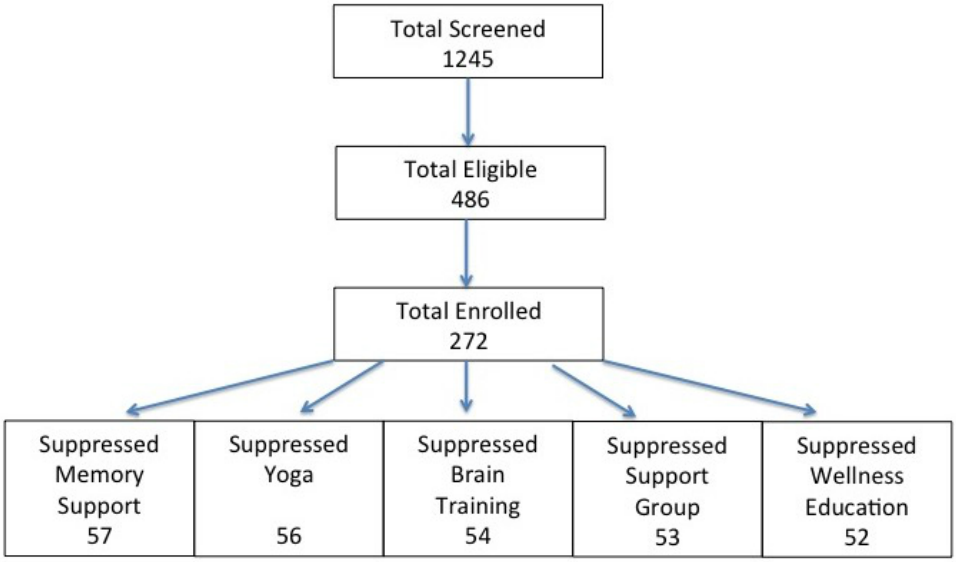

Table 3. Site by arm enrollment; per arm.

Suppressed	Yoga	Group	Education	Brain fitness	Memory support system	Total enrolled
Arizona	14	15	17	21 (11+10)	18	85
Florida	13 (5+8)	13	8	9	10	53
Minnesota	22	17	19 (9+10)	12	19	89
University of Washington	7	8	8	12	10	45
Total	56	53	52	54	57	272

Table 4. Sample demographics.

Variable	Participants (N=272)	Partners (N=272)
Age, mean (SD[a])	75.2 (7.6)	70.3 (10.1)
Education, mean (SD)	16.1 (2.8)	16.1 (2.7)
Female, n (%)	111 (40.8)	187 (68.7)
Nonwhite, n (%)	11 (4.0)	16 (5.9)
Cohabiting with study partner, n (%)	239 (87.9)	
Spouse of participant, n (%)		226 (83.1)
Median income, in US dollars	$75,000-99,000	$75,000-99,000
Taking anti-depressant, n (%)	106 (39.0)	60 (22.1)
Taking memory medication, n (%)	103 (37.9)	
Mini Mental State Exam, mean (SD)		28.9 (1.3)
Dementia Rating Scale, mean (SD)	128.8 (11.2)	

[a]SD: standard deviation.

Discussion

This paper describes the protocol for the study "Comparative Effectiveness of Behavioral Interventions to Prevent or Delay Dementia" (ClinicalTrials.gov Identifier: NCT0226575). Included is a description of the rationale, design, power analysis, and analysis plan. Moreover, because enrollment is complete and we are in follow-up phases of the study, we have included enrollment data from the trial.

Strengths

The study has several strengths. First, this is comparative effectiveness research, permitting comparison of different behavioral interventions. Second, the primary outcome was selected by prior patients. All participants received some form of treatment. The patient-centered comparative effectiveness design features have supported high retention of participants. Finally, the participants are well characterized.

Limitations

There are also several key limitations of this study. This was not a double-blinded trial, so the investigator was aware of the intervention component that was missing and could conceivably bias outcomes. Informed consent also resulted in participants' awareness that they are missing one component (eg, education), possibly impacting their expectations or leading them to identify and initiate that component on their own (eg, exercise). In an attempt to measure this possibility, we inquired at follow-up visits about other activities individuals engaged in outside of HABIT recommendations.

In addition, a weakness of our chosen comparative effectiveness design is that it does not permit comparison with no treatment. Still, our rather unique design of suppressing one of five treatments should allow us to examine the contribution of each component to the primary and secondary outcomes. Also, this grant period runs for only 3 years, limiting the number of sessions and length of the follow-up we can achieve for these participants.

This intervention targeted participants with amnestic MCI. This is because the intervention targeted memory impairments consistent with likely underlying AD pathology. This means we did not address other cognitive deficits such as language dysfunction. As such, these results may not be generalizable to individuals with nonamnestic MCI subtypes. These populations could certainly be targets for future research. Moreover, our cohort not well representative of the general population with MCI. Our cohort has high education attainment and high socioeconomic status. The treatment is intense, requiring 4 hours of participation per day, Monday through Friday for 2 weeks. This level of intensity may have served to further limit patient and partners' ability to participate.

Finally, we do not believe this intervention will have disease-modifying effects and therefore have no mechanism for assessing whether it did. The goal of the study is to assess the impact on QoL, self-efficacy, functional status, and other mood-related variables for individuals with amnestic MCI (and their partners) despite the probable progression of their disease pathology. We anticipate publication of our findings within the next couple of years.

Acknowledgments

The design and conduct of this trial was aided by patient and stakeholder advisory boards. This study was reviewed and approved by the institutional review boards of the Mayo Clinic (PR14-000885) and the University of Washington (#49235). All participants and partners have signed written consent during which they were informed of study procedures, potential risks, benefits, and their rights, including the right to withdraw consent. Study results will be published in the scientific literature, at professional conferences, to the patient and stakeholder advisory board, and to patient advocacy and community organizations. This study was supported

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Authors' Contributions

GS, MC, JF, and DL contributed to the design of the study and wrote the protocol; they are also overseeing the conduct of the trial. GS, MC, JF, DL VP, SH, AL, CH, MM, MGR, AC, MC, MB, AF, and JE have been involved in recruiting the participants and establishing eligibility. GS, MC, JF, DL, VP, SH, AL, SL, CH, MM, MGR, AC, MC, DH, JW, CHS, LK, PL, MB, and AF have been involved in delivering the intervention and collecting the data. MM, CH, AF, JE, and MB have primary responsibility for data entry. ND, SH, and JC are responsible for creating the database, ensuring data quality and security, and carrying out the eventual data analysis.

Conflicts of Interest

None declared.

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Abbreviations

AD: Alzheimer disease
CDR: clinical dementia rating
CES-D: Center for Epidemiological Studies Depression Scale
DVD: digital video disc
ECog: Everyday Cognition
FAQ: Functional Assessment Questionnaire
HABIT: Healthy Actions to Benefit Independence and Thinking
MCI: mild cognitive impairment
MMSE: Mini Mental State Exam
MSS: Memory Support System
QoL: Quality of Life

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Protocol

Improving Transition to Employment for Youth With Physical Disabilities: Protocol for a Peer Electronic Mentoring Intervention

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Abstract

Background: Although youth with disabilities have much to gain from employment readiness programs, they are often excluded from or have limited access to vocational programs. One encouraging approach to address gaps in vocational programming is through peer electronic mentoring (e-mentoring), which may facilitate a smoother transition to adulthood by offering support to enhance coping skills. Despite the increase in online communities, little is known about their impact on vocational mentoring for youth with physical disabilities and their parents.

Objective: The aim of this paper is to develop, implement, and assess the feasibility of an online peer mentor employment readiness intervention for youth with physical disabilities and their parents to improve their self-determination, career maturity, and social support compared to controls.

Methods: A mixed-methods feasibility randomized controlled trial (RCT) design will be conducted to develop and assess the feasibility, acceptability, and initial efficacy of the "Empowering Youth Towards Employment" intervention. Youth (aged 15 to 25) with physical disabilities and their parents will be randomly assigned to a control or experimental group (4-week, interactive intervention, moderated by peer mentors).

Results: Data collection is in progress. Planned analyses include pre-post measures to determine the impact of the intervention on self-determination, career maturity, and social support. A qualitative thematic analysis of the discussion forums will complement the surveys to better understand why certain outcomes may have occurred.

Conclusions: Our intervention includes evidence-informed content and was co-created by a multi-disciplinary group of researchers and knowledge users. It has the potential for widespread implications as a cost-effective resource to supplement educational and vocational programming for youth with disabilities.

Trial Registration: Clinicaltrials.gov NCT02522507; https://clinicaltrials.gov/ct2/show/NCT02522507 (Archived by WebCite at http://www.webcitation.org/6uD58Pvjc)

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KEYWORDS

social support; mentor; social inclusion; youth; disability; rehabilitation; occupational therapy

Introduction

Background

Although cultivating an appropriate labor supply is critical for economic growth, Canada currently faces a labor shortage [1-3]. One response to enhancing the labor force is to include under-utilized groups, such as people with disabilities, who are critical to a successful economy. Despite the strong business case for hiring people with disabilities, youth with disabilities have consistently low employment rates (eg, half or less) compared to youth without disabilities [3-6]. Although youth with disabilities have much to gain from employment readiness programs, they are often excluded from or have difficulty accessing high school and community vocational programs [4-6].

One approach to address gaps in vocational programming for youth with disabilities is through peer mentoring, which can facilitate a smoother transition to adulthood by offering informational, practical, and emotional assistance to enhance coping skills [7-11]. Peer mentoring interventions for youth without disabilities have been shown to be safe, feasible, and a cost-effective alternative to traditional vocational services [12-14]. Research on mentoring for youth without disabilities has beneficial impacts on job training, educational attainment, social skills, self-esteem, and work ethic [11,15,16]. One main challenge in implementing mentoring programs is finding peer mentors who are able to meet face-to-face. Thus, electronic mentoring (e-mentoring) can provide an excellent platform to address this hurdle by increasing the availability and accessibility of peer mentors [16]. In addition, despite the increase in online communities, little is known about their impact on vocational peer mentoring for youth with physical disabilities.

Focusing on adolescents and young adults is critical because disadvantages are compounded for those who start life with a disability [17,18]. Youth with disabilities represent a unique population that faces a challenging transition with respect to developmental tasks, social development, and role functioning [18]. Moreover, increased attention is being paid to “emerging adulthood”, which is a distinct developmental period between ages 18 to 25 years. This period is characterized by identity explorations, instability, self-focus, and development of executive functioning. Such traits are vital for job skills and independence [19]. Such development periods represent a critical window of opportunity to optimize and solidify positive behaviors and prevent impaired work productivity for youth with and without disabilities [7,17,19]. Job skill development is critical to employability and a successful transition to adulthood [17]. A recent systematic review of employment readiness programs for youth with physical disabilities revealed only 8 empirical studies. However, they showed that they have potential to improve self-confidence, self-awareness, goal setting, and knowledge of career options [20]. Common intervention components included experiential learning, mentorship, and family involvement [20]. This review revealed that there is a limited availability of such evidence-based programs for youth with physical disabilities in Canada. To date, we have not identified any vocational programs that involve e-mentoring that have been rigorously evaluated and published in the peer-reviewed literature.

Parental Support for Employment

Although there are many factors influencing employment such as individual (ie, self-care, self-efficacy, independence skills, etc) and socio-environmental factors (eg, accessible transportation, societal attitudes towards people with disabilities), in this study we focus on parental support [12,20,21]. Our previous research suggested this is an area that is worthy of further attention to enhance employability of youth with disabilities [20,21]. Parents are a vital source of support for young people (with and without disabilities) and play a key role in youth’s decision to obtain employment [21,22]. Although parents often provide a positive influence for youth without disabilities, this is often not the case for youth with disabilities who encounter overprotection or discouragement regarding employment [21]. Research consistently shows that parents raising a child with a disability often struggle with encouraging independent skills, especially with self-care and transportation, which are essential elements of work readiness [23-25]. Therefore, there is a critical need for interventions fostering positive parent expectations and promoting youth autonomy for those with disabilities. Specifically, researchers have noted that more parent-to-parent connections are needed to help youth with disabilities transition to adulthood and improve their competitiveness in the workforce [10,21,26]. Although some employment readiness interventions have a parental component, little is known about their effectiveness and few, if any studies in the peer-reviewed literature, have an e-mentor approach [20]. Our intervention actively involves parents and a separate parent-to-parent mentorship component to help empower them to encourage independence skills among youth with disabilities.

The Need for Peer Mentoring Among Youth With Disabilities

A method to help address gaps in vocational programming is through peer mentoring [27]. There is a strong empirical basis for using mentoring as an intervention for youth who may be disadvantaged in work and school, such as those with disabilities [27]. Evidence accrued from reviews on the impact of peer support programs among adults without disabilities, and youth with and without disabilities, shows that they are a cost-effective way to augment vocational and educational services and promote positive behaviors, improve self-efficacy, quality of life, and employment [7,27-31]. A meta-analysis of key components of peer mentor interventions of youth without disabilities included trained mentors, monitored implementation, structured activities, and parental involvement [27]. Peer mentors can offer tangible, informational, and emotional support and companionship for youth (with disabilities) and parents [22]. However, little is known about the effectiveness of peer mentorship for youth with disabilities. Implementing a peer mentor intervention for youth with disabilities is critical because they are an overlooked and vulnerable population with unique social and vocational needs. They experience periods of developmental, emotional and social changes, and major life transitions compared to other youth [17]. Further, youth with physical disabilities encounter

different challenges than youth with chronic illnesses because their condition is often visible and they also encounter difficulties in mobility, speech, independence, coping, stigma, and social exclusion [32]. Peer mentors could help address some of these issues.

Online Peer Support

The Internet is a medium for interaction that can influence learning and behavior change [33-35]. Virtual communities are increasingly being used for learning, informational, and social support [33-38] for people with and without disabilities. Given that technology is already an important component of adolescents' social networks where most youth seek information and communicate over the Internet, e-mentoring interventions have potential to benefit youth with disabilities [29-41]. E-mentoring (through a secure website) is a new approach to mentoring that can provide career-related and psychosocial support by addressing many of the challenges inherent in face-to-face mentoring such as providing unlimited access to mentors, greater flexibility in establishing and sustaining relationships, and improved accessibility by removing physical and geographical barriers [42]. Despite the increase in online communities, little is known about their use and impact for vocational mentoring for youth with physical disabilities.

Peer-Moderated Versus Un-Moderated Online Support Groups

A moderator refers to a person who facilitates and reviews postings of discussants, censors the material, and often helps participants to feel at ease [43,44]. A review of moderated support groups (both chat room and bulletin board format) for cancer found that peer support groups provided encouragement, empowerment, information, and a sense of cohesion [45]. Others argue that participation in electronic discussions is often minimal without a moderator because of the lack of collaboration and encouragement of active learning [46,47]. Moderators in online support groups for people with disabilities are often untrained volunteers or health professionals who stimulate discussions by posting questions or topics of interest to the group [43,44]. It remains unclear how trained peer-moderated (versus un-moderated) online communities can influence learning, specifically vocational skills among youth with disabilities. Thus, the aim of our study is to explore how a peer-moderated employment readiness intervention influences self-determination, career maturity, and social support.

Theoretical Framework of Peer Mentoring and Social Support

We draw on LaGreca's [48] model of social support to understand the role of peer mentoring in improving employment readiness skills among youth. Peer mentoring is a form of social support and is defined as "the provision of emotional, appraisal, and informational assistance by a created social network member who possesses experiential knowledge of a specific behavior or stressor and has similar characteristics as the target population" (page 321) [49]. A peer refers to someone who shares common characteristics such as age, gender, and disability status along with individual interests. Peers are important because they can offer someone to relate to and empathize with the individual in ways that a non-peer would be unable to (eg, a healthcare provider or parent) [42,50]. In LaGreca's model, there are 4 forms of social support: tangible, informational, companionship and belong, and emotional. [48]. Tangible support involves practical assistance and encouraging persistence and optimism for resolving problems, affirmation of a peers' feelings and behaviors, and reassurance that frustrations can be handled [48]. Informational support involves providing advice, suggestions, alternative actions, feedback, and factual information [48-50]. The third form involves companionship and belonging where the reciprocal nature of interaction with appropriate accommodations for a person's disability. Finally, emotional support refers to expressions of caring, empathy, encouragement, and reassurance and is often linked with enhanced self-esteem [48-50]. These forms of support are based on experiential knowledge rather than formal training. Therefore, peer support interventions fit within a social support model and are consistent with mentoring models where career-related support (ie, tangible and informational) and psychosocial support (ie, companionship, belonging, and emotional support) are provided [51]. Peer support may operate as a mediating process during an intervention including social comparison (ie, comparison of stresses, coping strategies, support resources), social exchange (reciprocity of support), and social learning (ie, role modeling, exchange of experiential knowledge) [48-50]. Within the context of our intervention, we hypothesize that peer mentors (for both youth and parents) will act as positive role models helping to increase all forms of social support while enhancing self-efficacy and parental empowerment [48-50].

Here, we use a mixed-method design to develop, implement, and assess the feasibility of an online peer mentor employment readiness intervention for youth with physical disabilities and their parents to improve their self-efficacy, career maturity, and social support compared to controls. A mixed-method design (ie, embedded qualitative randomized controlled trial [RCT]) allows us to test the impact of the intervention as well as the content of the discussion forums. We draw on a theoretical framework to inform our understanding of the role of peer mentoring in improving employment readiness skills among youth.

Methods

Objectives

The primary objectives of this project are (1) to develop and assess the feasibility, acceptability, and initial efficacy (ie, pilot RCT) of an e-mentor employment readiness intervention for youth with physical disabilities and their parents for improving self-determination, career maturity, and social support compared to controls; (2) to document the role of mentors in the discussion forum; and (3) to explore what types of social support are provided within the discussion forums. This protocol describes a methodology designed to develop and evaluate an online employment readiness intervention for youth with disabilities.

Design

Our design involves a feasibility RCT, embedded qualitative design [52] to assess the feasibility and initial efficacy of the

e-mentoring employment readiness intervention. Mixed-method designs are commonly used when qualitative methods are embedded within a RCT [52]. This mixed-method, prospective, intention-to-treat RCT study involves an intervention group that receives the employment readiness modules and a peer e-mentor and a control group that receives the employment readiness modules only but can interact with others in their group (no e-mentor). Pre- and post-surveys (immediately following the completion of the intervention) will be conducted with both groups (ie, intervention and control). The qualitative component of the study involves analyzing the content of the discussion forums (described below).

The gold standard Medical Research Council Framework for the development and evaluation of RCTs guided our design [53]. We focus on the development and feasibility phases (to establish theoretical underpinnings and modeling to test the feasibility of key intervention components) [53]. The rationale, design, content, and length of our intervention is based on the following systematic reviews conducted by our team: (1) employment readiness interventions for youth with physical disabilities [20]; and (2) best practices of peer mentorship for improving school and work outcomes for disabled youth [54]. In addition, we conducted the following scoping reviews: (1) improving the inclusion of people with disabilities in the workforce [55]; and (2) mentoring practices for a diverse workforce [56]. Needs assessments of youth with disabilities and their parents regarding informational support for employment were also conducted [17,21].

Sample and Recruitment

Participants (youth and parents) are recruited through invitation letters from a pediatric rehabilitation hospital, disability organizations, and community centers via referrals and advertisements. This method has been useful for obtaining reasonable response rates in previous studies on employment among youth with physical disabilities [17,21,52]. Inclusion criteria for youth participants involves the following: (1) able to read and write in English; and (2) youth with a physical disability—we draw on the World Health Organization's International classification of functioning to inform our understanding of disability which is defined as impairment, activity limitation, participation restriction whereby a disability and functioning are shaped by interactions between health conditions, and contextual factors (ie, diagnoses commonly seen at our hospital such as cerebral palsy, muscular dystrophy, spinal cord injury, amputation, etc); (3) currently enrolled in or have completed a high school diploma in the applied or academic stream (to screen for cognitive impairment); (4) aged 15 to 25; (5) have access to a computer and Internet; and (6) have no paid work experience. The rationale for this age group and also for not having paid work experience is youth with disabilities often start their first employment experience later than youth without disabilities [21]. We recognize that the intervention may be somewhat time intensive for the younger ages who may still be in school. However, we intend to run the intervention during the summer break, so this should not be a concern. Exclusion criteria involve those who recently completed or currently participating in another employment readiness or peer support intervention.

Inclusion criteria for parents include (1) the parent of a youth meeting the above inclusion criteria; (2) can read and write in English; and (3) have access to a computer with Internet. A youth or parent can participate if their respective child or parent does not.

Setting

For the purpose of this study, participants (youth and parents) access a separate password-protected area of the AbilityOnline website.

Youth Employment Readiness Modules

The content and length of our intervention is evidence-based (ie, informed by 2 systematic reviews and 1 scoping review conducted by our team) [20,54-56]. The youth intervention (delivered by youth peer mentors) consists of 12 modules (3 per week over 4 weeks) and includes the following: (1) introduction and goal setting; (2) aspirations (self-awareness and self-assessment); (3) and expectations (self-awareness and self-assessment); (4) job searching techniques; (5) marketing yourself (resumes and presentation); (6) job interviews; (7) managing disability at work (self-care, disclosure, accommodations); (8) getting ready to work (transportation and essential life skills); (9) family role in supporting employment; (10) learning from professionals with disabilities; (11) social networking and community resources; and (12) referrals and next steps. Each module contains informative webpages and interactive materials (articles, videos) which can be viewed at their own pace.

Parent Modules

The parent modules (which were co-created with parents of youth with disabilities) include (1) introductions, (2) life skills, (3) managing disability, (4) family role in supporting employment, (5) aspirations and expectations for work, (6) volunteerism, (7) finding a job or volunteer position, (8) social networking and community resources, (9) helping youth prepare for job interviews, (10) learning from professionals, (11) career pathways and transitions after high school, and (12) referrals and next steps.

Intervention

The purpose of the intervention (for both youth and parents) is to provide meaningful support and access to evidence-based employment resources. The intervention, which was co-created with a knowledge user advisory group, consists of a 4-week, multi-component, interactive treatment of employment readiness modules, homework, and discussions led by trained peer mentors. The group-based intervention (10 participants per group with 4 groups, plus mentor) is hosted on the existing secure online peer networking AbilityOnline website designed for youth with disabilities and their parents.

Youth mentors present each of the topics to mentored participants in monitored interactions. They provide their own personal experiences and examples related to each topic and respond to all posts, offering informational, emotional, and social support. The discussion forum is available to the entire group and available only to participants and mentors in that particular group (ie, they cannot see participants' discussions

that are in another group). There is an option where youth can have private chats between members or with a mentor (ie, others cannot see what they say). Although we are not monitoring the content of private discussions for research purposes we log the number of private chats for each participant. Participants (youth and parents) decide when they want to log in and contribute at a time that is convenient for them. Mentors post their availability when they will be on in case participants (youth and parents) want to discuss something in real-time. There are also chat rooms that are in real-time if participants want to connect with others who are online at the same time. We instruct youth and parents to use pseudonyms and we remind them that all information shared within the forum should remain confidential and not disclosed to others.

Parents' Intervention Forum

The parent's intervention forum follows a similar design to the youth forum and includes a peer-led discussion forum (separate from youth) that contains relevant resources (for each of the topics mentioned earlier) and hosted through the AbilityOnline website. The parent's forum consists of a 4-week, multi-component, interactive treatment of how to support their youth getting started with employment through modules and discussion. The group-based intervention (10 participants per group with 4 groups and a mentor) is hosted through AbilityOnline . A trained parent peer mentor emails each parent to determine module completion, posts their own personal experiences and reflections, responds to all posts, and offers informational, emotional, and social support.

Control Groups

The control groups (for both parents and youth) have access to the modules only and do not receive peer mentorship. A researcher posts the discussion topic for the week but does not reply or encourage any follow-up discussion. Youth and parent participants are able to discuss topics and interact with others in their group but it is not facilitated by a mentor.

Peer Mentor Training

All mentors (ie, 2 youth and 2 parents) are recruited through advertisements at a pediatric rehabilitation hospital, undergo rigorous screening (background checks and interviews to ensure appropriate fit and experience), and complete a Youth Peer Mentor Training Program [57] or Family Leader Training Program [58] prior to starting. Mentors (young adults with a disability with job experience or parents of disabled youth) are trained on how to use the AbilityOnline platform. Mentors introduce the topics in the same order and are trained to respond to participant's comments in a similar manner—providing informational, appraisal, and emotional support. Prior to working with youth or parents, mentors practice their skills with fellow mentors whose recent experiences are similar to those of mentored participants (eg, training on active listening, perspective taking, confidentiality, maintaining boundaries, positive modeling, trust building through interactive training, and mentoring).

Feasibility and Sample Size

To test the primary hypothesis that a peer-mentored employment readiness intervention will have better self-determination (Arc's self-determination) [59], career maturity inventory [60], and parental support (multi-dimensional scale of perceived social support) [61] compared to youth in a non-mentored group, it is expected that a *t* test will be used. Following the guidelines of Cohen [62] and Hertzog [63] we estimated that with an alpha of .05, power of 80%, and a medium effect size (ie, 0.50), a sample size of 80 (40 in each group; experimental and control) is needed [62]. This sample is suitable for a feasibility pilot [62-64]. Data collection will take 18 to 24 months (recruited in 10 by 8 groups), including control and experimental over 4 weeks.

Procedures and Randomization

Ethical approvals will be obtained from a pediatric rehabilitation hospital and a University Research Ethics boards prior to starting. Informed consent will be acquired from all participants prior to taking part. Once participants have consented, a blocked randomization method will be used. Using a block size of 10, participants are randomly assigned to the appropriate treatment condition as they enroll in the study until the block is completed. Then the following 10 participants are assigned to the next block [65,66]. Participants are blinded to each other, unaware of any manipulation. To avoid contamination, we asked participants not to share their password.

Quantitative Data Collection

After randomization, a member of the research team asks each participant (parents and youth) to complete an online survey (pre-test) via Fluid Surveys (approximately 30 minutes to complete), stored on a secure site at a pediatric rehabilitation hospital. When complete, they are given password-protected access to the intervention through AbilityOnline. Following the intervention, participants complete a post-test survey containing the measures listed below. Demographic measures include: age, gender, type of disability, any assistive devices, education level, and access. Use and comfort level with computers and the Internet is collected at baseline to describe control and experimental groups and to assess whether they have similar characteristics.

Primary youth outcome measures include the following standardized measures, all of which have good internal consistency, construct related and criterion validity, test-retest reliability, and have been widely used for youth with disabilities [59-61]: (1) Career Maturity Inventory-Attitude Scale [60,67], a 25-item agree-disagree scale where responses form the basis for 5 subscales relating to career decision-making, including orientation, involvement, independence, compromise, and decisiveness; and (2) Arc's Self-Determination Scale, a self-report measure that assesses self-determination for adolescents with disabilities [59] with subscales on autonomy, acting on the basis of preferences and abilities (post-school directions), goal setting, and task performance.

Measures used for both parents and youth include (1) the Multi-dimensional Scale of Perceived Social Support, a self-report measure assessing sources of social support [61]; (2) Family Empowerment Scale, a 34-item rating scale to measure empowerment in families with children who have a disability [68,69]; and (3) the Ragins and McFarlin Mentor Role

Instrument [70,71] that assesses perceptions of mentoring relationships based on 5 mentoring roles in the career-related dimension and 6 mentoring roles in the psychosocial dimension and was developed based on Kram's theory [51] of mentor roles. Secondary measures include online usage such as number of modules completed and usage patterns (ie, number of times logged in, length of time spent online, number and content of postings). These analytics will be built into the web-hosting Drupal platform [72].

Results

Data collection for this study is in progress. The proposed analysis is outlined in further detail below.

Quantitative Data Analyses

Quantitative data will be analyzed using SPSS, version 22. Rates of accrual, dropout, and compliance (ie, attendance and number of postings) will be calculated. Descriptive statistics will be used to provide an overview of sample characteristics using means and standard deviations for continuous factors and frequencies and proportions for categorical factors. We will use an intent-to-treat approach to our analysis. It is expected that *t* test and chi-squared analyses will be conducted to test intervention effects (comparing baseline primary outcome measures (time 1) and post-test (time 2) data. Separate analyses will be conducted for each outcome. To control for type I error rate, Holm's sequential correction will be applied. Effect sizes for *t* tests and Cohen *d* will be reported [62]. A *P* value of less than .05 will be used as the criterion for statistical significance.

Qualitative Data Analysis

Qualitative data analysis will be used to address objectives 2 and 3 and will consist of the following: (1) open-ended questions in post questionnaires including what participants liked most and least about each module and satisfaction with the intervention (benefits, challenges, and suggestions for improvement); and (2) transcripts of the intervention discussion forums. This data will be combined with the survey data to better understand why certain difference may have occurred.

Transcripts of all open-ended survey questions, discussion forums (for both the experimental and control groups), and open-ended questions on the survey will be entered into Nvivo, 10. The analysis will begin with at least 2 investigators independently reading all transcripts. Our research questions will guide the analysis of key themes emerging from the data. An open-coding content analysis will be used to understand the role of mentors (objective 2) and types of social support provided in the forums (objective 3) [73]. We will note key common meaning units (codes) around employment readiness, social support, role of peer mentors, aspirations and expectations of work environments, and co-creation of knowledge. A constant comparative approach will be used until consensus is reached among the research team on the final coding scheme. Several strategies will be used to ensure rigor and trustworthiness (transferability, dependability, conformability) of the qualitative findings including prolonged engagement, peer debriefing, and rich descriptive accounts with quotes reflective of the range of ideas expressed by participants [73,74].

Combining Data

A mixed-method, embedded qualitative RCT design [52] will help us understand any discrepancies between expected and observed outcomes, provide insight into participant experiences and reasons for their preferences, explain how e-mentors influenced employment readiness skills (for youth) and empowerment (for parents), and what types of social support were provided. Our objectives combine quantitative and qualitative data and we will follow the guidelines of embedded qualitative RCT analysis [52,73-75]. Our findings will inform the feasibility and initial efficacy of an e-mentor employment readiness intervention for youth with physical disabilities. We hypothesize that participants in the intervention group will have significantly higher career maturity scores, self-determination, perceived social support, and family empowerment compared to controls.

Discussion

Principal Findings

This project is timely and significant: the United Nations Convention on Rights of Persons with Disabilities [76] stresses the need for people to have opportunities for freely chosen work and access to guidance programs and training. There is currently a lack of e-mentoring employment readiness interventions for youth with physical disabilities. No RCTs have been conducted on the feasibility and efficacy of online employment readiness programs for youth with physical disabilities. The goal is for this innovative approach to optimize vocational skills for youth with disabilities.

Our research addresses several important gaps in the literature. First, there is a lack of theory-driven, evidence-based employment readiness interventions for youth with physical disabilities. The few programs that do exist have not been rigorously evaluated, have small sample sizes, and lack random assignment and comparison groups [18,42]. Applying a theoretical framework could help standardize the essential ingredients of a job readiness program including peer mentors [7,37]. Second, most programs are inaccessible to youth. Third, although there are an increasing number of online peer support programs, we have not seen any that are evidence-based in the peer-reviewed literature that focus on employment readiness for youth with physical disabilities. Fourth, little is known about the role of peer-moderated online support versus un-moderated support [43].

Conclusion

Although the intervention is being evaluated in the context of youth with physical disabilities, it has potential to be used across a range of other age groups and health conditions. Given that people with disabilities are an under-represented population within the labor market, the findings could help inform needed supports related to accessing employment for this diverse group. Our intervention, co-created by a multi-disciplinary group of researchers (community members, knowledge users, and policy advisors), can serve as a stepping-stone to greater accountability and standardization of support services for students with disabilities and has potential for widespread implications as a

cost-effective resource to supplement educational and vocational programming for youth with disabilities.

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Authors' Contributions

SL, JS, MK, and JL conceived the study and developed the initial study protocol. SL wrote the protocol for publication and provided ongoing oversight for the data collection during the study. All authors read and approved the final protocol for publication.

Conflicts of Interest

None declared.

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Abbreviations

RCT: randomized controlled trial
e-mentor: electronic mentor
e-mentoring: electronic mentoring

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Protocol

Self-Management and Clinical Decision Support for Patients With Complex Chronic Conditions Through the Use of Smartphone-Based Telemonitoring: Randomized Controlled Trial Protocol

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Abstract

Background: The rising prevalence of chronic illnesses hinders the sustainability of the health care system because of the high cost of frequent hospitalizations of patients with complex chronic conditions. Clinical trials have demonstrated that telemonitoring can improve health outcomes, but they have generally been limited to single conditions such as diabetes, hypertension, or heart failure. Few studies have examined the impact of telemonitoring on complex patients with multiple chronic conditions, although these patients may benefit the most from this technology.

Objective: The aim of this study is to investigate the impact of a smartphone-based telemonitoring system on the clinical care and health outcomes of complex patients across several chronic conditions.

Methods: A mixed-methods, 6-month randomized controlled trial (RCT) of a smartphone-based telemonitoring system is being conducted in specialty clinics. The study will include patients who have been diagnosed with one or more of any of the following conditions: heart failure, chronic obstructive pulmonary disease, chronic kidney disease, uncontrolled hypertension, or insulin-requiring diabetes. The primary outcome will be the health status of patients as measured with SF-36. Patients will be randomly assigned to either the control group receiving usual care (n=73) or the group using the smartphone-based telemonitoring system in addition to usual care (n=73).

Results: Participants are currently being recruited for the trial. Data collection is anticipated to be completed by the fall of 2018.

Conclusions: This RCT will be among the first trials to provide evidence of the impact of telemonitoring on costs and health outcomes of complex patients who may have multiple chronic conditions.

Trial Registration: International Standard Randomized Controlled Trial Number (ISRCTN): 41238563; http://www.isrctn.com/ISRCTN41238563 (Archived by WebCite at http://www.webcitation.org/6ug2Sk0af) and Clinicaltrials.gov NCT03127852; https://clinicaltrials.gov/ct2/show/NCT03127852 (Archived by WebCite at http://www.webcitation.org/6uvjNosBC)

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KEYWORDS

mHealth; smartphone; multiple chronic diseases; randomized controlled trial

Introduction

Patients with chronic illnesses, particularly those with multiple chronic conditions (MCCs), face numerous challenges in the self-management of their conditions, including complex decision making, varying and often conflicting clinical management advice, and frequent hospitalizations. A 2011 Canadian Institute for Health Information study found that 3 out of 4 Canadians aged 65 years and older reported having at least one chronic condition, whereas 1 in 4 seniors reported having 3 or more conditions [1]. Although 75% of all health care costs are solely devoted to managing chronic illnesses, 5% of the population who are patients with complex conditions consumes more than 50% of all dollars devoted to health care [2]. With the increasing prevalence of chronic illnesses and MCCs [1], the sustainability of our health care system is threatened. However, through enhanced patient self-care and clinical management, considerable reductions in health care spending and improved health outcomes could be achieved.

Digital health tools may empower patients and their informal caregivers (ie, family and friends) in more effective self-management of MCCs and serve as a critical decision support tool for their health care providers (HCPs). In particular, telemonitoring enables patients to track their vital signs and symptoms and to receive automated self-care instructions. The automated instructions can be based on current physiological measurements, self-monitored symptoms, and readily analyzed trends in both [3]. Automated real-time alerts and frequently collected and analyzed physiological data can also support clinical decisions by HCPs [3].

A growing body of research on telemonitoring interventions exists, but it focuses on single conditions such as diabetes, hypertension, or heart failure (HF) [4-6]. Several studies and systematic reviews have shown that the use of telemonitoring interventions for the management of chronic conditions leads to positive health outcomes and significant reductions in health care costs [7-11]. Contradictory studies that did not find improvements often had interventions that excluded a self-care component, were difficult to use, were not adhered to by patients, or did not target the most frequently hospitalized patients [12-16]. Due to the added complexity involved, few studies have investigated the application of telemonitoring to high-risk patients with MCCs, although these patients may benefit the most from such an intervention [17-22].

This randomized controlled trial (RCT) will investigate the use of a smartphone-based telemonitoring system for the management of complex patients. Complex patients will be defined as those who are at high risk for hospitalization, exacerbations of their chronic conditions, and disease progression, as well as patients with MCCs. Specifically, patients with HF, chronic obstructive pulmonary disease (COPD), uncontrolled hypertension, chronic kidney disease (CKD), insulin-dependent diabetes, and combinations of these chronic conditions will be included in the study because of the high prevalence and costs associated with these conditions. The central research question is as follows: what is the impact of a smartphone-based telemonitoring system for patients with complex chronic illnesses on health status (with SF-36 as the primary outcome measure)? Secondary outcome measures will include cost, self-management, clinical management, health outcomes, and health service utilization.

Methods

Research Ethics Board Approval

This study has received approval from the Research Ethics Board at the University Health Network (15-9995-BE) and Mount Sinai Hospital (MSH REB 16-0093-E).

Patient Inclusion and Exclusion Criteria

The patient inclusion and exclusion criteria are provided in Textboxes 1 and 2, respectively.

Patient Recruitment

Patients will be recruited during regularly scheduled visits to the University Health Network or Mount Sinai Hospital clinics associated with their chronic illnesses. After the clinician determines that the patient is eligible for recruitment, the clinician will ask the patient if they are willing to speak to the study coordinator regarding the study. All eligible participants based on the inclusion and exclusion criteria will be asked to sign a written consent form before being enrolled in the study. After the randomization into the intervention or control groups, the study coordinator will provide the patients in the intervention group and, if appropriate, their caregivers with training on the telemonitoring system. Patients will be compensated Can $24 for their participation in the study, which will cover the cost of parking for one clinic visit.

Textbox 1. Inclusion criteria of patients for the study.

- Adults (aged 18 years or older)
- Diagnosed with one or more of the following and with the indicated criteria:
  - Heart failure (HF)
    - Followed by a cardiologist at the Ted Rogers Centre of Excellence for Heart Function, University Health Network, who has the primary responsibility for management of the patient's HF
    - Reduced ejection fraction (EF<0.40)
  - Chronic obstructive pulmonary disease (COPD)
    - Followed by a respirologist at the Asthma and Airway Centre, University Health Network, who has primary responsibility for management of the patient's COPD
    - Spirometrically confirmed diagnosis of COPD of Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II or higher (defined as postbronchodilator forced expiratory volume in 1 s [FEV_1] <80% predicted and FEV_1/FVC ratio <70%, where FVC is the forced vital capacity)
    - Smoking history of >=20 pack-years or homozygous alpha-1 antitrypsin deficiency
    - Prescribed an action plan for the early self-treatment of acute exacerbations
  - Uncontrolled hypertension
    - Followed by a hypertension specialist at the Mount Sinai Hospital, who has primary responsibility for management of the patient's hypertension
    - For patients without diabetes: blood pressure ≥140/90 mmHg auscultatory (manual measurement) or ≥135/85 mmHg oscillometric (automated measurement)
    - For patients with diabetes: blood pressure ≥130/80 mmHg
    - On two or more blood pressure lowering medications
  - Diabetes
    - Followed by an endocrinologist at the University Health Network, who has primary responsibility for management of the patient's diabetes
    - Insulin-requiring diabetes (Type 1 or Type 2)
    - Performing self-capillary glucose monitoring
  - Chronic kidney disease (CKD)
    - Followed by a hypertension specialist at the Mount Sinai Hospital, who has primary responsibility for management of the patient's CKD
    - Grade 3b-5 (estimated glomerular filtration rate<45 mL/1.73 m^2)
    - Must have uncontrolled hypertension
- Patient or their caregiver speaks and reads English adequately to provide informed consent and understand the text prompts in the smartphone app
- Ability to comply with instructions using the telemonitoring system (eg, able to stand on the weighing scale and able to answer symptom questions)

Textbox 2. Exclusion criteria of patients for the study.

Exclusion criteria

- Patients on mechanical circulatory support
- Patients on the heart transplant list
- Terminal diagnosis with life expectancy <1 year
- Dementia or uncontrolled psychiatric illness
- Resident of a long-term care facility
- On dialysis
- Unable to provide informed consent
- Unable to speak or read English

To perform the randomization, the Web-based computer-generated randomization tool, Research Randomizer (Social Psychology Network, USA, [23]) will be used to generate the sequence of intervention and control group allocation. The study coordinator performing the recruitment will be blinded until the patient has consented to participate. After obtaining consent, the study coordinator will take the top card of the prepared stack of randomization cards and will tell the patient if they are in the intervention or control group. The participants will be block randomized (blocks of 4) and stratified into groups according to their primary condition (HF, COPD, hypertension, and diabetes). The HF group will further be stratified on the basis of New York Heart Association (NYHA) classification (NYHA class 2-3, NYHA class 4), the hypertensive patients will be stratified to those with and without diabetes, and the hypertensive patients will also be stratified to those with and without CKD. The stratification of the hypertensive patients is performed because the coordination of clinical management for the combination of hypertension and CKD and of hypertension and diabetes was established between specialists who were willing to participate in this study.

In addition to asking patients whether they are interested in participating in the study during their regularly scheduled clinic visit, an additional recruitment strategy may be employed to speed up patient enrolment. The research study coordinator, an independent third party who is not part of the clinical care team, will generate an eligible patient mail-out list. This list will be derived from the patient roster at the clinics. The list will be screened and verified by the clinic nurses/physicians to ensure appropriateness as determined by the study inclusion criteria. The research coordinator will mail-out an invitation letter including a study description and consent form. The study coordinator will arrange a time to discuss in person or over the phone with patients interested in learning more about the study.

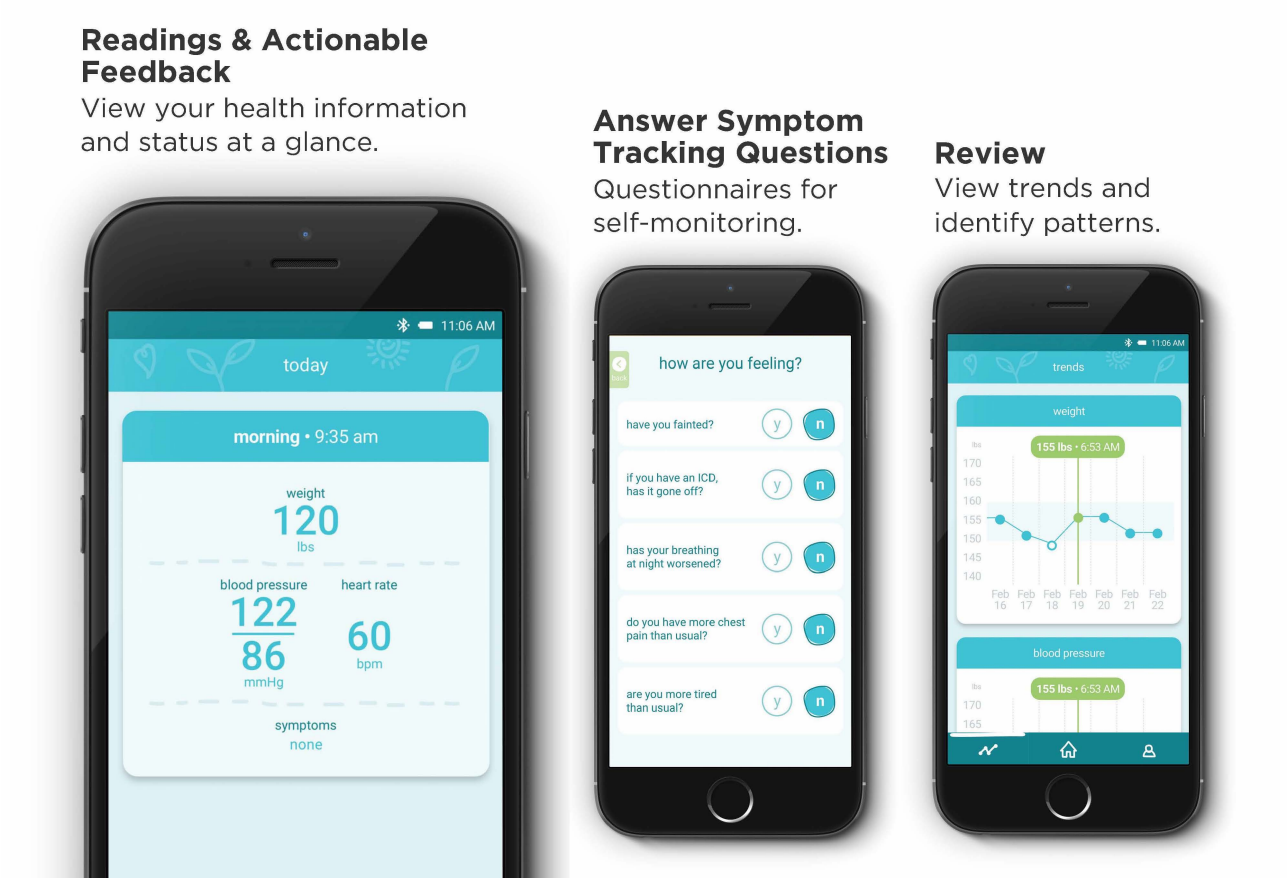
Sample Size Calculation

The primary outcome measure SF-36 was used to conduct a sample size calculation. Assuming a moderate effect size on the general health dimension of SF-36 of 10.5 points [24], a score of 57±21 for the control group [25], 80% power, and Cronbach alpha=.05 (two-sided), the sample size per group was calculated to be 63. Assuming that 15% of patients will be lost to follow-up (including mortality) [26,27], the sample size per group is 73. Hence, 146 patients will be enrolled during the trial and randomized 1:1 into control and telemonitoring groups.

Telemonitoring System

The telemonitoring system, named *Medly*, will enable patients with complex chronic illnesses, including MCCs, to take clinically relevant physiological measurements with wireless home medical devices and to answer symptom questions on the smartphone (Figure 1). The measurements will be automatically and wirelessly transmitted to the smartphone and then to a data server. Specifically, patients with HF will monitor daily weight (A&D Medical Bluetooth weighing scales), blood pressure/heart rate (A&D Medical Bluetooth blood pressure monitors), and symptoms; patients with COPD will provide self-reported symptoms; hypertensive patients will monitor their blood pressure; patients with diabetes will monitor blood sugar levels (iBGStar Bluetooth blood glucose meters); and patients with CKD will monitor blood pressure. Automated self-care instructions or messages that have been carefully developed with health care specialists will be sent to the patient based on the readings and reported symptoms [28]. If there are signs of deteriorating health of a patient, an alert will be sent to a clinician responsible for the particular chronic condition of concern in the respective specialty clinic(s) as appropriate. All the relevant patient data will be sent to the clinicians via an email alert, and they will be able to access historical and trending data of their patients through a secure Web portal.

Figure 1. Medly app screenshots.



Study Design

The control group will receive usual care, and the intervention group will receive usual care plus the telemonitoring intervention. Both groups will be followed for 6 months. Each intervention study participant will be provided with a smartphone. This phone will be loaded with the app and a limited data plan to enable data transfer. Patients will also be provided with relevant home medical monitoring devices (eg, weighing scales and blood pressure monitors for patients with HF, and blood pressure monitors for hypertensive patients). Patients will be asked to take measurements and record symptoms at a specified frequency at their homes. Home measurement frequency depends on the specific chronic condition(s). Patients with HF and COPD are generally asked to take daily measurements, whereas patients with hypertension and CKD take blood pressure readings several times per week as specified by the algorithm developed in conjunction with specialists. Patients with diabetes will be asked to follow the frequency of blood glucose measurements as recommended by their endocrinologist. Patients will be notified when they should take measurements at home through the smartphone app. Patient-specific baseline information will be entered into the telemonitoring system dashboard, such as an individual target weight range, target blood pressure range, medication list, and COPD action plan, before the patient starts using *Medly* at home.

Outcome Measures

The primary outcome will be health status as measured with SF-36 because this metric will be relevant to all chronic conditions under investigation. A secondary outcome measure will be the cost (from the health system and patient perspectives). The cost of health care will include hospitalizations, emergency department (ED) visits, clinic visits, medications, and the telemonitoring program as relevant to the different chronic illnesses. Disease-specific subanalyses on cost will also be conducted.

Other secondary outcome measures will include combined hospitalization for any reason or death from any cause within 6 months after enrolment, hospitalization, mortality, days in hospital, number of ED and clinic visits, and medications. Secondary outcome measures will also include general quality of life as measured by the EuroQol 5D-RL, anxiety and depression as measured with the Hospital Anxiety and Depression Scale [29], and patients' self-efficacy to self-manage their disease as measured with the Self-Efficacy for Managing Chronic Disease Scale [30]. See Table 1 for the assessment schedule.

The disease-specific outcome measures (generally obtained as standard of care) are listed below:

- Heart failure (HF)
  - Left ventricular ejection fraction
  - Brain natriuretic peptide
  - Self-care as measured by the Self-Care of Heart Failure Index [31]
  - HF-specific quality of life as measured by Minnesota Living with Heart Failure Questionnaire [32]

- Shortness of breath as measured using a visual analogue scale for dyspnea
- Blood work: creatinine, sodium, potassium, hemoglobin, and urate
- Prognostic score as determined by the Seattle Health Failure Model (requires: age, gender, NYHA class, weight, ejection fraction, systolic blood pressure, medication list [including diuretics], lab results [hemoglobin, lymphocytes, uric acid, total cholesterol, and sodium], and QRS interval)

- Chronic obstructive pulmonary disease (COPD)
  - Pre- and postbronchodilator-forced expiratory volume in 1 s
  - Symptoms score from the telemonitoring system
  - COPD Assessment Test score [33]
  - COPD-specific knowledge after 6 months of app usage as measured by the Bristol COPD Knowledge Questionnaire [34]
  - Patient self-efficacy at 6 months as measured by the COPD Self-Efficacy Scale [35]
  - COPD severity as measured by the BODE Index [36] at 6 months
  - Annualized exacerbation rate categorized as mild (managed in the ambulatory setting), moderate (requiring emergency room care), or severe (requiring hospital care)

- Chronic kidney disease (CKD)
  - Estimated glomerular filtration rate
  - Symptoms score from the telemonitoring system
  - Blood pressure as measured by an automatic blood pressure monitor

- Hypertension
  - Blood pressure as measured by the blood pressure monitor at the clinic using an automated device such as BpTRU and at home with the home blood pressure monitor provided. The latter involves patients measuring their blood pressure at home using a validated Bluetooth-enabled home blood pressure device twice in the morning and twice in the evening daily for 7 consecutive days. The second reading values will be averaged and the mean of the 14 readings will be used to compare baseline and exit values to assess mean change.

- Diabetes
  - Hemoglobin A_{1c}
  - Frequency and severity of hypoglycemia

Data Acquisition

Number of hospitalizations, days in hospital, number of ED and clinic visits, and medications will be determined through the hospital electronic medical records and a manual chart review of all participants' clinical records. Number of hospitalizations, days in hospital, and ED visits will be verified by patient participants through self-report with the help of a questionnaire. The cost of the intervention will be tracked, including equipment costs and human resources for clinical support, technical support, and program management. Standard cost values for a day in hospital, ED visit, etc will be used to estimate net cost savings or expenditures. Values for pre- and posttrial health outcome measures (eg, blood test results) will be obtained through hospital clinical records or through the *Medly* database for symptoms. Pre- and follow-up questionnaires (baseline, 1-month, and 6-months) will be administered to both control and intervention groups that contain the validated survey tools listed above. Participants will be able to complete the questionnaires at the clinic or complete it at home. Participants who choose to complete the questionnaire at home will be given a prepaid self-addressed envelope to mail the questionnaire back to the study team. The 1-month questionnaire will be given to participants upon enrolment with instructions to complete the questionnaire 1 month after starting the trial and to mail it back to the study team using the prepaid envelope. The study coordinator will call each participant in the 1-month period to remind participants to complete the questionnaire. Usage data, in terms of adherence to taking measurements and use of the different features, will also be data mined from the servers.

In addition to the quantitative metrics, all participants will be asked basic questions such as their self-care practice and their thoughts on telemonitoring at the start of the study. A subgroup of the intervention arm will also be interviewed individually to assess their experiences and perceptions regarding the use of *Medly* at the end of the study. The number of patients that will be interviewed will depend on when saturation of information is reached, typically 15-20 participants. The interviews will be conducted in a quiet and private space within a clinic (eg, consultation room or education room). Before the interview, participants will be informed that notes will be taken and they will be audiotaped for data analysis. The clinicians involved in the trial will also be asked to participate in interviews to determine their perceptions of *Medly*.

Data Analysis

For the primary analyses, posttrial data and change scores will be compared between the control and intervention groups using independent Student *t* test and Mann–Whitney test (for normally and not normally distributed data, respectively) based on intention-to-treat. Paired Student *t* test and Wilcoxon signed rank test will be performed to compare baseline and poststudy data within the control and telemonitoring groups. Secondary analyses seeking to assess the impact of the telemonitoring system over time by incorporating the 1-month time point will be analyzed using general linear mixed model procedures. Randomization of study participants should yield an equal distribution of possible confounding variables. However, adjustments may be required for unexpected variations in the baseline characteristics between groups (eg, age and gender). Similarly, depending on the combinations of diseases of the participants, subgroup analyses may be performed. All statistical analyses will be performed using the statistical software app SPSS (IBM Corporation, USA).

The cost evaluation will be performed by comparing any savings through reductions in hospitalization, emergency, and clinic visits through the use of the intervention. This will further include amortizing the equipment costs and factoring in additional clinical, technical, and management resources. An

analysis of indirect costs will also be performed, including such factors such as days absent from work.

Interview data will be analyzed using a conventional content analysis approach [37]. Two researchers will analyze the transcripts independently and will discuss the themes until a consensus is reached. The software program NVivo will be used to help organize the themes (QSR International, Doncaster, Victoria, Australia).

Table 1. Schedule of outcome assessments. X represents that data is collected for the specified outcome measure at that time point.

Outcome measures	Baseline	1 month	6 months
Questionnaires			
SF-36 (primary outcome)	X	—	X
Demographics	X	—	—
EuroQol 5D-5L	X	X	X
Hospital Anxiety and Depression Scale	X	—	X
Self-Efficacy for Managing Chronic Disease Scale	X	—	X
Self-Care of Heart Failure Index (only for patients with HF[a])	X	X	X
Minnesota Living with Heart Failure Questionnaire (only for patients with HF)	X	X	X
Visual analogue scale (only for patients with HF)	X	X	X
COPD[b] Assessment Test (only for patients with COPD)	X	X	X
Bristol COPD Knowledge Questionnaire (only for patients with COPD)	X	X	X
BODE Index (COPD only)	X	X	X
Health service utilization			
Number of hospitalizations in the previous 6 months	X	—	X
Number of days in hospital in the previous 6 months	X	—	X
Number of ED[c] visits in the previous 6 months	X	—	X
Number of clinic visits in the previous 6 months	X	—	X
HF-specific clinical outcomes			
Left ventricular ejection fraction	X	—	X
Brain natriuretic peptide	X	—	X
Blood work: creatinine, sodium, potassium, hemoglobin, urate	X	—	X
Seattle Health Failure Model	X	—	X
COPD-specific clinical outcomes			
Pre- and postbronchodilator (FEV_1)[d]	X	—	X
Exacerbation rate in the previous 6 months	X	—	X
CKD[e] -specific clinical outcomes			
Estimated glomerular filtration rate	X	—	X
Blood pressure	X	—	X
Hypertension-specific clinical outcomes			
Blood pressure	X	—	X
Diabetes-specific clinical outcomes			
Hemoglobin A_{1c}	X	—	X
Frequency and severity of hypoglycemia in the previous 6 months	X	—	X

[a]HF: heart failure.

[b]COPD: chronic obstructive pulmonary disease.

[c]ED: emergency department.

[d]FEV_1: forced expiratory volume in 1 s.

[e]CKD: chronic kidney disease.

Results

Participants are currently being recruited for the trial. Due to longer than anticipated development of the *Medly* platform, the telemonitoring system could not be rolled out to patients across various chronic diseases as originally intended. *Medly* has been rolled out for patients with HF, and the functionality for telemonitoring of patients with hypertension is anticipated to be available by the end of 2017. Functionality for telemonitoring of the remaining chronic diseases will follow. As of November 1, 2017, a total of 60 patients with HF have been recruited into the trial. Data collection is anticipated to be completed by the end of 2018.

Discussion

Principal Findings

This RCT aims to investigate the impact of a smartphone-based telemonitoring system on patients with complex chronic conditions, including those with MCCs. The mixed methods design of the trial will enable triangulation from a variety of data sources, including questionnaires, chart reviews, and interviews.

Evidence from previous trials indicate that positive health outcomes are achievable from telemonitoring, particularly for patients who have the most severe conditions. However, very few clinical trials have been conducted to investigate the impact of telemonitoring across MCCs [17-22]. This is largely because of the following three reasons:

First, it is difficult to develop a telemonitoring platform that can be tailored to effectively manage several combinations of chronic conditions because of the disparate needs of different chronic conditions. We have used our experience of over 10 years of designing, developing, and evaluating apps for chronic disease management using a user-centred design process to develop the *Medly* platform.

Second, determining appropriate outcome measures that are appropriate across MCCs is difficult because many metrics are disease specific. For example, reduction in hospitalization may be the primary goal of telemonitoring of patients with HF but would not be a suitable measure for chronic diseases such as hypertension. Therefore, health status as measured by SF-36 was chosen as the primary outcome measure because it is relevant to all interested chronic conditions.

Third, performing a trial of patients with MCCs requires coordination of several specialities that are typically not integrated and do not have ideal communication channels between them. For our clinical trial, we have clinical specialists as part of the research team who will be managing the patient participants. These clinical specialists are very familiar with the telemonitoring system and have already worked together in the past to coordinate care for certain complex patients.

Significance of Research

Patients with multiple chronic illnesses account for the largest expenditure of health care dollars and require the most support to manage their complex conditions. This RCT will be among the first to provide evidence of the impact of telemonitoring on costs and health outcomes of complex patients who may have MCCs. We anticipate that our health app for the management of MCCs will be a cost-effective and scalable tool that will improve health outcomes and quality of life, while empowering and reassuring patients and their informal caregivers.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

CIHR peer-review comments.

[PDF File (Adobe PDF File), 350KB - resprot_v6i11e229_app1.pdf]

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Abbreviations

CKD: chronic kidney disease
COPD: chronic obstructive pulmonary disease
ED: emergency department
FEV $_1$: forced expiratory volume in 1 s
HCP: health care provider
HF: heart failure
MCCs: multiple chronic conditions
RCT: randomized controlled trial

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Protocol

In-Person Versus eHealth Mindfulness-Based Intervention for Adolescents With Chronic Illness: Protocol for a Randomized Controlled Trial

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Abstract

Background: Eight-week mindfulness-based interventions (MBIs) have a beneficial impact on mental health and well-being in adolescents with chronic health conditions. Usually delivered in person in a group setting, these programs are difficult to access for teens with disabilities or who do not have in-person MBIs available in their communities.

Objective: This paper outlines the rationale, development, and design of a randomized controlled trial comparing the effects of an MBI delivered in person or via eHealth in adolescents with a chronic illness. Quantitative outcomes will include mindfulness skills acquisition (primary outcome), effects of the MBI on self-reported mood, anxiety, self-esteem, illness perception, and physiological stress (via salivary cortisol), and qualitative outcomes will include individual practice, participant appreciation, and adaptation of the MBI for eHealth.

Methods: This is a randomized noninferiority mixed methods study comparing 2 MBI arms: in-person and eHealth. Participants are eligible to participate if they are aged 13 to 18 years, have a diagnosis of chronic medical condition, live close enough to the recruitment hospital to participate in the in-person arm of the study, and are currently followed by a health care provider. Each participant will receive an adapted 8-week MBI delivered either in person at a tertiary pediatric hospital or via a secure audio-visual platform allowing group interactions in real time. Groups will be facilitated by 2 experienced mindfulness providers. Quantitative and qualitative data will be collected through standardized research questionnaires administered via a secure, youth-friendly online platform and through semistructured interviews, participant log books, facilitator log books, and salivary cortisol analysis. Qualitative data will be analyzed using a grounded theory model.

Results: Data collection is currently underway. Data analysis, manuscript writing, and additional publications are expected to be completed in the winter and spring of 2018.

Conclusions: Based on previous results from in-person trials conducted in adolescents and eHealth trials conducted in adults, we anticipate that both modes of delivery will significantly improve mindfulness skills acquisition, mood, anxiety, self-esteem, illness perception, and stress and that the magnitude of the effects will be correlated to the level of home practice. We predict that participants in both arms will show similar levels of home practice and that both modes of delivery will have high levels of feasibility and acceptability. If successful, this study could provide evidence for the use of eHealth in the delivery of 8-week MBIs in clinical adolescent populations, potentially increasing availability to MBIs for a large group of youth with mobility issues or living away from large urban centers.

Trial Registration: ClinicalTrials.org NCT03067207; https://clinicaltrials.gov/ct2/show/NCT03067207 (archived by WebCite at http://www.webcitation.org/6v4ZK8RBH)

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KEYWORDS

mindfulness; meditation; chronic illness; adolescent; eHealth; randomized; protocol

Introduction

Chronic illnesses in adolescents are common and have significant repercussions on normal development and well-being [1]. For instance, adolescents with chronic health conditions may experience challenges in negotiating the tasks of adolescents, such as the achievement of independence, and often report frustration with the management of their condition [2]. It is estimated that approximately 30% of adolescents have at least one moderate or severe chronic health condition such as asthma, depression, or diabetes [3]. Chronic illness can impact mental health, brain development, sleeping patterns, social functioning, school performance, and family relationships [4]. Emerging research shows that teen-adapted mindfulness-based interventions (MBIs) can provide important benefits in these areas and be a useful adjunct in the treatment of chronic health conditions [5]. Drawing from meditation practices rooted in a number of Buddhist traditions, most contemporary forms of mindfulness meditation studied in the setting of clinical research are presented in a secular context and seek to promote purposeful and nonjudgmental awareness of one's thoughts, feelings, and bodily sensations [6]. Research performed in the elementary and high school systems has shown that MBIs have a positive impact on mood, anxiety, and resilience, as well as cognitive and social-emotional development [7-9]. High-quality data in clinical youth populations is emerging and suggests similar results [10-17].

There has been a recent increase in the number of moderated and self-directed eHealth resources promoting well-being in adults and youth [18]. Research has shown that MBIs for adults with chronic diseases, delivered via phone or the Internet, have excellent feasibility and positive effects on mood and life satisfaction [19-21]. Building on the results of promising in-person pilot trials showing high validity and acceptability among adolescent study participants [11,12,15,22-28], our research will address the critical barrier of access to MBIs by exploring a new avenue for youth—eHealth—with the objective of offering equal opportunities to adolescents with reduced mobility due to illness or disability or who live in areas making it difficult or impossible for them to access in-person mindfulness groups.

To our knowledge, to date, the feasibility, acceptability, and effectiveness of youth-adapted in-person and eHealth mindfulness interventions has not been compared head-to-head in a clinical youth population. There is also a clear need for the development and adoption of eHealth interventions to support children and youth in challenging contexts such as chronic illnesses. Adolescents living in rural or underserved areas have a lower degree of access to quality care, which can adversely impact their well-being [29]. For example, a recent systematic review of psychological interventions for adolescents and young adults living with chronic illnesses emphasizes the importance of conducting high-quality randomized studies exploring new ways to support young people with chronic health conditions [30].

This article outlines the rationale, development, and design of a randomized controlled trial comparing the effects of an MBI delivered in person or via eHealth in adolescents with a chronic illness. Our primary aim is to compare the impact of an MBI for adolescents with chronic health conditions delivered either in person or via eHealth on mindfulness skills acquisition with the overarching goal of setting the stage for a larger multicenter trial within this population. The secondary objectives are to gather quantitative data on the effects of the MBI related to mood, anxiety, self-esteem, illness perception, stress (via salivary cortisol), and qualitative data on individual practice, adaptation of the MBI for eHealth, and participant experience. We hypothesize that the eHealth mode of delivery will be noninferior to the in-person mode of delivery and that the feasibility and acceptability of the MBI will be high in both groups.

Methods

Overview

This trial will use a mixed methods approach gathering (1) quantitative self-report data via validated questionnaires, (2) qualitative data on the participant's and facilitator's individual experience of the program using logbooks and semistructured interviews, and (3) biological data in the form of salivary cortisol measures as a surrogate marker for stress. Our mixed methods approach has been designed to help us better understand the potential impact, benefit, and effectiveness of an MBI on adolescents with chronic illness from both a clinical and experiential perspective.

Population

Adolescents aged 13 to 18 years with a diagnosis of chronic illness or disability receiving care at a large pediatric tertiary care hospital in Toronto, Canada, are eligible to participate. Teens with a condition lasting more than 1 year with associated functional impairment or requiring ongoing medical care will be considered to have a chronic illness [31]. Multiple clinics within the hospital have been targeted for recruitment including but not limited to Neurology, Neurosurgery, Rheumatology, Gastroenterology, Endocrinology, Hematology, and Medical Psychiatry. Examples of chronic illnesses that eligible patients may have include thalassemia, sickle cell anemia, inflammatory bowel disease, migraines, epilepsy, juvenile rheumatoid arthritis, lupus, and somatic symptom disorder.

Patients diagnosed primarily with a mental health condition such as depression and anxiety are eligible to participate provided they also have a chronic physical symptom (eg, chronic pain, headaches, abdominal pain). Participants must be fluent in English and have the intellectual capacity to provide independent consent and complete research questionnaires. To participate in the study, potential participants will need to live close enough to the recruitment hospital to commit to 8 in-person sessions delivered at the referring hospital. Youth who have previously participated in an MBI will be eligible to participate. Exclusion criteria include acute suicidal ideation unknown to or unaddressed by the referring health care provider and developmental disability such as moderate-to-severe intellectual disability impacting ability to take part in the study.

Recruitment and Enrollment

Recruitment for this study will primarily take place in outpatient clinics of a tertiary care pediatric hospital when patients arrive for their scheduled initial or follow-up appointments. Participants will be referred for inclusion in the study by a member of their health care team after discussion with the patient and family. Nurse practitioners and social workers will also screen clinic lists to proactively identify potentially eligible participants. Brief presentations of the study will occur at divisional rounds and with small groups of health providers to increase awareness about the study. Posters and brochures will be distributed throughout clinics and offices.

Recruitment will occur until a convenient sample size of 60 participants is reached or until a maximum of 3 months of active recruitment has occurred (whichever happens first). Based on the results of a pilot study performed by our research team with 19 female adolescents with chronic pain [15], we anticipate that a period of 3 months will be sufficient to enroll the targeted number of participants (average enrollment rate: 5 participants per week).

A research assistant (CV) will contact every interested participant by phone to confirm eligibility and provide additional information about the sessions. If the participant is deemed preliminarily eligible and is interested in the trial, an intake meeting will be scheduled. The meeting will take place in person or via a secured password-protected online platform (for participants who are unable to meet in person). The platform, called Zoom Video Conferencing (Zoom Video Communications Inc), will allow individual or group audiovisual meetings through a mobile phone, tablet, or computer. Meetings (both in person and via the online platform) will be led by a member of the research team with expertise in mindfulness-based cognitive therapy (MBCT) and will include an introductory video on mindfulness and a detailed explanation of the MBI, study design, and differences between the in-person and eHealth arms. A discussion about the importance of committing to individual practice and maximal attendance for mindfulness sessions will take place. The limits of confidentiality will be discussed with emphasis on sessions being a safe space where participants feel they can express themselves freely and, if placed in an eHealth group, where they will be in view of their webcam at all times, without other people in the room. Consent will be discussed with the research assistant (CV) at the end of the information meeting. Participants will be notified that both in-person and eHealth sessions will be video-recorded for internal validity purposes, and videos will only be accessed by a team member with extensive mindfulness meditation experience (coauthor CMH).

Attrition and Compliance

Based on the results of a pilot study by Chadi and colleagues [15], we expect attrition rates to be low (between 10% and 20%) and compliance (attendance for mindfulness sessions) to be high, with a mean attendance rate of 6 to 7 sessions out of 8. To our knowledge, no study examining 8-week MBIs delivered via eHealth in adolescents is currently available. Extrapolating from studies conducted in adults [22,28], we anticipate that attrition rates will be comparable for in-person and eHealth groups.

Participants having completed at least 4 of the 8 mindfulness sessions will be considered to have attended sufficiently to be included in data analysis. Pilot data on individual home practice suggests that participants will be practicing between 2 and 10 times per week for a median duration of 8 minutes per practice [15].

Study Design

The study will be conducted as a randomized noninferiority trial comparing 2 arms: an in-person and an eHealth arm, as shown in Figure 1. Each arm will consist of 2 groups with a target of 15 participants each: 1 early intervention group, 1 wait-list group. An additional feasibility arm will take place if the targeted number of study participants (60) is not reached and will be offered to participants who are interested in participating in the study but are not able to commit to the in-person mode of delivery. It will consist of 2 groups, 1 early eHealth group and 1 wait-list eHealth group.

All participants will receive the mindfulness intervention either in person or via eHealth by the end of the 6-month study period. No participants will be excluded from participation based on financial or technical limitations. Should participants not have access to an Internet connection and a mobile phone, tablet, or computer at home, the research assistant will speak with participants and their parent or guardian to explore alternate available resources (ie, connecting at school, at a local library, through a local health center, at a relative's or friend's home).

Figure 1. Experimental design of a randomized longitudinal trial comparing in-person versus eHealth delivery of an 8-week mindfulness-based intervention for adolescents with chronic illness.

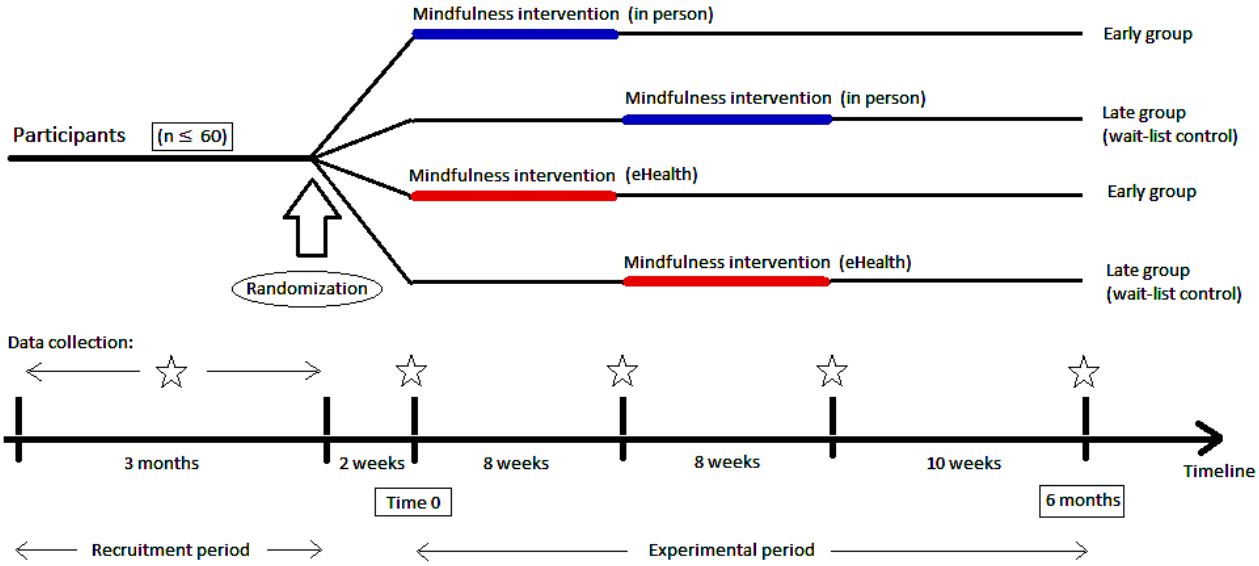

Table 1. Overview of data collection.

Time point/group	Baseline	Time 0	Week 8	Week 16	6 months
Early groups: experimental arm (distance or eHealth). MBI[a] begins at time 0.	Background data; Research questionnaires	Salivary cortisol; Participant and facilitator logs (weekly for 8 weeks)	Salivary cortisol; Research questionnaires; Semistructured interviews	Research questionnaires	Research questionnaires
Wait-list control groups: experimental arm (distance or eHealth). MBI begins at week 8.	Background data; Research questionnaires	—	Salivary cortisol; Research questionnaires; Participant and facilitator logs (weekly for 8 weeks)	Salivary cortisol; Research questionnaires; Semistructured interviews	Research questionnaires

[a]MBI: mindfulness-based intervention.

At the end of the recruitment period, once eligibility criteria have been verified, randomization will take place to separate participants in the 4 different groups within the in-person and eHealth arms of the study.

Randomization and Blinding

This study will be a single-blinded study (data analysis only). Participants will be coded using Arabic numerals. A research assistant (CV) will receive all questionnaires and saliva samples. Mindfulness facilitators will be unaware of participant identification numbers. Participants will be assigned to 1 of 4 experimental groups following a computer-generated randomization list (permuted block design, using blocks of 2 or 4). No stratification will be used. The allocation sequence will be generated by a statistician not otherwise involved in the project and passed on to a research assistant after patient identification data has been collected (ensuring that those participating in data analysis are kept blind to the allocation of each participant). Allocation sequence will be password-protected and only accessible to the statistician and research assistant. The research assistant will contact participants by phone to inform them to which group they have been randomized.

Data Collection

Data collection will take place at baseline (the day of the intake meeting), immediately before and after the MBI, and at the end of the 6-month study period, as detailed in Table 1.

All participants will provide background information at intake including age, birthdate (month/year), grade at school, past medical history, medication, and previous exposure to contemplative sciences (including yoga, meditation, and mindfulness). Participants will provide data through research questionnaires and salivary cortisol as well as individual semistructured interviews with the research assistant as detailed in Table 2. Participants will also provide information about individual practice using electronic participant logs during the 8 weeks of the MBI and when completing research questionnaires at the end of the sixth month of the study period. Data from research questionnaires and participant logs will be collected via the TickIT platform (GASQ Service GmbH), a youth-friendly, secure, digital assessment platform, via computer, tablet, or mobile phone [32]. Data compilation will take place through the TickIT platform as well.

Table 2. Summary of primary and secondary outcome measures.

Outcome	Measurement	Description	Length
Mindfulness skills acquisition (primary outcome)[a]	Mindful Attention Awareness Scale for Adolescents (MAAS-A) [41]	14-item scale evaluating level of mindfulness as a quality of attention informed by an awareness of the present experience	Approximately 3 min
Illness perception[a]	Illness Perception Questionnaire (brief) [47]	9-item measure of health-related quality of life for adolescents including those with acute and chronic health conditions. Provides an overview of how the illness is affecting overall level of functioning	Approximately 3 min
Mood and anxiety[a]	Depression Anxiety Stress Scale (DASS-21) [48]	21-item scale assessing mood and anxiety symptoms in adolescents based on self-evaluation of symptoms in the past 7 days	Approximately 5 min
Self-esteem[a]	Rosenberg Self Esteem Scale [49]	10-item scale assessing self-esteem and overall satisfaction with life	Approximately 3 min
Stress (biological marker)	Salivary cortisol levels [42]	Self-collected saliva samples using cotton swabs (Salivettes). Analysis by immunoassay	1 minute per sample
Individual practice	Data reported in participant log books	Participants will be encouraged to detail individual home practice in a digital log book noting frequency, duration, and type of practice	Approximately 5 min per week
Participant appreciation	Verbatim transcription of semistructured interviews	Individual interviews with study participants will be conducted at the end of the 8-week MBI[b] using the Zoom eHealth platform	15 to 30 min
Facilitator feedback	Data reported in facilitator log books	Facilitators will use pre- and postsession log books to detail impressions and adaptations of the MARS-A[c] program for the eHeath platform	Approximately 15 min per entry

[a]All measurement scales included in this table have been validated in clinical youth populations and have shown favorable psychometric profiles (Cronbach alpha>.80).

[b]MBI: mindfulness-based intervention.

[c]MARS-A: Mindful Awareness and Resilience Skills for Adolescents.

All interviews will take place through the Zoom electronic audio-visual platform and will be led by a female research assistant, coauthor CV (MD). The research assistant will use an interview guide adapted from a study led by coauthor SAK [33]. She will be encouraged to take field notes during the interviews and will have received individual training in conducting semistructured interviews by coauthors EW (MEd) and SAK (PhD), who both have experience leading semistructured interviews and focus groups with youth. Participants will complete the interview in a private room, at home, with no other nonparticipants or researchers present and will be informed that the research assistant is a medical doctor, has limited experience with mindfulness, and has interest in understanding the effects of mindfulness in adolescents with chronic medical conditions. The research assistant will have met with each participant at baseline either in-person or virtually through the Zoom platform for a recruitment meeting. Recordings will be password-protected and only the research assistant (who will also be transcribing the recordings) will have access to them. Transcriptions will be de-identified using a patient code available only to the research assistant. Transcripts will be returned to participants for comment and correction if there is ambiguity at the time of analysis. Data will be analyzed using a grounded theory model [34] until data saturation is reached. Data for secondary outcomes will be collected for all participants. It is expected that research questionnaires will take 15 to 20 minutes to complete.

Saliva samples for cortisol analysis will be drawn at wake-up, at 12:00 PM, at 5:30 PM, and at 7:00 PM on the first and eighth (last) MBI session to capture fluctuations in cortisol levels throughout the course of the day. Participants will receive a reminder phone call the day before each saliva sampling occurs. This will allow for the comparison of pre-post cortisol level differences between participants in the in-person and eHealth arms. Participants in the eHealth arm will be provided with prepaid postage for return of saliva samples, which they will be able to send from home. It has been shown that saliva samples can be exposed to room or exterior temperatures for at least 72 hours without affecting cortisol values [35]. Once received, saliva samples will be kept frozen until they are sent to a specialized laboratory for analysis by enzyme immunoassay [36].

Intervention

The intervention will consist of the 8-week Mindful Awareness and Resilience Skills for Adolescents (MARS-A) program [23,37], an evidenced-informed in-person MBI adapted specifically for youth with chronic health conditions. This program was developed by coauthors DV and JL at British Columbia Children's Hospital and the University of British Columbia. MARS-A is based on 3 established evidence-based MBIs for adults and adolescents: mindfulness-based stress reduction (MBSR) [6,38], mindfulness-based stress reduction for teens (MBSR-T) [13], and MBCT [39,40]. The content of the program will be the same for in-person and eHealth groups

with only minor adjustments for the eHealth group to allow all participants to remain in view of their Web camera during the sessions. All participants will be offered eight 90-minute weekly evening sessions—this represents an adaptation from adult MBSR and MBCT sessions which are typically 150 minutes in length—led by 2 experienced mindfulness providers with committed daily meditation practices (for this study, coauthor NC with the assistance of coauthor EW), who have been trained in facilitating MARS-A and who will also adapt the program for the online group. Also, while the MARS-A program usually includes a silent half-day retreat, this will not be included in the intervention so as not to disadvantage participants in the eHealth group for whom it might not be feasible to create a silent environment for a longer period of time. Sessions will include short meditation practices, breathing exercises, guided discussion (mindful inquiry), and mindful movements adapted to the context of chronic illness. All participants will also receive a copy of a self-help book for adolescents, *The Mindful Teen: Powerful Skills to Help You Handle Stress One Moment at a Time* [37] (by coauthor DV), to encourage regular practice and maintenance of newly acquired mindfulness skills. Every session will start with a brief review of home practice and will close with a discussion of the home practice for the following week. Participants will receive a weekly reminder email before each session to encourage them to complete home practice exercises and to remind them about the date and time of the next in-person or online mindfulness session. A summarized thematic overview of the MARS-A program can be found in Table 3.

Participants in the in-person groups will meet at the hospital in a designated teen-friendly room containing chairs and yoga mats. Sessions will take place once a week after school from 5:30 PM to 7:00 PM. Participants will have a 5-minute break at the middle of each session, and a snack will be provided.

Participants in the eHealth groups will be encouraged to find a quiet room with as little outside noise and distraction as possible. They will be required to have access to the Internet, a desktop or laptop computer equipped with a webcam or a tablet or mobile phone with webcam function. Participants and facilitators will be connected using the secure password-protected audio-visual platform Zoom Video Conferencing allowing up to 50 different computer connections. With this interface, participants and instructors can see and hear each other and interact in real time. This interface also allows for audio and video recording of mindfulness sessions and allows hosts to restrict access to meeting members who might not behave appropriately during sessions. All in-person and eHealth mindfulness sessions will be recorded and reviewed by a clinical psychologist with experience and expertise in mindfulness for adolescents (coauthor CMH) to ensure delivery of similar content between groups.

Table 3. Thematic overview of the Mindful Awareness and Resilience Skills for Adolescents curriculum.

Week	Theme	Content
1	Stress, Depression and Health—Introduction to Mindfulness for Adolescents	Introduction to mindfulness and group expectations Introduction to stress and depression Group and home practices: breathing practice, sitting meditation, and the body scan
2	Foundations of Mindfulness	Developing a practice Key elements of mindfulness Group and home practices: body scan, mindful eating, sitting meditation
3	Informal Mindfulness Practice and Gratitude	Introduction to informal mindfulness practice Gratitude and pleasant events Group and home practices: mindful movement, 3-minute breathing space, walking meditation
4	Unpleasant Experiences, Physical Sensations, Physical Pain	Discussion: making peace with pain, suffering, and unpleasant physical sensations Group and home practices: mindful stretching, 3-minute breathing space, body scan
5	Seeing Thoughts as Thoughts	Cognitive exercise: thought distortions Discussion: mindfulness of thoughts, rumination Group and home practices: sitting meditation, short breathing practices
6	Handling Emotions	Discussion: handling emotions Group and home practices: mindful stretching, walking meditation, 3-minute coping space
7	How to Best Take Care of Yourself	Discussion: taking care of yourself Developing an action plan for future practice Group and home practices: loving-kindness meditation, sitting meditation, 3-minute coping space
8	Continuation of Practice	Course review and evaluation Discussion: maintaining a practice End of course celebration Group practices: mindful stretching, silent sitting, 3-minute breathing space

All participants will be invited to complete daily mindfulness meditation exercises at home. Participants will be asked to fill a practice log tracking the type, duration, and frequency of individual mindfulness home practice at the beginning of each mindfulness session using the TickIT online platform used for research questionnaires.

Outcome Measures

The primary outcome measure for this study is mindfulness skills acquisition, assessed by the Mindful Attention Awareness Scale for Adolescents (MAAS-A) [41]. This 14-item Likert-type scale has been previously validated in large samples of youth with chronic health conditions. Secondary outcomes will include quantitative and qualitative measures as detailed in Table 2: illness perception, mood and anxiety, self-esteem, cortisol levels (biological marker for stress) [42], individual practice, personal experience during the program, and facilitator feedback about adaptation of the MARS-A curriculum for the eHealth platform. The authors chose salivary cortisol levels as the biological marker for this study because of the possibility of using a noninvasive sampling method (ie, in comparison with blood tests) and based on promising, yet inconsistent reports of the effects of MBIs on cortisol levels and recommendations for future study [43]. They also chose cortisol in an attempt to reproduce the findings of a pilot study by Chadi and colleagues [15] where reductions in cortisol levels during a mindfulness session had been shown to increase significantly pre- and post-MBI in a similar population of youth with chronic pain.

Power Calculations

Sample size was determined on a realistic estimate based on recruitment rates from previous pilot studies. We estimate that 3 months will suffice to recruit 60 participants. With half the participants in the in-person groups and half the participants in the eHealth groups, the study will have 80% power of confirming noninferiority of the eHealth mode of delivery with a margin of 0.45 points on the MAAS-A scale. This margin reflects the change in MAAS-A scores found in the initial validation study of the MAAS in adolescents using an in-person program [41]. Unfortunately, the convenient sample size of 60 participants used for this study will not allow sufficient power to demonstrate noninferiority of secondary outcomes assessed by standardized questionnaires, based on recent mindfulness studies using these measures in adolescent populations [44,45].

Data Analysis

Quantitative and qualitative data analysis will take place as described in Table 2. All quantitative analyses will be conducted using SPSS 24th edition (IBM Corp). Descriptive statistics will be used to identify participant demographics and disease characteristics. Quantitative self-report data will be analyzed using 1-way analyses of variance and analyses of covariance as well as paired *t* tests to assess pre-post MBI changes and to compare outcomes in the in-person versus eHealth arms as well as between the early versus wait-list control groups. A margin of 0.45 will be used as a prespecified noninferiority margin. For the primary outcome (mindfulness skills acquisition), the noninferiority question will be based on a confidence interval of 95% (2-sided) in relation to the noninferiority margin for the different treatment groups.

Transcribed interviews will be analyzed using inductive content analysis [46]. Inductive qualitative content analysis allows for a systematic classification of the data to identify categories based on patterns. By not imposing a preexisting coding schema, inductive content analysis allows for novel insights and understanding from the perspectives of participants grounded in their experiences of attending the MBI either in-person or via eHealth. Coding will be completed in a phased approach using NVivo software (QSR International Pty Lmd). In phase 1, 3 investigators (NC, EW, CV) will review 2 transcripts independently using an inductive open coding approach and then meet to develop codes based on group consensus. Codes will be discussed such that the 3 investigators agree upon (1) the major and minor themes that codes represented and (2) codes could be assigned to meaning units (phrases to several sentences). In phase 2, the same 3 investigators will code an additional 2 transcripts independently using the developed codes and meet again to discuss and confirm the coding structure. In phase 3, 2 investigators (NC, EW) will independently code the remaining transcripts. Investigators will be in contact to discuss findings should any new codes emerge from the data. Should any new codes arise, all previously coded transcripts will be reviewed for new codes. If there are disagreements among the 2 investigators, the third investigator will code to arrive at a consensus and ensure consistency with original coding structure. In phase 4, the 3 investigators will meet to collapse all resulting codes into categories. Given the ongoing communication and coding to consensus, interrater reliability will not be calculated. Major and minor themes will be presented using participant quotes (identified by participant number) in the final account of study results.

Ethics and Participant Safety

This study has received full approval from the Research Ethics Board of the Hospital for Sick Children in Toronto and has undergone a local institutional scientific review. To our knowledge, the MARS-A program does not pose any significant risks to the physical and psychological safety of participants, although some participants might experience temporary unpleasant physical, emotional, or psychological experiences while discussing symptoms related to pain, disability, or a chronic health condition. All participants will be expected to continue medical treatment as usual with their health care provider for the duration of the intervention. Activities requiring movement, such as mindful movement and walking, will be tailored to the capacities and needs of each participant and slightly adapted for the eHealth group to allow participants to stay in view of their Web camera. There is no anticipated risk with the testing of salivary cortisol. Questionnaires that will be used have been validated in studies involving large numbers of adolescents. It is possible that study participants may feel some mild degree of stress and anxiety when asked about depressive or anxious symptoms while completing the questionnaires. The process of expert mindful inquiry and facilitation itself is designed to help participants handle distress in the supportive environment of the mindfulness intervention [50]. At any time during the study, if participants disclose symptoms suggesting

a new physical or psychological condition, they will be connected with their referring provider or with an emergency contact identified by the participant during the preparticipation meeting. Confidentiality will be addressed to fulfill the requirements of the local institutional review board.

All parking costs will be reimbursed at the end of the study period, whether participants complete the study or not. Participants who complete the project and submit all research questionnaires will receive a Can $20 (US $16) gift card at the end of the study period. Participants will also receive a certificate of completion of the MARS-A curriculum at the end of the study period regardless of the number of mindfulness sessions attended.

Results

Data collection is currently underway. Data analysis, manuscript writing, and additional publications are expected to be completed in the winter and spring of 2018.

Discussion

Anticipated Results

Based on previous pilot data collected by our team [11,15,23,25], we anticipate excellent levels of feasibility, acceptability, and satisfaction among participants in the in-person groups. In a study by Chadi and colleagues [15] conducted in 19 adolescent females with chronic pain, using a similar MBI, the rate of attrition was low (17%), attendance was high (84%), and participants reported positive changes in the way they coped with their condition. We anticipate similar results in the eHealth groups, based on data from adult studies [18]. We hypothesize that both the in-person and eHealth modes of delivery will provide similar and significant improvements in mindfulness skills, mood, anxiety, self-esteem, and illness perception when compared to wait-list controls and that the magnitude of these effects will be correlated with the regularity of home practice. We project that participants in in-person and eHealth groups will have similar levels of home practice. In addition, we anticipate a significant reduction in pre-post session (5:30 PM to 7:00 PM) stress levels for both in-person and eHealth groups. Finally, we anticipate that all participants will see benefits of having incorporated mindfulness in their everyday life, such as improved level of functioning, sleep, or coping with illness, which will be captured by our semistructured interviews.

Strengths and Limitations

Anticipated difficulties described in previous studies of MBIs in clinical youth populations [26,51] such as recruitment and retention will be addressed in several ways: an efficient referral process, individual intake meetings with participants, regular communication with participants via phone and email, and incentive measures (gift cards) at project completion.

An important limitation of this study will be the small size of the sample, which was determined by several factors including funding constraints and recruitment capacity at the study site. Nevertheless, the information provided by the wide range of outcome measures and the 2 complementary approaches of the mixed methodology will provide clinically relevant information related to the eHealth delivery of MBIs in adolescents with chronic health conditions. Another limitation will be that mindfulness is challenging to measure quantitatively as a single construct. The authors are aware of some level of critique [52] that has been formulated about the MAAS scale but believe that this scale remains the best measure to test the hypothesis that the eHealth and in-person modes of delivery of the MBI are comparable in terms of teaching mindfulness content and skills.

This study will help evaluate the effectiveness of an MBI delivered to teens via technology—a highly relevant medium to connect with adolescents given their overall affinity for electronics and the Internet. Definitive results from this study will help elucidate effective ways to reach adolescents with chronic illnesses who have mobility issues or are geographically remote from urban centers, an important step in research aiming to explore how teens can integrate mindfulness in their everyday life on a long-term scale.

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Authors' Contributions

NC conceptualized the study, drafted the initial manuscript, and will lead the MBI. MK, SA, and DV contributed to the design of the study and revised the study protocol. EW will co-lead the MBI and participate in data analysis. CMH will review the content of mindfulness sessions and participate in data analysis. CV will lead participant recruitment and participate in data collection and analysis. JL and DV designed the MARS-A curriculum. All authors have revised the manuscript and will contribute to data interpretation.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Scientific peer review and acceptance letter from Mind and Life Institute.

[PDF File (Adobe PDF File), 221KB - resprot_v6i11e241_app1.pdf]

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Abbreviations

DASS-21: Depression Anxiety Stress Scale
MAAS-A: Mindful Attention Awareness Scale for Adolescents
MARS-A: Mindful Awareness and Resilience Skills for Adolescents
MBI: mindfulness-based intervention
MBCT: mindfulness-based cognitive therapy
MBSR: mindfulness-based stress reduction
MBSR-T: mindfulness-based stress reduction for teens

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Protocol

Pulmonary Rehabilitation With Balance Training for Fall Reduction in Chronic Obstructive Pulmonary Disease: Protocol for a Randomized Controlled Trial

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide. A growing body of evidence shows that individuals with COPD have important deficits in balance control that may be associated

with an increased risk of falls. Pulmonary rehabilitation (PR) is a key therapeutic intervention for individuals with COPD; however, current international guidelines do not include balance training and fall prevention strategies.

Objective: The primary aim of this trial is to determine the effects of PR with balance training compared to PR with no balance training on the 12-month rate of falls in individuals with COPD. Secondary aims are to determine the effects of the intervention on balance, balance confidence, and functional lower body strength, and to estimate the cost-effectiveness of the program.

Methods: A total of 400 individuals from nine PR centers across Canada, Europe, and Australia will be recruited to participate in a randomized controlled trial. Individuals with COPD who have a self-reported decline in balance, a fall in the last 2 years, or recent near fall will be randomly assigned to an intervention or control group. The intervention group will undergo tailored balance training in addition to PR and will receive a personalized home-based balance program. The control group will receive usual PR and a home program that does not include balance training. All participants will receive monthly phone calls to provide support and collect health care utilization and loss of productivity data. Both groups will receive home visits at 3, 6, and 9 months to ensure proper technique and progression of home exercise programs. The primary outcome will be incidence of falls at 12-month follow-up. Falls will be measured using a standardized definition and recorded using monthly self-report fall diary calendars. Participants will be asked to record falls and time spent performing their home exercise program on the fall diary calendars. Completed calendars will be returned to the research centers in prepaid envelopes each month. Secondary measures collected by a blinded assessor at baseline (pre-PR), post-PR, and 12-month follow-up will include clinical measures of balance, balance confidence, functional lower body strength, and health status. The cost-effectiveness of the intervention group compared with the control group will be evaluated using the incremental cost per number of falls averted and the incremental cost per quality-adjusted life years gained.

Results: Recruitment for the study began in January 2017 and is anticipated to be complete by December 2019. Results are expected to be available in 2020.

Conclusions: Findings from this study will improve our understanding of the effectiveness and resource uses of tailored balance training for reducing falls in individuals with COPD. If effective, the intervention represents an opportunity to inform international guidelines and health policy for PR in individuals with COPD who are at risk of falling.

Trial Registration: ClinicalTrials.gov NCT02995681; https://clinicaltrials.gov/ct2/show/NCT02995681 (Archived by WebCite at http://www.webcitation.org/6ukhxgAsg)

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KEYWORDS

COPD; pulmonary rehabilitation; balance; exercise; falls; economic analysis

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality and is expected to be among the top three causes of death in the world by the year 2020 [1]. As the population ages, the prevalence of COPD is expected to increase, which will impact health care resource utilization [1]. In 2010, the Centers for Disease Control and Prevention reported the medical costs attributable to having COPD were US $32.1 billion and by the year 2020, this is expected to increase to US $49 billion [2].

Although treatment of COPD is often focused on respiratory function, secondary impairments in skeletal muscle function, mobility, and exercise capacity are well recognized [3-5]. There is now strong evidence that individuals with COPD also have important deficits in balance control and an increased risk of falls [6-17], which has been linked to increased morbidity and mortality in this population [18,19].

Balance impairment is widely recognized as one of the most important modifiable risk factors for falls in older adults [20]. Numerous studies have documented impairments in clinical and laboratory measures of balance in individuals with varying COPD severity compared to controls [6,11,12,14-17,21,22]. Underlying mechanisms for reduced balance in COPD may include decreased levels of physical activity [11,12], peripheral muscle weakness [11], altered trunk muscle mechanics [16], hypoxemia [23], and somatosensory deficits [24]. Our work has also shown that individuals with COPD have a unique profile of balance impairment, with marked deficits in three specific subsystems of balance: biomechanics (ie, strength, range of motion, and posture), transitions (ie, change in body positions), and gait (ie, stability while walking) [17].

There is growing recognition of an increased fall risk in people with COPD [7-10]. In addition to impaired balance, other fall risk factors in COPD include the use of multiple medications, muscle weakness, cognitive impairment, and comorbidities such as osteoarthritis and osteoporosis [7]. COPD was second only to osteoarthritis in its association with the number of falls in a large cohort study of elderly women [9] and was the only chronic condition that predicted falls in a further cohort study of 16,000 participants [8]. Patients with COPD have reported a higher prevalence of falls (40%-55%) [10,11,15,17] than the general elderly population and in two prospective studies [7,10], the annual fall rate in COPD was up to five times higher than expected based on age alone. Fall-related injuries as well as associated hospitalizations are also common in people with COPD [18,25]. In those with more severe disease and depression, a history of falling is a strong predictor of mortality [19]. These data emphasize the need for the development of fall prevention strategies specific to individuals with COPD.

Pulmonary rehabilitation (PR) is recommended as standard management for COPD as there is strong evidence for its effect on improving symptoms, exercise tolerance, and health-related quality of life [26-29]. The program typically consists of supervised exercise training, disease-specific education, self-management, and psychosocial support. While exercise is viewed as the cornerstone of PR, it is largely focused on aerobic exercise to increase endurance and resistance training. International guidelines for PR do not include balance training nor fall prevention strategies and few programs include a balance assessment [26-31]. We have shown that the exercise component of conventional PR has only minimal effect on measures of balance and fall risk [32]. Therefore, to reduce falls, exercise that includes targeted balance training is needed [33]. We recently undertook a pilot randomized controlled trial (RCT) [34] to examine the effects of adding balance training alongside PR, which specifically addressed the unique profile of balance deficits we had identified in COPD [17]. We reported large and clinically important improvements in balance performance among those in the intervention group compared to controls who completed typical PR [34]. We have also found such an intervention to be easily implementable into clinical practice [35]. This study builds on our existing experience to rigorously test the effect of the intervention on balance and fall reduction in individuals with COPD.

The objectives of this study are to (1) evaluate the long-term effects of a tailored, balance exercise program on the 12-month rate of falls in individuals with COPD who are enrolled in outpatient PR compared to PR with balance exercise training; (2) determine the effects of a tailored, balance exercise program on the secondary outcomes, including measures of balance, balance confidence, and functional lower body strength; and (3) conduct an economic analysis to evaluate the cost-effectiveness of the program compared to PR with no balance training.

Methods

Ethics

The protocol has received ethics approval from the Joint West Park Healthcare Centre/Toronto Central Community Care Access Centre/Toronto Grace Health Centre Research Ethics Board (REB) (Canada); the University of Toronto REB (Canada); the Nova Scotia Health Authority REB (Canada); the University of Aveiro REB (Portugal); the University of British Columbia/Providence Health Care REB (Canada); the National Health Service REB (United Kingdom); the University of Alberta REB (Canada); the Alfred Health REB (Australia); the Royal Prince Alfred Hospital REB (Australia); and the Western Health REB (Australia).

Adverse events will be collected after individuals have consented and been enrolled in the study. Adverse events that meet the criteria for a serious adverse event (SAE) will be reported to the local REB. An SAE is defined as any adverse event that results in the following patient outcomes: death, life-threatening condition, hospitalization (initial/ prolonged), disability/ permanent damage, intervention required to prevent permanent impairment or damage, or any other medically important event [36].

Formal amendments will be submitted to each REB in consultation with local investigators should there be any modifications to the protocol. Modifications to the protocol will be final and agreed upon by all investigators before amendment applications are submitted.

Trial Registration and Reporting

The trial is registered with ClinicalTrials.gov (NCT02995681) and our protocol is reported according to the Standard Protocol Items: Recommendation for Intervention Trials (SPIRIT) checklist [37].

Study Design

We will conduct a multi-center RCT with allocation concealment as well as blinding of the outcome assessors and data analysts to group allocation. A participant flowchart is outlined in Figure 1.

Setting

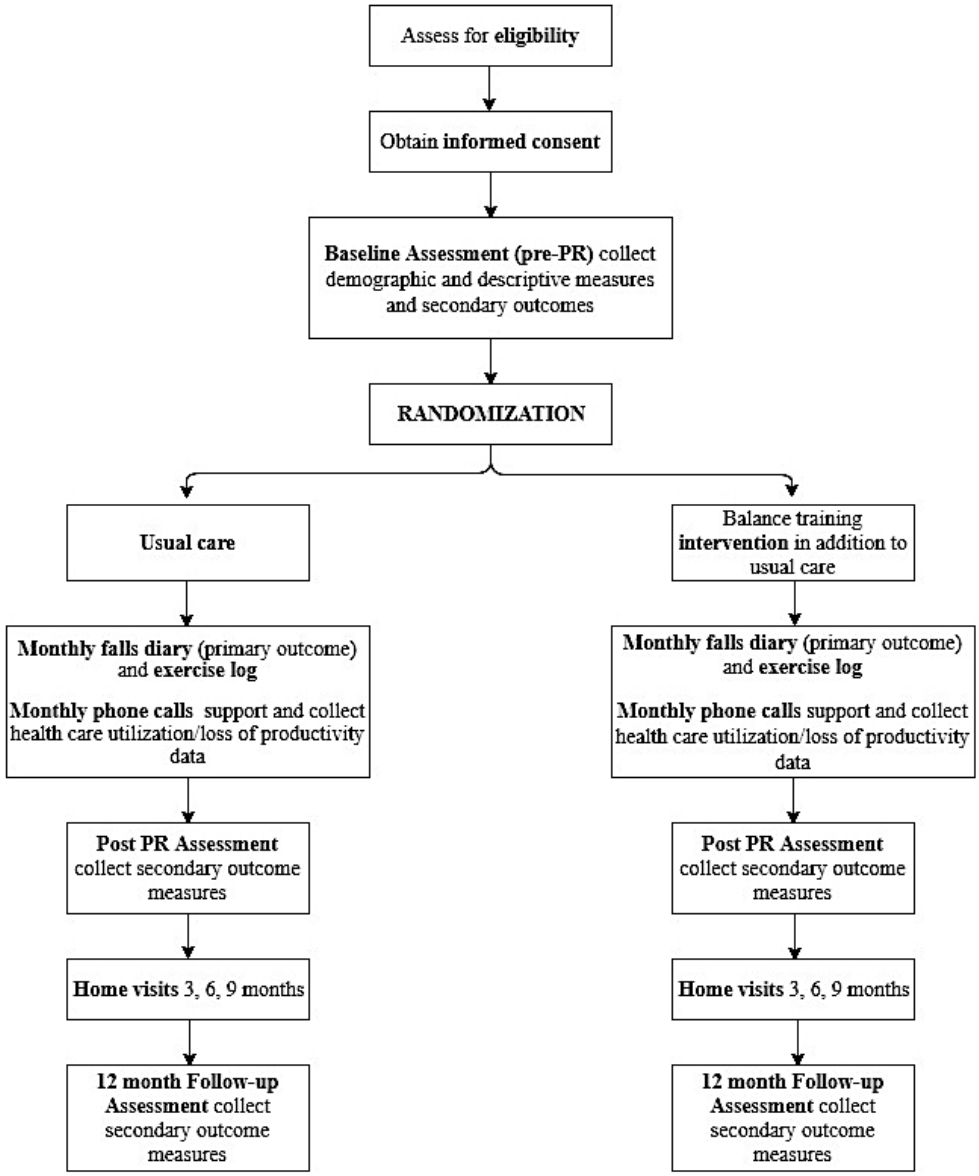
Outpatient PR programs at nine sites across four countries—Canada, United Kingdom, Portugal, and Australia—are participating in the study. PR programs in Canada, United Kingdom, and Australia are publicly funded through government-run health plans. PR programs in Portugal are only partially funded by the government.

Participants

Individuals will be considered eligible for the study if they meet the following inclusion criteria: (1) have a diagnosis of COPD based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria—postbronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio <70% [38]; (2) have a self-reported decline in balance, a fall in the last 2 years, or a recent near fall; and (3) are able to provide written informed consent.

Individuals will be excluded if they meet the following exclusion criteria: (1) are unable to communicate because of language skills (eg, communication deficit; non-English speaking in Canada, United Kingdom, or Australia; or non-Portuguese speaking in Portugal); (2) are hearing or cognitively impaired (eg, dementia or neurological condition); or (3) have evidence of a neurological or musculoskeletal condition that severely limits mobility and postural control (eg, cerebrovascular accident, Parkinson's disease, or lower limb amputee).

Figure 1. Participant flow diagram. PR: pulmonary rehabilitation.



Recruitment

Individuals will be recruited upon enrolment in PR programs at each participating site. Study information sheets were developed specific to each site and translated as required. A member of the research team not involved in the individual's clinical care will meet with potential participants to provide information about the study. If the individual agrees to participate, written informed consent will be obtained.

Recruitment will continue until the overall target population size is reached for the study. Each clinical site involved in the trial was selected based on investigator expertise and data on previous experience with study recruitment rates.

Retention

Participants may withdraw from the study for any reason at any time. Investigators may also withdraw participants from the study if they demonstrate a sudden and severe deterioration in balance (eg, due to dizziness from a medication change or a newly diagnosed medical condition) that would jeopardize their safety during balance training.

Every effort will be made to perform study assessments on individuals who withdraw from the study or who do not sufficiently adhere to the usual care or intervention protocols.

Allocation

A computer-generated block randomization table will be created by a member of the research team not involved in recruitment. A randomization schedule will be provided for each site. After an individual has been enrolled in the study and the baseline assessment has been completed, the central research coordinator will consecutively allocate participants using sealed opaque envelopes and advise each site coordinator of group allocation.

Intervention

Control: Usual Care

Participants randomized to the control group will receive usual outpatient PR. The PR programs across the nine sites are given

two to three times per week for a total duration of 8-12 weeks depending on the site. All PR programs are offered in accordance with international guidelines [26-29,31] and consist of all core components of rehabilitation including aerobic and resistance exercise, self-management education, and psychosocial support.

Upon discharge from outpatient PR, participants will receive the usual individualized home-based exercise program which will include walking and lower extremity resistance exercises two to three times a week. To control for attention between the two groups and maximize data collection, in addition to usual care, participants will receive monthly phone calls from a physiotherapist to provide support and problem solve any issues, as well as home visits at 3, 6, and 9 months.

Intervention: Tailored Balance Training

Participants randomized to the intervention group will receive a 30-minute balance training session twice per week in addition to usual PR, and will be asked to complete a third session at home each week, for a total of 90 minutes of balance training per week. This is in keeping with best practice guidelines for older adults and the design of our previous RCT in COPD [32,35,39]. The balance exercises (see Multimedia Appendix 1) will be tailored to emphasize the areas found to be most deficient in COPD [17]. Participants will receive balance training in a separate location or at a separate time from the control group. Sessions will be supervised by physiotherapists using a circuit training approach. While participants may work through stations in groups, each participant will receive individualized exercise prescription based on their baseline balance assessment, as well as recommendations for individualized exercise progression. Our previous trial demonstrated the feasibility of this approach [34]. Participants will also receive an instruction booklet that outlines their individual exercises for the once-weekly, home-based balance training session during PR.

After completion of PR, participants will complete the prescribed home-based balance training program three times per week. The home-based program will follow for the duration of the 12-month follow-up period.

Participants will receive monthly phone calls from their physiotherapist to provide support and problem solve any issues, as well as home visits at 3, 6, and 9 months to ensure proper technique and progression at home.

Outcomes

Outcome measures will be collected by a blinded assessor at baseline, at the end of PR, and at 12-month follow-up.

Primary Outcome

The primary outcome measure will be incidence of falls at 12-month follow-up. A fall will be defined as “an incident in which the body unintentionally comes to rest on the ground or other lower level which is not as a result of a violent blow, loss of consciousness, sudden onset of paralysis as in a stroke or an epileptic seizure” [40]. Based on published consensus [41], the participants will be asked, “Have you had any fall including a slip or trip in which you lost your balance and landed on the floor or ground or lower level?” Falls will be measured using monthly fall diary calendars, which are the recommended methodology for falls reporting in clinical trials [41]. All participants will receive the fall diary calendars at the time of the baseline assessment.

Participants will be asked to record falls and time spent performing their home exercise program on the fall diary calendars. They will also be asked to contact the research assistant in the event of a fall or health-related event to ensure all relevant information is included and to return completed diaries in prepaid envelopes to the research center each month. Participants who do not return the calendars or those with unclear data will be telephoned to collect the information.

Secondary Outcomes

Clinical Measures of Balance

The Berg Balance Scale (BBS) [42] is one of the most widely used and psychometrically robust clinical measures of balance for older adults. It assesses 14 tasks such as transfers, reaching, turning around, and single-legged stance. Evidence supports the BBS’s construct validity and sensitivity to change following PR in individuals with COPD [43]. Test-retest reliability and predictive validity for fall risk have been demonstrated in community-dwelling older adults [44]. The total score is out of 56 with higher scores indicating better balance. Among patients with moderate to severe COPD undergoing PR, a change of 5-7 points is clinically important [45].

The Balance Evaluation Systems Test (BESTest) [46] is a comprehensive 36-item balance evaluation tool that assesses six subsystems of balance control: biomechanics, stability limits/verticality, anticipatory postural adjustments for postural transitions, reactive postural response strategies, weighting of sensory information, and postural stability during gait. Evidence supports the BESTest’s construct validity in COPD [43] and sensitivity to change, as well as test-retest reliability and concurrent validity in adults with and without balance disorders [46]. Total scores range from 0% to 100% and a change of 13-17 points on the BESTest is clinically important in patients with COPD [45].

Balance Confidence

The Activities-Specific Balance Confidence (ABC) scale [47] requires patients to indicate their confidence in performing 16 activities without losing their balance or becoming unsteady. The ABC scale has good test-retest reliability and predicts falls in older adults residing in the community [41,44]. In patients with COPD, the ABC scale has demonstrated construct validity as well as criterion validity for falls [43]. Total scores range from 0% to 100% with higher scores for better balance confidence. A change of 19% reflects a clinically important difference for this measure in COPD [45].

Functional Lower Body Strength

The 30-second repeated chair stand test [48] will be used as a measure of functional lower body strength. The reliability and validity of this measure has been established in people with COPD and the measure is correlated to maximal voluntary force from a seated leg press [49]. The repeated chair stand test is

sensitive to change after balance training in people with COPD [34].

Descriptive Measures

Descriptive measures will include sociodemographic variables (gender, age), anthropometry (height, weight, body mass index), smoking history, oxygen use, rollator walker use, spirometry measures (FEV_1, FVC, FEV_1/FVC ratio, FEV_1% predicted, FVC % predicted), a measure of exercise tolerance (6-minute walk test [6MWT]) [50], comorbid conditions, and medication use. We will also use the Baseline Dyspnea Index (BDI) [51] and the Falls Risk for Older People-Community setting (FROP-Com) [52] to further characterize the study sample. A home exercise log will be used to describe participant self-reported adherence to the intervention.

Health Status

Health status is an important patient-reported outcome that describes health-related quality of life of patients. The European Quality of Life 5-Dimension Questionnaire (EQ-5D-5L) will be used to measure health status. It consists of five questions covering dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression with five response options indicating *no*, *mild*, *moderate*, *severe*, and *extreme* problems for each dimension [53]. The answers to the five questions included in this instrument can be converted to health utility which is an index score anchored at 0 (equivalent to dead) and 1 (for full health), with negative scores for worse than dead. The EQ-5D-5L-derived health utilities will be calculated using the recently developed scoring algorithm for Canada [54] and United Kingdom [55] and the interim algorithm for Australia and Portugal [56]. The EQ-5D-5L will be administered at baseline and at 6- and 12-month follow-up, and then used to determine quality-adjusted life years (QALY) for each respondent. For this study, the resulting adjustment is an adjustment on quality of life as we do not anticipate any differences in survival.

Economic Analysis

An economic analysis will be conducted alongside the trial using the primary outcome (ie, number of falls) and health utilities as effect measures. We will use methods consistent with standard texts and guidelines for economic evaluation [57]. The time horizon of the analysis will be the period of study follow-up (ie, 12 months). Both societal and health care payers' perspectives will be used for the analysis.

Health care resource utilization and loss of productivity related to falls and COPD will be collected during monthly phone calls to participants. During the monthly phone calls, the participants will be asked if they have had any health care appointments (ie, family doctor, walk-in/urgent care clinic, or specialist), emergency room visits, or hospital stays related to having COPD or a fall. If the participant responds "yes," the physiotherapist will then ask for details about which health care professionals were seen; what tests, medications, or treatments were ordered; and, if they were hospitalized, for how long.

The time it takes for therapists to administer the rehabilitation exercises, monthly phone calls, and home visits in both intervention and control groups will also be recorded. These resource utilizations will be converted to direct medical costs using country-specific unit costs. Indirect costs may include the productivity loss for patients, if still working, or family members who provide care/assistance to the participating patient.

Data Collection

All subject data will be deidentified and coded with a unique study identifier. Data collection forms and digital files will be securely stored as per the REB protocols.

Each site will be responsible for entering deidentified participant data into a digital database and securely sharing it with the lead investigators and central data analyst for analysis. Only the lead investigators and central data analyst will have access to the final dataset.

A data monitoring committee will be set up to monitor the trial for possible harmful effects. The committee will evaluate any adverse events to recommend whether the study should continue, be modified, or stopped due to safety concerns.

Data Analysis

The data analysts on the research team will be blinded to group allocation. Descriptive summary statistics will be reported using mean, median, and standard deviation for continuous measures, and frequency and counts for categorical variables. For the primary outcome, we will use random effect Poisson (Negative Binomial) regression model to compare the number of falls at 12-month follow-up between intervention and control groups adjusting for potential confounders, repeated measures, and clustering of participants within centers. For secondary outcomes, we will use random effect linear regression to compare intervention and control groups adjusting for potential confounders and clustering of the observations. For all measures, we will perform intention-to-treat and per protocol analysis.

We will estimate the total cost for the intervention and control groups and calculate the difference between the two groups. Similarly, for the effect measures, we will calculate the difference in the number of falls and in the QALY between groups. The summary measure for the economic analysis will be the incremental cost per number of falls averted (cost-effectiveness analysis) and the incremental cost per QALY gained (cost-utility analysis) for the intervention group compared with the control. Given that this economic analysis will be using data primarily from study participants, nonparametric bootstrap will be used to calculate the 95% confidence interval around the incremental ratios. The decision uncertainty will be presented using cost-effectiveness acceptability curves that show the probability of the intervention being cost-effective compared with the control group at a wide range of willingness to pay for a QALY [57].

No interim or subgroup analysis is planned. We will perform both intention-to-treat and per protocol analyses.

Sample Size Calculation

First, we calculated the sample size for an individually randomized two-arm study with 80% power and 5% type I error. We estimated the rate of falls for the control group as 120 per 100-person years, consistent with prospective studies

documenting fall rates in similar populations of patients with COPD in Canada and Australia [7,10]; the rate of falls in the intervention group was estimated as 84 per 100-person years, which corresponds to a 30% reduction in the rate of falls. A 30% reduction in fall rate is widely used as a clinically significant threshold in fall prevention studies and is consistent with meta-analyses demonstrating the effect of multi-component exercise on fall rate. Based on this data, the estimated number of participants in each arm with 1-year follow up is 124 patients. However, our study is a multicenter study in which participants are clustered within nine centers. Assuming a coefficient of variation of size 0.10, we need, on average, 19 participants in each arm per site, corresponding to a total of 171 participants in each arm, to account for the clustering of the study [58].

Assuming a similar clustering effect for the secondary outcomes with a sample size of 171 participants in each arm and nine centers, our study has 80% power with 5% type I error to detect differences of the following magnitudes (MCID: minimal clinically important difference):

1. Berg Balance (SD=6.15, MCID=5) differences of 3.0 units or larger.
2. BESTest (SD=13, MCID=13) differences of 6.4 units or larger.
3. ABC (SD=23.2, MCID=19) differences of 11.5 units or larger.
4. Chair stand (SD=4.8, MCID=3) differences of 2.4 units or larger.

These values are close to half the standard deviation of the outcome measures and are sufficient to detect clinically important changes [45].

We anticipate a loss to follow-up of 15%-20% based on previous trials in PR and have inflated our sample size to 400 participants (200 in each arm) to account for this. Should a participant be unable to attend an assessment session at a study center, we will minimize loss to follow-up by offering to complete assessments in the participants' homes.

Results

A Canadian Institutes of Health Research (CIHR) project grant was received to fund the study. Recruitment began in January 2017 and is anticipated to be completed by December 2019. Results are expected to be available in 2020.

Discussion

Principal Findings

The high incidence of falls and balance problems in people with COPD underscores the need for evidence-based approaches to fall prevention in this population. While studies have shown that balance training alongside PR improves measures of balance and mobility, the long-term impact on falls has not been determined. This international multi-center trial will be the first RCT of tailored balance training in people with COPD who are enrolled in outpatient PR. It is also the first study of balance training that includes an economic analysis to consider the cost-effectiveness of the intervention.

If participation in tailored balance training does decrease falls compared to usual PR, this approach will represent an innovative and potentially cost-saving strategy to prevent falls and reduce health care utilization in COPD. Our results will be relevant for guiding clinical and policy-based decision-making, given the high prevalence of COPD and potential for severe consequences of falls in this population.

Conclusions

In conclusion, this study will provide evidence on the effectiveness of tailored balance training for individuals with COPD who have a history of falling or a self-reported decline in balance skills. If effective, the results of this study could be used to inform future international guidelines and health policy for PR in this population.

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Authors' Contributions

MKB, DB, and RSG conceived of the study, participated in its design, and drafted the protocol. JA, PGC, GD, KH, SLH, AEH, AL, AM, EHS, and MKS participated in the design and provided feedback on the protocol. RM developed the sample size calculation and drafted the data analysis section of the protocol. FX developed the economic analysis section of the protocol. CE is managing the study and helped draft the protocol manuscript. All authors read and approved the final protocol manuscript. All authors will participate in drafting future publications.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Balance training exercise flow sheet.

[PDF File (Adobe PDF File), 44KB - resprot_v6i11e228_app1.pdf]

Multimedia Appendix 2

CIHR peer-review report.

[PDF File (Adobe PDF File), 553KB - resprot_v6i11e228_app2.pdf]

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Abbreviations

6MWT: 6-minute walk test
ABC: Activities-Specific Balance Confidence
BBS: Berg Balance Scale
BDI: Baseline Dyspnea Index
BESTest: Balance Evaluation Systems Test

CIHR: Canadian Institutes of Health Research
COPD: chronic obstructive pulmonary disease
EQ-5D-5L: European Quality of Life 5-Dimension Questionnaire
FEV1: forced expiratory volume in 1 second
FROP-Com: Falls Risk for Older People-Community setting
FVC: forced vital capacity
GOLD: Global Initiative for Chronic Obstructive Lung Disease
MCID: minimal clinically important difference
PR: pulmonary rehabilitation
QALY: quality-adjusted life years
RCT: randomized controlled trial
REB: Research Ethics Board
SAE: serious adverse event
SPIRIT: Standard Protocol Items: Recommendation for Intervention Trials

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Protocol

Dry Needling for Patients With Neck Pain: Protocol of a Randomized Clinical Trial

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Abstract

Background: Neck pain is a costly and common problem. Current treatments are not adequately effective for a large proportion of patients who continue to experience recurrent pain. Therefore, new treatment strategies should be investigated in an attempt to reduce the disability and high costs associated with neck pain. Dry needling is a technique in which a fine needle is used to penetrate the skin, subcutaneous tissues, and muscle with the intent to mechanically disrupt tissue without the use of an anesthetic. Dry needling is emerging as a treatment modality that is widely used clinically to address a variety of musculoskeletal conditions. Recent studies of dry needling in mechanical neck pain suggest potential benefits, but do not utilize methods typical to clinical practice and lack long-term follow-up. Therefore, a clinical trial with realistic treatment time frames and methods consistent with clinical practice is needed to examine the effectiveness of dry needling on reducing pain and enhancing function in patients presenting to physical therapy with mechanical neck pain.

Objective: The aim of this trial will be to examine the short- and long-term effectiveness of dry needling delivered by a physical therapist on pain, disability, and patient-perceived improvements in patients with mechanical neck pain.

Methods: We will conduct a randomized, double-blind, placebo-controlled trial in accordance with the CONSORT guidelines. A total of 76 patients over the age of 18 with acute or chronic mechanical neck pain resulting from postural dysfunction, trauma, or insidious onset who are referred to physical therapy will be enrolled after meeting the eligibility criteria. Subjects will be excluded if they have previous history of surgery, whiplash in the last 6 weeks, nerve root compression, red flags, or contraindications to dry needling or manual therapy. Participants will be randomized to receive (1) dry needling, manual therapy, and exercise or (2) sham dry needling, manual therapy, and exercise. Participants will receive seven physical therapy treatments lasting 45 minutes each over a maximum of 4 weeks. The primary outcome will be disability as measured by the Neck Disability Index. Secondary outcomes include the following: pain, patient-perceived improvement, patient expectations, and successful blinding to the needling intervention. Outcome measures will be assessed at 4 weeks, 6 months, and 12 months by an assessor who is blind to the group allocation of the participants to determine the short- and long-term treatment effects. We will examine the primary aim with a two-way, repeated-measures analysis of variance with treatment group as the between-subjects variable and time as the within-subjects variable. The hypothesis of interest will be the two-way group by time interaction. An a priori alpha level of .05 will be used for all analyses.

Results: Recruitment is currently underway and is expected to be completed by the end of 2017. Data collection for long-term outcomes will occur throughout 2017 and 2018. Data analysis, preparation, and publication submission is expected to occur throughout the final three quarters of 2018.

Conclusions: The successful completion of this trial will provide evidence to demonstrate whether dry needling is effective for the management of mechanical neck pain when used in a combined treatment approach, as is the common clinical practice.

Trial Registration: ClinicalTrials.gov NCT02731014; https://clinicaltrials.gov/ct2/show/NCT02731014 (Archived by WebCite at http://www.webcitation.org/6ujZgbhsq)

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KEYWORDS

neck pain; dry needling; physical therapy

Introduction

Neck pain is common, with 30%-50% of the population afflicted in a given year [1]. Symptoms of neck pain persist longer than 12 months in 37% of patients [2]. Neck pain is ranked fourth highest out of all 291 conditions studied in the Global Burden of Disease 2010 study measured by years lived with disability [3]. In the United States, estimated increases in expenditures for patients with spine pain have increased 65% from 1997 to 2005 [4]. Patients with neck pain account for 10%-20% of all patients seen in outpatient physical therapy [5,6].

Commonly, physical therapists utilize patient education, exercise, mobilization, manipulation, massage, and electrophysical modalities when treating patients with mechanical neck pain. Yet the most recent Cochrane reviews on patient education [7], exercise [8], and manual therapy (ie, joint mobilization [9] and massage [10]) find a lack of high-quality evidence to support these interventions independently. There is some evidence that multi-modal physical therapy treatment consisting of a combination of exercise and mobilization/manipulation seems to be more effective than either intervention alone [11].

Dry needling has emerged as a treatment modality that is widely used in the clinical environment to address a variety of musculoskeletal conditions including neck pain [12-14]. Dry needling is growing in popularity despite a lack of clinical trials examining its effectiveness, likely due to the ease of applying dry needling in a clinical setting [15,16]. Dry needling is a technique in which a fine needle is used to penetrate the skin, subcutaneous tissues, and muscle with the intent to mechanically disrupt tissue without the use of an anesthetic [17].

Most commonly, dry needling targets myofascial trigger points (MTrPs), which are described as localized hypersensitive spots in a palpable taut band of muscle [18-28]. These hyperirritable spots can be classified as active MTrPs when they produce spontaneous pain and, when palpated, reproduce a patient's familiar pain. Latent MTrPs do not produce spontaneous pain and are only painful upon palpation [29]. Many studies have shown that MTrPs are prevalent in patients with chronic neck pain [30-34]. It has been reported that MTrPs in the neck and shoulder commonly result in limited range of motion in the neck, neck pain, headache, and dizziness [28,33,35].

There have been five recent studies examining dry needling performed by a physical therapist for patients with neck pain. Four of the trials examined the short-term effectiveness of dry needling: three in chronic mechanical neck pain [21,24,28] and one in acute mechanical neck pain [23]. The results of these studies demonstrated that dry needling decreases pain intensity and increases pain pressure threshold in the short term; the longest follow-up was 4 weeks. One recent trial examined the long-term effectiveness of dry needling, which was performed on patients with chronic nonspecific neck pain [36]. At 6-month follow-up, the dry needling and passive stretching group demonstrated significant and clinically relevant improvements in pain, disability, and range of motion when compared to passive stretching alone. These results suggest that dry needling warrants further investigation for the treatment of neck pain.

Recent systematic reviews suggest that dry needling can be recommended in the short and medium term to reduce neck and shoulder pain [37] and for musculoskeletal pain [38]. Yet those reviews concluded that there was limited evidence to support dry needling's effectiveness in the long term for reducing pain or improving function, especially when compared to other physical therapy interventions. Both authors recommended further studies with adequate sample sizes to examine dry needling effectiveness in both the short and long term on reducing pain and improving function.

The majority of the studies included in the recent reviews compared dry needling to control, sham, or to another intervention directly. Not only is this not consistent with how dry needling is commonly used clinically by physical therapists, but emerging evidence suggests that dry needling, when performed in combination with other interventions, may be more effective at reducing lower back pain than when performed alone [39]. This suggests that dry needling, when combined with other interventions (ie, multi-modal treatment), may result in an improved treatment effect when compared to dry needling performed in isolation.

The majority of existing studies lack adequate sample sizes, only collect short-term outcomes, frequently examine dry needling as a stand-alone intervention, and only treat one muscle for one to two sessions, which is not consistent with how dry needling is commonly performed clinically. Typically, clinicians will perform an examination to locate active and latent MTrPs and needle numerous active trigger points in a single session. They may then dry needle the patient over many sessions to achieve optimal effects. With the high prevalence of neck pain and its contribution to prolonged disability in patients, it is essential to identify optimal treatment approaches [1-3,5,6,40,41]. Therefore, the aim of this randomized clinical trial is to examine the long-term effects of a combination of manual therapy, exercises, and dry needling to the cervicothoracic region on pain and disability in individuals with acute or chronic mechanical neck pain resulting from postural dysfunction, trauma, or insidious onset who are referred to physical therapy.

We hypothesize that patients who receive dry needling, manual therapy, and exercise will achieve greater reductions in pain

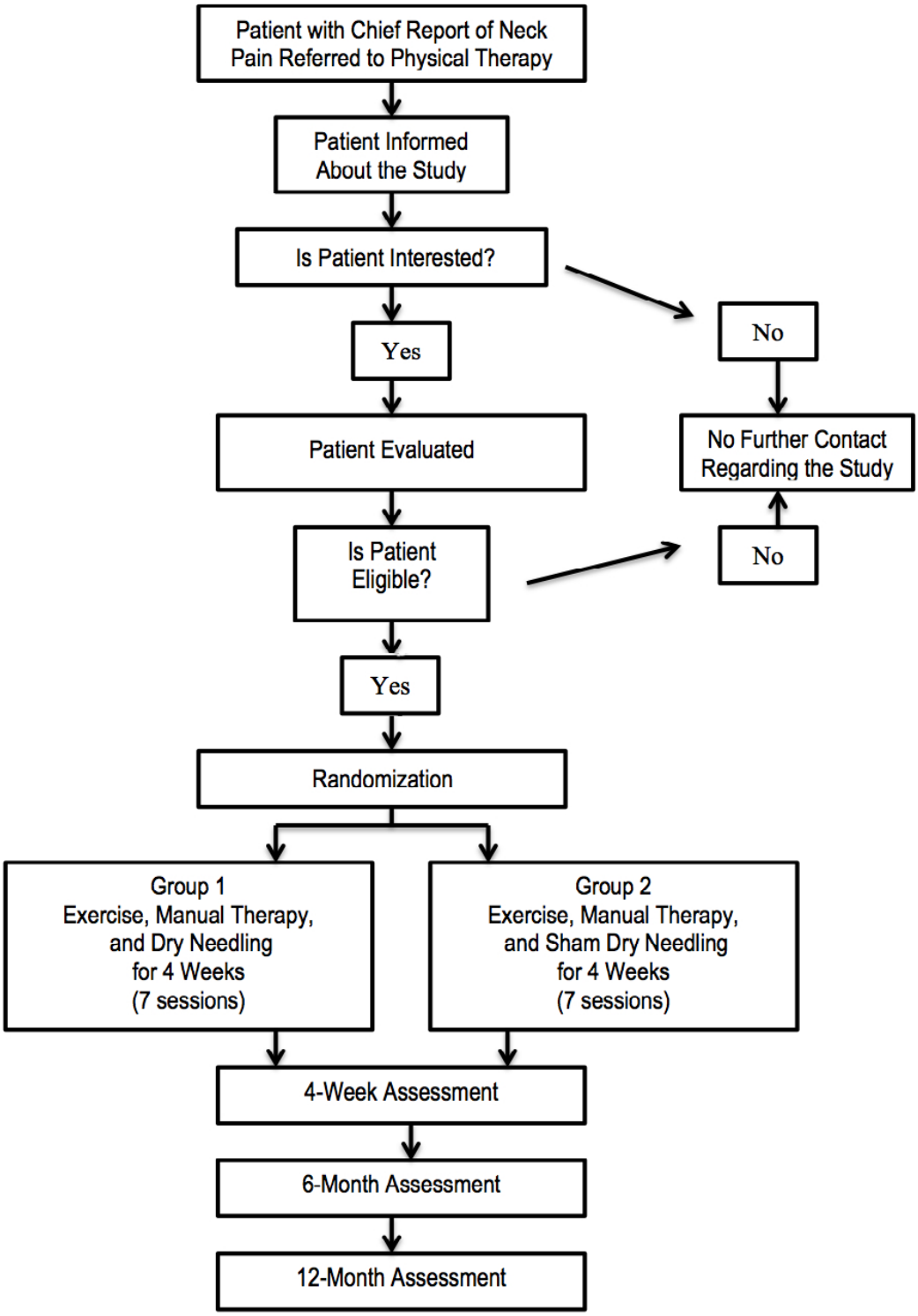
and disability in the short term (ie, 4 weeks) and long term (ie, 6 and 12 months) compared to those who receive sham dry needling, manual therapy, and exercise.

Methods

Design

We will conduct a randomized, double-blind, placebo-controlled trial according to the CONSORT guidelines (see Figure 1) [42,43]. Approval by both the Institutional Review Board at Concord Hospital (Concord, NH, USA), where the trial will be performed, and the University of Newcastle Human Research Ethics Committee (Callaghan, Australia), where the primary author (ERG) is currently enrolled as a PhD candidate, have been obtained. Consecutive subjects presenting to Concord Hospital physical therapy clinics (Concord, NH, USA) and Franciscan St. Francis Health physical therapy clinics (Indianapolis, IN, USA) with mechanical neck pain will be screened for eligibility criteria.

Figure 1. Flowchart of the study trial.



Subjects

Each physical therapy clinic, upon receiving a patient referral for neck pain, attempts to schedule the patient with the therapists who have agreed to assess and treat participants in the trial. Upon arrival for their initial assessments, patients are informed about the potential opportunity to participate in the study if they meet inclusion/exclusion criteria. A combination of physical examination and self-report measures will be used to assess each patient's potential eligibility to participate. Inclusion criteria for the study include the following: aged 18 years or older, a primary complaint of neck pain, and a Neck Disability Index (NDI)>10 points=20% [44]. Patient exclusion criteria include the following: red flags (ie, tumor, fracture, metabolic diseases, rheumatoid arthritis, osteoporosis, prolonged history of steroid use, symptoms of vertebrobasilary insufficiency, pregnancy, cervical spinal stenosis, or bilateral upper extremity symptoms); use of blood thinners; history of whiplash injury within the past 6 weeks; evidence of central nervous system involvement, including hyperreflexia, sensory disturbances in the hand, intrinsic muscle wasting of the hands, unsteadiness during walking, nystagmus, loss of visual acuity, impaired sensation of the face, altered taste, or the presence of pathological reflexes such as positive Hoffman's and/or Babinski reflexes; two or more positive neurologic signs consistent with nerve root compression (ie, muscle weakness involving a major muscle group of the upper extremity, diminished upper extremity muscle stretch reflex, or diminished or absent sensation to pinprick in any upper extremity dermatome); prior surgery to the neck or thoracic spine; workers' compensation or pending legal action regarding their neck pain; insufficient English-language skills to complete all questionnaires; and inability to comply with treatment and follow-up schedule.

If a patient is determined to have met inclusion/exclusion criteria, they will be asked if they would like to participate in the study. If they choose to provide informed consent, each patient will complete the baseline questionnaires as well as the baseline outcome assessments. Demographic information will be collected for descriptive purposes, including age, gender, employment status, past medical history, mechanism of injury, location and nature of the patient's symptoms, number of days since onset, number of previous episodes of neck pain, and treatment for previous episodes. Once patients are admitted to the study, no patient will be removed from the study for noncompliance and an intention-to-treat analysis will be used.

Outcome Measures

Overview

All subjects will complete several commonly used instruments to assess their level of disability and neck pain. The primary outcome measure will be the NDI to capture the effect of treatment on the level of disability. Secondary outcome measures will include the Visual Analog Scale (VAS) to assess pain, the Global Rating of Change Scale (GROC) to measure the patient's perceived recovery, the patient perception of the intervention to determine if they felt they received the genuine dry needling intervention, and patient expectations to determine which treatments they believed would be most beneficial for their current condition. The self-report measures that will be used include those discussed in the following sections.

Primary Outcome

The NDI was created to measure pain-related disability associated with activities of daily living in people with neck pain [45,46]. The NDI contains 10 focused sections. Each item is scored on a 6-point scale and can reach a maximum score of 5; therefore, the maximum score is 50. This score will be calculated as a percentage, with higher scores indicating higher levels of disability [46]. Content, construct validity, and reliability of the NDI has been previously shown in patients with neck pain [46,47]. The NDI has been used by researchers to evaluate the effect of treatments on patients' perceived levels of functioning and disability [48-51].

Secondary Outcomes

Visual Analog Scale

The VAS is a single-item measure of pain using a 100-mm horizontal line anchored on the left side, which represents *no pain*, while the right side represents *the worst pain imaginable*. Patients mark a score by making a vertical line where they feel best represents their pain intensity. The VAS has been shown to be reliable [52] and valid [53].

Patient Global Rating of Change

The GROC will be used, which is a 15-point global rating scale described by Jaeschke et al [54]. The scale ranges from –7 (*a very great deal worse*) to zero (*about the same*) to +7 (*a very great deal better*). The global rating will be administered at the follow-up examinations only.

Patient Perceptions

Patient perceptions about the intervention will be used to determine whether the sham was an effective placebo. Patients will be asked for their perceptions on the dry needling intervention they received in order to determine if they felt they received genuine treatment. The following questions will be asked: What did you think of the dry needling intervention? Would you be willing to have the dry needling intervention again if you were attending physical therapy? Do you think you received the real dry needling intervention?

Patient Expectations

Patient expectations will be assessed at enrollment into the trial. Patients will be asked to rate each intervention on a 5-point Likert scale as to whether they believe each specific intervention will significantly help to improve this episode of their neck pain.

All outcome assessments will be performed by an individual blind to group assignment and will be performed at baseline, 4 weeks, 6 months, and 12 months. The latter two assessments will be mailed to the patients to improve return rate (see Table 1) [55].

Table 1. Summary of outcome measures and time points for collection.

Outcome measure	Baseline	4 weeks	6 months	12 months
Neck Disability Index	Yes	Yes	Yes	Yes
Visual Analog Scale	Yes	Yes	Yes	Yes
Global Rating of Change	No	Yes	Yes	Yes
Patient perception of intervention	No	Yes	Yes	Yes
Patient expectations	Yes	No	No	No

Intervention

Overview

Once the baseline examination is complete, equal numbers of patients will be randomly assigned to one of two groups: (1) manual therapy, exercise, and dry needling (MTEX-Needle group) or (2) manual therapy, exercise, and sham dry needling (MTEX-Sham group). A random-number generator will be used to conduct the randomization. The randomization procedure will be conducted prior to the initiation of the study using a computer program randomizer by an individual not involved in patient recruitment. The randomization will be concealed according to the following procedure. The group assignment will be recorded on a label that will be placed inside an envelope and the envelope will be sealed. After the baseline examination is complete, the randomization envelope will be handed to a treating therapist and treatment will begin according to group assignment. Treatment will be initiated immediately following the baseline examination, unless prohibited by time constraints; in this case, the patient will be scheduled for a follow-up session within 3-5 days to receive the first treatment. Patients in both groups will attend physical therapy for seven treatments over a maximum of 4 weeks. Each treatment session will last for a total of 45 minutes of one-on-one treatment time with the treating physical therapist.

To ensure that the clinicians involved in administering the treatment are familiar with the procedures of the study, they will be required to participate in a 2-hour training session. During the training session, the manual therapy, exercise, and dry needling techniques will be reviewed to ensure treatments are applied in a standardized manner consistent with the treatment algorithm outlined below. The majority of the training time (ie, 1 hour) will be dedicated to ensuring standardization of the application of the dry needling and sham needling techniques. The second hour will be spent reviewing the manual therapy techniques, therapeutic exercises, and algorithms to help standardize their prescription, as well as data collection procedures. Due to the pragmatic nature of this study design, even when the treatment algorithm is followed for manual therapy and exercise, there will likely be some variation in the interventions selected by each therapist based on each patient's relevant examination findings. As this is a pragmatic trial designed to mimic usual clinical practice, this individualization of a patient's treatment is acceptable and expected. All therapists applying all interventions will be licensed physical therapists who have also completed the required postgraduate training that enables them by their state practice act to utilize dry needling, and who regularly use the technique in practice.

Manual Therapy: 15 Minutes

Individuals randomized to both groups will receive manual therapy to address joint mobility of the cervical and thoracic spine. Mobilization of the cervical spine and thrust manipulation targeting the thoracic spine will occur at the beginning of each treatment. The treatment algorithm, combined with physical examination findings, will guide clinicians to allow them to determine which techniques will be used and is outlined below (see Table 2).

Physical Examination Techniques That Will Guide Manual Therapy Intervention

Cervical/Thoracic Spine Active Range of Motion and Behavior of Symptoms

The examiner will record a single range of motion measurement for flexion and extension using an inclinometer as described by Hole [56]. Bilateral rotation will be measured using a standard long-arm goniometer [57]. Reliability coefficients for cervical spine range of motion parameters range from .81-.84 (inter-class correlation [ICC] 2,1) [56]. Thoracic rotation active range of motion will be assessed qualitatively. Patients will be asked to place their hands on opposite shoulders and to rotate the trunk. Care will be taken to maintain the cervical spine in neutral while the patient rotates the trunk to the left and right as far as possible. The behavior of symptoms and the presence of side-to-side asymmetry will be recorded.

Spring Testing

Spring testing of the cervical and thoracic spine over the spinous processes of the vertebrae will be tested with the patient prone [58,59]. The stiffness at each segment will be judged as normal, hypomobile, or hypermobile. Interpretation of whether a segment is hypomobile will be based on the examiner's anticipation of what normal mobility should feel like at that level and compared to the mobility detected in the segment above and below. In addition, pain provocation at each segment will be judged as painful or not painful and, if painful, whether the symptoms are local (ie, under the examiner's hand) or referred (ie, away from the examiner's hand). Spring testing for the neck will be performed over the spinous processes of C2-C7. Spring testing for the thoracic spine will be performed over the spinous processes of T1-T5. The reliability of spring testing from our previous work showed poor reliability in the cervical spine and fair-to-moderate reliability in the thoracic spine [60].

Table 2. Manual intervention algorithm for treatment selection.

Assessment	Treatment
Clinicians assess cervical spine mobility and range of motion, including overpressure and repeated movements, if indicated	If hypomobility or limited range of motion is identified in the cervical spine, the therapist will utilize cervical thrust manipulation or nonthrust mobilizations; this may include central and unilateral posterior-anterior, side glides, and occipito-atlanto joint (C0-1) Thrust manipulations may be repeated up to two times if reassessment of the patient shows improvements in range of motion, mobility, and/or pain Nonthrust mobilizations generally performed two to three times ×30 repetitions at each hypomobile level and may be repeated again (two to three times ×30 repetitions) if the patient shows improvements in range of motion, mobility, and/or pain
Clinicians assess thoracic spine mobility and range of motion	If hypomobility or limited range of motion is identified in the thoracic spine, the therapist will utilize thoracic thrust manipulation and/or nonthrust manipulation (may include central and unilateral posterior-anterior techniques to the thoracic spine and ribs) Thrust manipulation will be used unless contraindications noted (history or self-report of osteopenia/osteoporosis, etc) Thrust manipulations may be repeated up to two times if reassessment of the patient shows improvements in range of motion, mobility, and/or pain Nonthrust manipulations generally performed two to three times ×30 repetitions at each hypomobile level and may be repeated again (two to three times ×30 repetitions) if the patient shows improvements in range of motion, mobility, and/or pain

Table 3. Exercise intervention algorithm for treatment selection.

Assessment	Treatment	Progression
Muscular endurance of the cervical flexors was evaluated with the deep neck flexor endurance test and evaluated based on hold time in seconds	Prepare participant in supine, hook-lying position and ensure craniocervical and cervical regions are in a neutral position (support with a folded towel if necessary). Teach the craniocervical flexion action. Use instructions of "feel the back of your head slide up the bed as you nod your chin." Goal: 10 × 10-second holds	Begin with craniocervical flexion. Cue patient to "keep chin tucked in, lift, and hold your head up." Goal: 10 × 10-second holds
Craniocervical and cervical extensors	Patient either prone on elbows or in four-point kneeling position. Suboccipital muscles—Focus on a neutral neck position: (1) Require the participant to perform craniocervical extension (chin down) and (2) Require the participant to perform craniocervical rotation (the saying "no" action). Assess quality of movement and for smooth coordination. Goal: 3 sets of 5	Patient either prone on elbows or in four-point kneeling position. Deep cervical extensors: the craniocervical region remains in neutral and the axis of motion is now at C7. Instruct the participant to curl their neck first into flexion and then to curl their neck back to extension. The participant will often require manual facilitation to achieve the correct action. To assist in maintaining the craniocervical neutral position, let the participant imagine they have a book between their hands and they must keep their eyes on the book as they lift their head. Check that muscles such as splenius capitis are not overactive. Goal: 10 × 10-second holds
Muscle length test: upper trapezius, latissimus dorsi, pectoralis minor, pectoralis major, levator scapulae, anterior and middle scalenes, and the suboccipital muscles; also scored as tight or normal	Stretching of muscles determined to have decreased length Patient to perform 3 × 30-second stretches for each muscle Goal: 3 sets of 30-second holds for each muscle	Self-overpressure to stretching of muscles will be added as appropriate
Manual muscle tests performed for the lower trapezius, rhomboids, middle trapezius, and serratus anterior	Patient to perform exercises without exacerbation of symptoms Progressed based on patient response All patients begin with thin elastic bands Goal: 3 sets of 10	Patient will be progressed to medium, heavy, and extra heavy for resistance as appropriate, based on the patient's ability

Exercise: 15 Minutes

Individuals randomized to both groups will receive exercise designed to improve performance of both the deep neck flexor musculature as well as the scapular musculature. The physical examination will guide exercise interventions. See the exercise intervention treatment algorithm in Table 3 [61]. Exercise will be performed after manual therapy and before dry needling. The goal of this program is to increase endurance and control of the muscles in the cervicothoracic region. The exercise portion will also include a stretching program targeting the cervicothoracic muscles, which have been placed in a shortened position as a result of poor postures. Patients will be instructed to perform the exercises as a home program twice daily. Each patient will be provided with a home exercise log that includes pictures as well as descriptions of all exercises. This exercise log will be used to encourage patient compliance.

The patient will be instructed to maintain usual activity levels within the limits of pain. Advice to maintain usual activity has been found to assist in recovery from neck pain. Patients will be instructed to do all activities that do not increase symptoms and to avoid activities that aggravate symptoms.

Physical Examination Techniques That Will Guide Exercise Intervention

Neck Flexor Endurance

Endurance of the neck flexors will be assessed with the patient lying supine in a hook-lying position. The patient will retract the chin and lift the head and neck until the head is approximately one inch above the plinth. Once in position, a line will be drawn across one of the skin folds along the patient's neck while the therapist maintains support just under the patient's occiput. When either the line edges begin to separate or if the patient's head touches the therapist's hand for more than one second, the test will be terminated. This technique has been demonstrated to have moderate reliability (ICC of .67) [62].

Muscle Length Assessment

Length of the upper trapezius, latissimus dorsi, pectoralis minor, pectoralis major, levator scapulae, anterior and middle scalenes, and the suboccipital muscles will be assessed according to the descriptions provided by Cleland et al [60]. Percent agreement between examiners in our previous work ranged from 77% to 85% [63].

Muscle Strength Assessment

Strength of the upper quadrant will be tested according to the techniques described by Kendall [64]. Percent agreement between examiners in our previous work ranged from 81% to 91% [63].

Dry Needling: 15 Minutes

Individuals randomized to the MTEX-Needle group will receive dry needling targeting the posterior musculature of the cervical and thoracic spine. Dry needling will occur after the manual therapy and exercise at each treatment session. The physical examination findings will guide clinicians to allow them to determine which specific muscles will be targeted (see Table 4). Examples of posterior muscles that can be treated include the trapezius, levator scapulae, splenius capitis, semispinalis, spinalis capitis, multifidi, and suboccipital muscles. The therapist will needle at least six sites up to a maximum of 10 based on identification of MTrPs. If six sites failed to be identified, the therapist will address as many sites that are present and document the number of sites treated. Once the needle has been inserted manually into the trigger point, the needle will be pistoned in an up-and-down fashion so that 2- to 3-mm vertical motions occur (ie, fast-in and fast-out technique as described by Hong) at approximately 1 Hz for 25-30 seconds, with the aim of eliciting local twitch responses [65]. The maximum number of sessions of dry needling each participant will receive is six sessions, but therapists are instructed that if the patient has complete resolution of trigger points they do not need to continue with dry needling in subsequent sessions. The therapist also may discharge a patient at the therapist's and patient's discretion, as would normally be done in clinical practice.

Physical Examination That Will Guide Dry Needling Intervention: Trigger Point Assessment

The neck and upper quarter will be examined for the presence of the following: a hypersensitive spot in a palpable taut band, palpable or visible local twitch on pincer palpation, and reproduction of referred pain elicited by palpation of the sensitive spot. These criteria have been shown to exhibit good interexaminer reliability (κ=.84-.88) when applied by an experienced clinician [66].

Sham Dry Needling: 15 Minutes

Park Sham acupuncture needles (AcuPrime) will be used to perform sham dry needling in all patients randomized to the MTEX-Sham group. These needles have been reported to be indistinguishable from real needles in a patient who has not experienced dry needling before [67]. The device consists of two plastic tubes that slide into one another and allow the blunted needle to cause a pricking sensation when pushed against the skin. This sham needle allows the patient to have the feeling that the needle is entering the skin while also maintaining therapist-patient contact time and treatment explanation. Sham dry needling is proposed to have less effect when compared to true dry needling [68]. Sham dry needling sites will be determined in the exact same fashion as in the MTEX-Needle group by the physical therapist after assessment. Therapists will be asked to sham needle at least six sites up to a maximum of 10, but the muscles that are (sham) treated will be left at the discretion of the physical therapist. The number of sites and specific muscles (sham) treated will be recorded by the therapist. Only posterior muscles of the cervical spine and upper thoracic spine, the same muscles targeted in the dry needling group, will be treated in order to ensure patients will be blinded to whether they received the real or sham needling.

Data Analysis

Descriptive statistics, including frequency counts for categorical variables and measures of central tendency and dispersion for continuous variables, will be calculated to summarize the data.

Baseline demographic data will be compared across treatment groups to assess the adequacy of the randomization.

Table 4. Dry needling intervention algorithm for treatment selection.

Assessment	Treatment
Trigger point assessment performed on the trapezius	Patient in prone, therapist identifies the hypersensitive spot in the trapezius
	The overlying skin will be cleansed with alcohol
	Once the needle has been inserted manually into the trigger point, the needle will be pistoned in an up-and-down fashion so that 2- to 3-mm vertical motions occur (ie, fast-in and fast-out technique as described by Hong) at approximately 1 Hz for 25-30 seconds, with the aim of eliciting local twitch responses
	After needle is removed, pressure with a cotton ball will be maintained to prevent excessive bleeding
	The number of sites and specific muscles treated will be recorded by the therapist
Trigger point assessment performed on the levator scapulae	Patient in prone, therapist identifies the hypersensitive spot in the levator scapulae
	The overlying skin will be cleansed with alcohol
	Once the needle has been inserted manually into the trigger point, the needle will be pistoned in an up-and-down fashion so that 2- to 3-mm vertical motions occur (ie, fast-in and fast-out technique as described by Hong) at approximately 1 Hz for 25-30 seconds, with the aim of eliciting local twitch responses
	After needle is removed, pressure with a cotton ball will be maintained to prevent excessive bleeding
	The number of sites and specific muscles treated will be recorded by the therapist
Trigger point assessment performed on the splenius capitis, semispinalis, spinalis capitis, and multifidi	Patient in prone, therapist identifies the hypersensitive spot in the splenius capitis, semispinalis, spinalis capitis, or multifidi
	The overlying skin will be cleansed with alcohol
	Once the needle has been inserted manually into the trigger point, the needle will be pistoned in an up-and-down fashion so that 2- to 3-mm vertical motions occur (ie, fast-in and fast-out technique as described by Hong) at approximately 1 Hz for 25-30 seconds, with the aim of eliciting local twitch responses
	After needle is removed, pressure with a cotton ball will be maintained to prevent excessive bleeding
	The number of sites and specific muscles treated will be recorded by the therapist
Trigger point assessment performed on the suboccipital muscles	Patient in prone, therapist identifies the hypersensitive spot in the suboccipital muscles
	The overlying skin will be cleansed with alcohol
	Once the needle has been inserted manually into the trigger point, the needle will be pistoned in an up-and-down fashion so that 2- to 3-mm vertical motions occur (ie, fast-in and fast-out technique as described by Hong) at approximately 1 Hz for 25-30 seconds, with the aim of eliciting local twitch responses
	After needle is removed, pressure with a cotton ball will be maintained to prevent excessive bleeding
	The number of sites and specific muscles treated will be recorded by the therapist

We will compare baseline variables between groups by using independent *t* tests or Mann-Whitney U tests for continuous data and chi-square tests of independence for categorical data. An intention-to-treat analysis will be utilized, in which all participants will be analyzed in the group to which they were originally assigned. All dropouts and the reasons for dropping out of the study will be reported. An a priori alpha level of .05 will be used for all analyses. All data will be checked to ensure they meet the assumptions for the inferential statistical analyses described below. If they do not meet the necessary assumptions, appropriate nonparametric procedures will be utilized. We will examine the primary aim with a two-way repeated-measures analysis of variance with treatment group (ie, manual therapy, exercise, and dry needling vs manual therapy, exercise, and sham dry needling) as the between-subjects independent variables and time (ie, baseline, 4 weeks, 6 months, and 12 months) as the within-subjects independent variable. The hypothesis of interest is the two-way group × time interaction. Bonferroni-corrected post hoc tests will be used to determine difference between group means.

Power Analysis

Sample size and power calculations were performed using G*Power version 2 statistical software (Heinrich-Heine-Universität Düsseldorf) based on the minimal clinical improvement of 12 points on the NDI [51,69], assuming a standard deviation of 16 points, two-tailed, and an alpha level of .05. This requires a minimum sample size of 29 subjects per group. A total of 76 patients with a primary complaint of neck pain who meet the inclusion/exclusion criteria and consent to participate will be enrolled into the study. This sample size will yield greater than 80% power to detect both statistically significant and clinically meaningful changes in the NDI; additionally, this will control for dropouts prior to the 4-week follow-up.

Risks

The risks associated with a patient's participation in this study are minimal. Patients may experience an increase in pain intensity from completing the range of motion exercise due to a muscle or ligament injury. Based on our clinical experience, the chance of this happening is rare, which means it occurs in less than 1% of people. We have attempted to minimize this risk by having a licensed physical therapist examine all patients and instruct them in the proper exercise technique. In addition, a therapist will re-examine a patient at any time, if appropriate. It is also possible that patients will experience mild muscle soreness after the manipulation is performed. Based on our clinical experience, the chance of this happening is common, which means it occurs in 1%-25% of people. However, this soreness typically resolves within 1-48 hours after manipulation. We have minimized the risks associated with manipulation by ensuring that the licensed physical therapists participating in this study already routinely use manipulation in the management of patients with neck pain. We have further minimized this risk by ensuring that each physical therapist participating in this study has been specifically trained in the use of the manipulation techniques to be used in this study. Furthermore, all potential subjects will be screened to ensure they do not exhibit any exclusion criteria that may place the individual at increased risk for a serious complication.

When dry needling treatment is performed, it is possible that patients will experience the following common adverse events: bruising, bleeding, pain during treatment, pain after treatment, or aggravation of symptoms 1.7%-7.6% of the time (~2-8 out of 100). Uncommon adverse events include the following: drowsiness, headache, or nausea 0.13%-0.26% of the time (~1-3 out of 1000). Possible rare adverse events include fatigue, altered emotions, shaking, itching, claustrophobia, or numbness 0.01%-0.04% of the time (1-4 out of 10,000). Dry needling is very safe; however, the most serious side effect from dry needling is pneumothorax (ie, lung collapse due to air inside the chest wall), which can occur in less than 0.01% (<1 out of 10,000) treatments. This risk is very low and in a recent survey of physical therapists who use dry needling, Brady et al reported that no episodes of pneumothorax occurred in over 7600 treatments. We have minimized the risks associated with dry needling by ensuring that the licensed physical therapists participating in this study already routinely use dry needling in the management of patients with neck pain. We have further minimized this risk by ensuring that each physical therapist participating in this study has been specifically trained in the use of the dry needling techniques to be used in this study. Furthermore, all potential subjects will be screened to ensure they do not exhibit any exclusion criteria that may place the individual at increased risk for a serious complication.

Should any adverse event occur, it would be appropriately managed by the treating physical therapist by activating emergency services if immediate medical attention is required; standard clinical advice will be used in the case of minor events, such as transient soreness.

Results

This trial is registered at ClinicalTrials.gov (NCT02731014) and recruitment is currently underway and is expected to be completed by the end of 2017. Data collection for long-term outcomes will occur throughout 2017 and 2018. Data analysis, preparation, and publication submission is expected to occur throughout the final three quarters of 2018. See Table 5 for the study timeline and milestones.

Table 5. Timeline and milestones.

Activity	2016 (quarter)		2017 (quarter)				2018 (quarter)			
	3	4	1	2	3	4	1	2	3	4
Participant recruitment	X	X	X	X	X	X				
Data collection for long-term outcomes			X	X	X	X	X	X	X	X
Data analysis, preparation, and submission for publication								X	X	X
Publication submissions										X

Discussion

Principle Findings

Neck pain is commonly unresponsive or does not fully resolve with current treatment strategies, with 37% of patients going on to experience chronic neck pain of greater than one year [2]. Dry needling may be one intervention that could lead to improved outcomes when used in conjunction with exercise and manual therapy [11,39]. Anecdotally, in the clinical setting, a patient's pain level commonly limits their ability to participate in active exercise interventions. As dry needling appears to have a significant treatment effect on reducing pain and increasing pressure pain threshold [38], it may facilitate a patient's ability to perform a prescribed exercise program. In addition, it may improve patient compliance with exercise, which may lead to improved results from an exercise program.

Therefore, the aim of this trial is to determine if the addition of dry needling to an exercise and manual therapy treatment program will further reduce pain and improve disability in patients with mechanical neck pain, as compared to exercise and manual therapy and sham needling.

We hypothesize that patients who receive dry needling, manual therapy, and exercise will achieve greater reductions in pain and disability in the short term (ie, 4 weeks) and long term (ie, 6 and 12 months) compared to those who receive sham dry needling, manual therapy, and exercise.

As the use of dry needling by physical therapists becomes more widespread, and more therapists are trained in this approach, research is needed to support or refute its effectiveness. The results of this trial will assist in providing long-term outcomes examining the effectiveness of dry needling, which are currently lacking in the literature.

We anticipate the potential challenges to this study to include the following: difficulty with patient recruitment, patient compliance with follow-up schedule, and patients lost to follow-up over the 1-year, long-term, follow-up period. To address these challenges, we have utilized two large clinics in different locations in the United States to improve the ability to recruit patients in a timely manner. Further, we will provide a small financial reimbursement for patients as incentive for completion of the 4-week, 6-month, and 12-month follow-up in order to assist with compliance and reduce the numbers lost to follow-up.

Limitations

We recognize that there are a number of potential limitations in the study design. The treating therapists cannot be blinded to group assignment, which may influence the verbal and nonverbal interaction with subjects. To try to manage this limitation, all therapists will be trained to maximize the consistency with which the dry needling intervention and the sham intervention will be performed.

We have chosen to allow therapists to perform individualized dry needling treatment specific to each patient within the outlined treatment algorithm to be consistent with clinical practice and improve external generalizability. We believe that providing treatment specific to the patient's presentation will improve outcomes. We understand this may be seen as a limitation as it may lead to variation in the treatments that will be applied by therapists, which may mask the difference between groups. However, individualized treatment better reflects clinical practice.

Another potential limitation is that we are not including physical measures such as range of motion or pain pressure threshold in our analyses. We have chosen to limit our outcomes to validated questionnaires in an effort to decrease loss to follow-up, especially at the long-term time points.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

APTA Grant review peer review report.

[PDF File (Adobe PDF File), 564KB - resprot_v6i11e227_app1.pdf]

Multimedia Appendix 2

CONSORT - EHEALTH checklist (V.1.6.1).

[PDF File (Adobe PDF File), 683KB - resprot_v6i11e227_app2.pdf]

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Abbreviations

GROC: Global Rating of Change Scale
ICC: inter-class correlation
MTEX-Needle: manual therapy, exercise, and dry needling
MTEX-Sham: manual therapy, exercise, and sham dry needling
MTrP: myofascial trigger point
NDI: Neck Disability Index
VAS: Visual Analog Scale

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Protocol

The Importance of Trust in the Adoption and Use of Intelligent Assistive Technology by Older Adults to Support Aging in Place: Scoping Review Protocol

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Abstract

Background: Intelligent assistive technologies that complement and extend human abilities have proliferated in recent years. Service robots, home automation equipment, and other digital assistant devices possessing artificial intelligence are forms of assistive technologies that have become popular in society. Older adults (>55 years of age) have been identified by industry, government, and researchers as a demographic who can benefit significantly from the use of intelligent assistive technology to support various activities of daily living.

Objective: The purpose of this scoping review is to summarize the literature on the importance of the concept of "trust" in the adoption of intelligent assistive technologies to assist aging in place by older adults.

Methods: Using a scoping review methodology, our search strategy will examine the following databases: ACM Digital Library, Allied and Complementary Medicine Database (AMED), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Medline, PsycINFO, Scopus, and Web of Science. Two reviewers will independently screen the initial titles obtained from the search, and these results will be further inspected by other members of the research team for inclusion in the review.

Results: This review will provide insights into how the concept of trust is actualized in the adoption of intelligent assistive technology by older adults. Preliminary sensitization to the literature suggests that the concept of trust is fluid, unstable, and intimately tied to the type of intelligent assistive technology being examined. Furthermore, a wide range of theoretical lenses that include elements of trust have been used to examine this concept.

Conclusions: This review will describe the concept of trust in the adoption of intelligent assistive technology by older adults, and will provide insights for practitioners, policy makers, and technology vendors for future practice.

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KEYWORDS

assistive technology; trust; older adult; adoption; technology; aging in place; artificial intelligence; scoping review

Introduction

Technologies that amplify or augment human abilities have matured and proliferated in recent years. Robotics, home automation, and other forms of mobile systems are examples of technologies that assist human users in tasks, and have become subtly commonplace in people's lives. While the term *assistive technology* has been historically aligned with devices

used by individuals with physical or cognitive deficits (eg, wheelchairs, speech-generating devices [1]), newer forms of assistive technologies possessing elements of artificial intelligence have emerged in recent years. The term *intelligent assistive technologies* includes a broad range of technological systems used to support or extend human abilities [2], and are labelled as *smart* or *intelligent* due to their ability to sense and respond to user needs and a changing environment . The term is also used to describe a platform capable of operating autonomously or within larger networks of related devices [3]. Due to the intelligent nature of these devices, they can be used to support human users with a multitude of everyday tasks, such as household cleaning and maintenance, transportation, food and meal preparation, and various self-care management and recreational activities. Examples of intelligent devices relevant to older adults include autonomous vehicles, sensor-driven home emergency response systems, and personal robots [3].

While once only used for basic sensory and detection purposes [4], the consumer-level scaling of current generation smart and intelligent technology has produced systems that support more nuanced and complex aspects of people's daily living [3,5]. Home automation [6], service robots [7], wearable biometric sensors [8], relational companion agents [9], and *Internet of Things* applications [10] are now available to consumers to support a multitude of tasks, both in the home and the workplace. While there is broad societal interest in the use of these forms of smart technologies, they are increasingly being used to assist older adult populations (>55 years of age) to age in place [6,10-15]. With the global population of people over 65 expected to triple by 2050 [16], it has been proposed that assistive and other forms of artificially intelligent technology may play helpful roles in the early detection and management of age-related conditions [3]. Furthermore, by enabling older adults to *age in place* or, "live in one's own home and community safely, independently, and comfortably, regardless of age, income, or ability level" [17], older adults will be able to remain supported in their home and community, and potentially delay the use of institutional care [3]. Older adults who experience physical, mental, or cognitive deficits have been specifically identified as people who could benefit from these forms of intelligent assistive technologies to support their aging in place [6,18]. For instance, there has been a steadily growing body of literature exploring the use of these forms of intelligent assistive technologies to support the early detection and management of a variety of conditions, including Alzheimer's disease and dementia [19]. Other potential user groups, such as those experiencing mental health challenges [20], visual or auditory impairments [21], or medically fragility [22] have all been explored by researchers as conditions that can be supported through the appropriate use of intelligent assistive technology.

Over the last decade, a sizable body of research has been generated exploring the use of intelligent assistive technology in older adult populations. Topics include a diverse range of intelligent assistive technology, including devices that accomplish isolated or specific tasks like vacuuming, cleaning, and remote lighting control [12,23-26]. More recently, personalized companionship, virtual presence, virtual assistant, and sensory technologies that offer customized lifestyle supports based on various socio-contextual inputs (ie, diet, sleep, activity, time of day) have also become popularized [10,26]. Some intelligent assistive technologies also possess the ability to leverage multimodal interaction between other distinct smart devices to surround an individual with personalized support. For instance, Amazon Echo (a conversational virtual assistant device) can help a human user complete tasks via voice commands (eg, create shopping lists, provide news/traffic information) [27]. The Echo assistant can also control other home automation technology (eg, smart lighting, cleaning service robots) to generate an interlinked, intelligent network of assistive technology around a human user [27]. Given the autonomous nature of some intelligent assistive technologies, researchers are interested in exploring the possibility of personalized, fluid, human-technical relationships with these devices [28-31].

As assistive technologies acquire and demonstrate intelligence through their functionality, human users may begin to perceive them more like autonomous agents [32]. Due to this perception, human users assume more risk as they move from predictable and controllable interactions with nonintelligent devices (ie, traditional assistive technology) to intelligent devices where responses and outcomes may become less predictable. One concept noted to be important in the building of this kind of human-technical relationship is *trust* [33] . Trust is a construct we assign to a human's willingness to rely on the actions of an autonomous agent (ie, intelligent assistive technology), whose behaviors are not directly controlled by an individual [34]. To date, the concept of trust regarding older adults' adoption of intelligent assistive technology has been examined directly or indirectly through a variety of fashions, including: (1) whether human users felt comfortable following the directions of an intelligent assistive technology [29,31,35]; (2) if the technology espoused a perceivable feeling of trustworthiness [31]; and (3) if the technology, in its function or presence, became a trusted technological entity [36]. While numerous articles have addressed various constructs associated with the role of trust in older adults' adoption of technology [23,29,31,35,36], there has yet to be a broad search and summary of current literature in the domain.

The increasing embeddedness and omnipresent nature of many intelligent assistive technologies suggests that a review of the state of the research in the domain is timely. To address this gap, we describe the protocol for a scoping review that will seek to explore the concept of trust in relation to older adults and their adoption and use of intelligent assistive technologies that support aging in place.

Methods

Scoping Review

Scoping reviews are commonly undertaken, "to examine the extent, range and nature of a research activity" [37] in a given domain, especially, "when it is difficult to visualize the range of material that might be available" [38]. A scoping review methodology using the approach advised by Arksey and O'Malley [38] and advanced by Levac et al [37] was selected

over more time-intensive synthesis approaches (ie, systematic review, meta-analysis).

Step 1: Identification of the Research Question

Levac et al [37] recommend that research questions for scoping reviews be "broad" in nature, but linked with a specific and, "clearly articulated scope of inquiry." Using these conceptual recommendations, the operational research question to be used in this review was derived through research team discussion: "How important is *trust* to the adoption and use of intelligent assistive technology that allows older adults to age in place?"

Step 2: Identification of Relevant Studies

In this scoping review we will draw upon a variety of scholarly reference databases, including: ACM Digital Library, Allied and Complementary Medicine Database (AMED), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Medline, PsycINFO, Scopus, and Web of Science. We will also capture grey literature through Dissertation Abstracts and Google Scholar searches. Academic literature generated over the last decade (2006-2017) will be targeted, given the rapid evolution of technology in this research domain. Through consultation with a health sciences librarian, research team meetings, and exploration of other review publications on similar topics, search syntax and inclusion/exclusion criteria were developed (Textbox 1). The search syntax targets keywords related to the three major variable components comprised in the research question: (1) older adult population, (2) the intelligent assistive technology, and (3) the concept of trust. The search syntax included "older adult*" OR "senior*" OR "baby boomer*" OR "aging in place" OR "elder*" AND "robot*" OR "assistive technolog*" OR "technolog*" OR "smart technolog*" OR "artificial intelligence" OR "intelligent technolog*" OR "intelligent assistive technolog*" AND "trust*" OR "reliab*" OR "engage*" OR "adopt*" OR "accept*" OR "depend*" OR "confiden*" OR "rely". The search syntax will be run in each of the reference databases, and results will be extracted as RIS files and saved separately. All results arising from the reference databases will be imported into the Covidence (Veritas Health Innovation) software platform for review.

Textbox 1. Inclusion and exclusion criteria for the scoping review.

Inclusion criteria

- English language research papers and conference abstracts
- 2006 to 2017
- Aged >55 years and above, or defined otherwise as older adult, elderly, or senior
- Research that examines intelligent assistive device use by older adult population for some activity to support *aging in place*, related to activities of daily living, health, or physical/mental behaviors (aged >55 years, or defined otherwise)
- Quantitative and qualitative research studies

Exclusion criteria

- Book reviews, textbooks chapters, opinion papers, and commentaries
- Intelligent assistive technology/devices examinations that lack "intelligent" definition (eg, magnification books, wheel chairs without digital brains)
- Intelligent assistive technology/devices that are used to support other activities (eg, farming, employment)
- Aged <54 years, if not defined by authors as being older adult, senior, or elderly
- Nonresearch studies

Step 3: Selection of Studies

Two members of the research team (AM, JL) will independently screen all retrieved titles and abstracts for applicability to the review's research question. Discrepancies resulting from the independent initial screen will be discussed between the two research team members until consensus is reached. After this initial independent screening, other members of the research team (RB, JM) will review the full-text articles of short-listed results and, as suggested by Levac et al [37], develop a post hoc inclusion and exclusion criteria that will be applied to the short-list.

Step 4: Extracting Data From Studies

A preliminary researcher-developed data charting tool has been generated to facilitate the extraction of data from the studies (Table 1). Levac et al [37] suggest that both the process of extracting data from studies and the development of the charting tool should be an iterative, data-driven process, whereby increased familiarity with the study findings reciprocally assists in developing/refining the charting tool. Using a descriptive analytical method, findings emerging from each study will be qualitatively summarized in a narrative fashion, and common themes and results will be identified. Through this process, it is expected that the charting tool will evolve as data is extracted from the respective studies, and important findings related to the research question (not *a priori* conceptualized) are added to the data fields.

Table 1. Data extraction table.

Data	Details for extraction
Article information	Author
	Year
	Title
	Journal
	Abstract
	Study type
	Theoretical/conceptual model
Population	Definition of older adult
	Inclusion criteria
	Research setting location
Intervention	Description/type of intelligent assistive technology or system
	Measures (if applicable)
Trust	Operational definition of *trust*
	Measure or qualitative aspects relevant to *trust*
Study findings	Brief overall study findings description

Step 5: Collating and Summarizing Data

To better organize the synthesis findings, we will use tables to help accentuate the abstracted themes. Frequency data related to a numerical count of studies that explore specific themes or elements related to the research question will be calculated. Similarly, tables will also provide a clear and concise visualization of subthemes and issues arising from the main synthesis findings. Both NVivo 11 (QSR International) and Microsoft Excel (Microsoft Corp) software applications will be used to assist in coding and quantifying emergent findings from the studies. Most of the findings will be reported in a narrative fashion, qualitatively describing the current state-of-the-art in terms of trust and older adults' adoption/use of intelligent assistive technology. Drawing methodological insights from the constant comparative technique [39], all study findings will be constantly compared against other findings in an effort to develop a cohesive thematic description of the state-of-the-art regarding the research question.

Results

This review will provide insights into how the concept of trust is actualized in the adoption of intelligent assistive technology by older adults. Preliminary sensitization to the literature suggests that the concept of trust is fluid, unstable, and intimately tied to the type of intelligent assistive technology being examined. Furthermore, a wide range of theoretical lenses that include elements of trust have been used to examine this concept.

Discussion

Preliminary Findings

To date, we have generated some preliminary insights into the concept of *trust* in the adoption of intelligent assistive technology by older adults to support aging in place, through an initial search of literature in the domain to derive sensitizing constructs for the review team. Sensitizing constructs provide, "a starting point for a qualitative study" [40]. First, the vernacular in this area of inquiry is diverse and unstable. The various uses of neologisms and other specific terms to denote various typologies of intelligent assistive technology is remarkable, and will likely become a finding that is embedded into the data extraction tool. Second, given the nonspecificity of the search algorithm, a broad range of intelligent technologies will likely be identified in the research domain over the last decade. Smart assistive living environments, ambient assisted living, social robots, virtual presence, and personalized cloud technologies (among others) have all been featured in the sensitizing literature. Third, the operational definition of the older adult population included in this study has varied significantly in other studies, ranging from 50 [41] to 90 years of age [42]. Finally, conceptualizations of trust also appear to vary significantly between studies. A range of different theoretical perspectives have commonly been used to operationalize the measurement of the concept of trust, including the Technology Acceptance Model [43], Systems Engineering Initiative for Patient Safety [33], and other sociological frameworks [34]. Consequently, the concept of trust has also been defined in a variety of ways, often related to the functional features of the technology, such as its usefulness, learned nature, or some element of situational presence with a human user [44-46].

Limitations

A potential limitation of this scoping review will be the lack of an explicit quality assessment of the included articles. The lack of a quality assessment review of the articles is common in scoping review methodologies, as the primary goal of this type of review is to generate rapid insights into an emerging domain to inform future inquiry. Furthermore, given the primordial state of research in this area (ie, no randomized controlled trial studies were found in any of the preliminary scan of articles arising from the search syntax), applying a formalized quality assessment component to this review may inadvertently exclude pilot studies and other research designs that produce findings with constrained external validity, or those that are qualitative in nature.

Conclusion

As a research domain that will undoubtedly become more complex and diverse in the coming decade, it is essential that stakeholders have a deeper understanding of the construct of *trust* in relation to older adults and their adoption and use of intelligent assistive technology. To date there has been no formative research synthesis exploring the concept of trust in the adoption of intelligent assistive technology by older adults. This review will provide a range of stakeholders with a better understanding of how these forms of intelligent technologies can serve older adult populations. Furthermore, the review will assist with appropriate scaling of these innovations to address the specific adoption needs of the older adult population in what can be an unfamiliar technological landscape. We are confident that our review will generate useful preliminary insights into how trust must be factored into older adults' adoption of intelligent assistive technology to support their aging in place. Finally, our development of a detailed data extraction tool will provide the groundwork for future explorations of the role of trust in the adoption of intelligent technologies in other consumer populations (eg, youth/adolescents, expectant mothers, parents).

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Reviewer scores from review of SSHRC grant.

[PDF File (Adobe PDF File), 109KB - resprot_v6i11e218_app1.pdf]

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Protocol

Surgical Interventions for the Treatment of Supracondylar Humerus Fractures in Children: Protocol of a Systematic Review

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Abstract

Background: The treatment of supracondylar humerus fracture in children (SHFC) is associated with complications such as functional deficit, residual deformity, and iatrogenic neurological damage. The standard treatment is closed reduction and percutaneous Kirschner wire fixation with different configurations. Despite this fact, there is still no consensus on the most effective technique for the treatment of these fractures.

Objective: The aim of this systematic review will be to evaluate the effect of surgical interventions on the treatment of Gartland type II and III SHFC by assessing function, complications, and error as primary outcomes. Clinical outcomes such as range of motion and pain and radiographic outcomes will also be judged.

Methods: A systematic review of randomized controlled trials or quasi-randomized controlled trials evaluating the surgical treatment of SHFC will be carried out in the Cochrane Central Register of Controlled Trials, PubMed, Literatura Latino-Americana e do Caribe em Ciências da Saúde, and Excerpta Medica Database. The search will also occur at ongoing and recently completed clinical trials in selected databases. Data management and extraction will be performed using a data withdrawal form and by analyzing the following: study method characteristics, participant characteristics, intervention characteristics, results, methodological domains, and risk of bias. To assess the risk of bias of the included trials, the Cochrane Risk of Bias Tool will be used. Dichotomous outcome data will be analyzed as risk ratios, and continuous outcome data will be expressed as mean differences, both with 95% confidence intervals. Also, whenever possible, subgroup analysis, sensitivity analysis, and assessment of heterogeneity will be performed.

Results: Following the publication of this protocol, searches will be run and included studies will be deeply analyzed. We hope to obtain final results in the next few months and have the final paper published by the end of 2018. This study was funded by a government-based noncommercial agency, Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP).

Conclusions: This study may provide surgical treatment effects evidence for SHFC. The results will assist clinical practice by demonstrating the effectiveness and potential complications of these interventions and might serve as a reference for future clinical trials on the topic.

Trial Registration: PROSPERO CRD42014009304; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=9304 (Archived by WebCite at http://www.webcitation.org/6usiDHzD7)

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KEYWORDS

supracondylar humerus fracture; children; surgical treatment; systematic review

Introduction

Overview

Supracondylar humerus fractures are the most frequent elbow fracture in the pediatric population [1,2]. They are associated with significant complications, such as neurovascular injuries and malunion [3,4,5]. Cubitus varus is the most common residual deformity from supracondylar fractures [6-10], usually due to malreductions [7,9,11-13] that promote distal fragment rotational displacement [14]. Other causes are medial column comminution developing reduction loss during the follow-up [15] and growth arrests caused by physeal injuries [16-21].

The most common mechanism of injury is a fall to the extended arm, this corresponding to over 95% of cases [22]. Another mechanism is direct trauma to the posterior region of the flexed elbow, generating an anterior deviation of the distal fragment of the fracture. The most widely used classification for these fractures is described by Gartland (ie, type I: undisplaced or minimally displaced, type II: displaced, but with intact posterior cortex, and type III: completely displaced with no cortical contact) [23]. Nerve damage associated with trauma occurs in about 11.3% of patients and vascular lesions in less than 1% of these fractures. The ulnar nerve is the most commonly injured nerve in flexion fractures. It may also be iatrogenically damaged during percutaneous fixation of the medial column of the distal humerus [24]. The objective of surgical treatment of displaced and unstable fractures (Gartland types II and III) is to obtain a stable reduction, prevent neurovascular injuries, avoid compartment syndrome [3,4,5,25], and lower the risk of residual deformities, particularly cubitus varus. The standard treatment is closed reduction and percutaneous Kirschner wire (K-wire) fixation [26]. This fixation can be achieved by different configurations; the most commonly used are 2 crossed wires and fixation in the lateral column.

Biomechanics trials [27] show that the disposition of 2 crossed K-wires, 1 in the lateral column of the distal end of the humerus and the other in its medial end [28,29], is the configuration that provides the greatest stability when fixating these fractures. However, there is a risk of iatrogenic injury, mainly in the ulnar nerve [30,31] due to its close anatomical relationship with the posterior surface of the medial epicondyle. To minimize this complication, alternatively the fractures can be fixated with parallel or divergent K-wires only at the lateral column of the humerus [32]. This configuration is less stable [33,34] and could lead to residual deformities such as cubitus varus. In sum, there is still no consensus on the most effective technique for the treatment of displaced supracondylar humerus fractures [35].

Objectives

The aim of this study is to evaluate the effectiveness of surgical interventions for the treatment of Gartland type II and III supracondylar humerus fractures in children and their complications. Therefore, we developed the following PICOS (patient, problem, or population; intervention; comparison, control, or comparator; outcome; study design) strategy: the population will consist of individuals with immature skeletons and acute history of displaced supracondylar fracture (Gartland type II or III); the intervention will be the surgery performed with insertion of 2 parallel or divergent K-wires at the lateral column of the humerus; the control will be patients submitted to the surgery with the insertion of 2 crossed K-wires (one at the lateral column of the humerus distal end and the other at its the medial end); the outcome will be the function assessed by validated scores and the complications; and the study design will be systematic review of the literature.

Our hypothesis is that fracture fixation with 2 K-wires at the lateral column will properly restore elbow function and minimize the risk of iatrogenic injury to the ulnar nerve.

Methods

Criteria for Considering Studies for This Review: Types of Studies, Participants, and Interventions

This will be a systematic review of randomized controlled trials or quasi-randomized controlled trials on the surgical treatment of supracondylar humerus fractures in children, without restrictions to language, status, or year of publication.

This protocol was developed according to the criteria described in the Cochrane Handbook of Interventions Reviews [36] and the Preferred Reporting Items for Systematic Review and Meta-Analysis protocols [37].

The participants include children (immature skeleton) with displaced supracondylar fracture (Gartland type II or III) and a history of acute trauma (less than 2 weeks), no prior deformity of the studied elbow, and an absence of concomitant fractures in the ipsilateral limb.

The 2 surgical interventions described for the treatment of acute supracondylar fractures are insertion of 2 crossed K-wires, 1 at the lateral column of the distal end of the humerus and the other at its medial end, and insertion of 2 parallel or divergent K-wires only at the lateral column of the humerus.

Ethics Approval

This study was registered and authorized by the Research Ethics Committee of Universidade Federal de São Paulo (protocol number 108538/2015).

Primary Outcomes

The primary outcomes will be the functional results, complications, and errors resulting from interventions. A validated elbow function score using the method by Flynn et al [12], the Disabilities of the Arm, Shoulder, and Hand Questionnaire [38], or the Mayo Elbow Performance Score [39] will measure function.

Complications will be interpreted according to type, severity, and date of occurrence. Some examples of complications are nerve iatrogenic injuries (ulnar, radial, or median), infections caused by the introduction of the K-wire, compartment syndrome, and deformities (cubitus varus or valgus). The complication's severity will be classified as major (eg, permanent neurological damage with return to function through surgical procedure, deep infection requiring surgical intervention) or minor (eg, transient neurological injury with spontaneous return of function, superficial infection requiring antibiotic therapy). The date of the occurrence of complications

will be dated as early (occurring up to 4 weeks after surgery or until the removal of wires) or late (more than 4 weeks after surgery or after wire removal).

Any surgical procedure other than the preestablished treatment protocol will be classified as an error based on the principle of intention to treat. An example of such a procedure is the inclusion of a third medial or lateral K-wire to add stability to the construct.

Secondary Outcomes

Secondary outcomes will be divided into clinical and radiographic outcomes. Clinical outcomes will assess the variation in elbow range of motion and pain. The variation in range of motion is the change in the arc of total elbow movement in the late postoperative period compared to the contralateral limb, measured in degrees. Pain will be estimated using a validated instrument [40,41].

The radiographic outcomes will appraise variation of the carrying angle [42-44], variation of Baumann's angle [45,46], and heterotopic ossification presence. The carrying angle is determined by drawing 2 lines in anteroposterior elbow radiographs, 1 along the humeral shaft long axis and the other along the ulna long axis. Baumann's angle is obtained by the intersection of 2 lines, 1 parallel to the humeral shaft and the other parallel to the epiphyseal line of the lateral condyle drawn in elbow anteroposterior radiographs. This angle should be approximately 72°. The analysis of the carrying angle and Baumann's angle will consider variations in these angles in the immediate postoperative radiograph compared to the follow-up radiograph (removal of synthesis material or 3 months postoperatively). In both angles, the difference to the contralateral side will be calculated. The heterotopic ossification will be judged dichotomously (positive or negative).

Search Strategy

The searches will be carried out in the Cochrane Library, PubMed, Excerpta Medica Database, and *Literatura Latino-Americana e do Caribe em Ciências da Saúde* (LILACS). In addition, ongoing and recently completed clinical trial protocols will be searched in the ISRCTN Registry (www.isrctn.com), International Clinical Trials Registry Platform, ClinicalTrials.gov, Cochrane Central Register of Controlled Trials, LILACS , and *Plataforma Brasil*. There will be no restrictions to language or publication status. Subject headings and their search synonyms will be used. In MEDLINE (PubMed), the first 2 phases of the Cochrane highly sensitive search strategy for reports of randomized controlled trials [47] will be combined with the subject-specific search: "supracondylar," "humerus," "fractures," and "surgery."

Selection of Trials

Two authors will independently select and evaluate potentially eligible trials for inclusion in the review through the title and abstract. All potentially eligible trials will be reviewed in their entirety, including those that cannot be identified based on title or abstract. Any differences will be resolved through discussion and, when necessary, a third author will solve the conflict.

Data Management and Extraction

Two authors will extract the following data using a data extraction form: (1) study methodology characteristics, including study design and duration, whether the protocol was published before patient recruitment, possible funding sources, and trial registration; (2) participant characteristics, including location, number of recruited participants, number of evaluated participants, inclusion criteria, exclusion criteria, age, and injury classification; (3) intervention characteristics, including intervention duration, surgery type, and any complications; (4) results, including follow-up time and follow-up loss; and (5) methodological domains and bias risk assessment as described below. Both researchers will enter their data on forms.

Included Trials Bias Risk Assessment

The bias risk of the included trials will be evaluated independently by 2 authors using the Cochrane Risk of Bias tool [48]. This will be done using the following criteria: random sequence generation, allocation concealment, participant blinding, outcome assessment blinding, incomplete outcome data, selective reporting, and other biases (eg, financial incentives use, population imbalance between groups). Each of these criterion will be explicitly judged and classified as low risk of bias, high risk of bias, or unclear risk of bias. Disagreements between the authors about the risk of bias for each of the domains will be resolved by consensus.

Statistical Analysis

The Review Manager (Cochrane Collaboration) tool will be used for the statistical analysis. The dichotomous data will be analyzed by calculating the relative risk with a 95% confidence interval. The Mantel-Haenszel statistical method will be used, and continuous data will be analyzed using mean and standard deviation.

When the data of 2 or more trials is derived from the same validated assessment tool (with the same units of measurement), the data will be grouped as mean difference. The statistical method will be the inverse variance method. However, when primary trials express the same variables in different instruments or different units of measurement, standardized mean difference will be applied.

Unit of Analysis

The randomization unit in the included trials usually is the individual participant. Exceptionally, as in case of trials including children with bilateral fractures, the data is evaluated per fracture, instead the individual.

Dealing With Missing Data

In order to include all participants randomized to an intervention, intention-to-treat analysis will be performed. In case of inadequate information regarding the estimated effects, number of patients, mean, uncertainty measures (standard deviation or error), or number of events, the authors of the primary studies will be contacted.

Assessment of Heterogeneity

The heterogeneity of the effects between the included trials will be visually analyzed using forest plots and the I^2 test.

Heterogeneity is considered significant when I^2 is greater than 50%.

Data Synthesis

Where appropriate, the authors will group the results of both surgical techniques and compare them using the fixed or random effects model with 95% confidence interval.

Bias in the Meta-Analysis

If more than 10 trials are available, the publication bias and effect bias of small trials will be assessed visually with the funnel plot when possible. If asymmetry is found upon visual inspection, we will attempt to identify the reason.

Confidence in Cumulative Evidence

The Grading of Recommendations Assessment, Development, and Evaluation tool (www.gradepro.org) will be applied to describe the quality of the evidence and the strength of the recommendations.

Results

Following the publication of this protocol, searches will be run and included studies will be deeply analyzed. We hope to obtain final results in the next few months and have the final paper published by the end of 2018. This study was funded by a government-based noncommercial agency, *Fundação de Amparo à Pesquisa do Estado de São Paulo* (FAPESP).

Discussion

Supracondylar humerus fracture fixation with crossed wires (medial and lateral) and fixation with 2 lateral wires can provide satisfactory results, although the complications inherent to these methods are not well established [49]. A complication reported is ulnar nerve injury due to medial K-wire insertion during the surgery, possibly by its proximity to the medial epicondyle. Conversely, inserting the wires only in the lateral column can reduce stability, leading to distal humerus malunion [50,51] despite all patients having their affected limb immobilized after surgery. Both neurological damage and precarious stability can cause patient limbs functional deficit. Also, assessment of residual varus deformity should be performed, as we believe that its main cause is poorly executed reduction during surgical procedure.

In the literature, we find few systematic reviews on the topic and, in most cases, these reviews include trials with low levels of evidence such as case series and nonrandomized clinical trials [52-57]. We did not find reviews with prior publication protocol, something that increases the chance of bias in the analysis. The last review on the subject was published a few years ago [58]. Since then, new trials have been published and should be included in our study.

We also observed that, in these revisions, the primary outcome was the iatrogenic injury to the ulnar nerve, but we believe that function and complications are the foremost outcomes to be assessed, given that most ulnar nerve injuries are transient and do not require a new intervention. Therefore, further evaluation of the literature on the supracondylar fracture surgical treatment with better methodological quality should be carried out covering functional, clinical, and radiographic outcomes as well as complications and treatment errors.

The main limitation is expected to be the difficulty finding trials with adequate sample size as well as the lack of standardization in the evaluation methods of the results. The results of this study may provide support and scientific evidence for decision making in orthopedic clinical practice regarding displaced supracondylar fractures of the distal humerus in children, serving as a guide for future trials with better methodological quality.

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Authors' Contributions

OLC, FTM, and MJST contributed to protocol preparation. OLC, JCB, FTM, NSBM, MHM, FF, and MJST contibuted to manuscript preparation. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-review reports.

[PDF File (Adobe PDF File), 129KB - resprot_v6i11e232_app1.pdf]

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Abbreviations

FAPESP: Fundação de Amparo à Pesquisa do Estado de São Paulo
K-wire: Kirschner wire
LILACS: Literatura Latino-Americana e do Caribe em Ciências da Saúde
PICOS: patient, problem, or population; intervention; comparison, control, or comparator; outcome; study design

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Protocol

Immune-Enhancing Formulas for Patients With Cancer Undergoing Esophagectomy: Systematic Review Protocol

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Abstract

Background: Adult patients with an esophageal cancer can potentially be compromised with postoperative leaks or fistulae if patients' nutritional status is in a vulnerable stage. Currently in Australia, there is a growing need for clinicians to know whether use of immune-enhancing formulas (IEFs) containing Arg, omega-3, and RNA are a cost-effective approach compared with isonitrogenous-isocaloric formulas to reduce postoperative infectious complications in esophagectomy patients. Since IEFs may carry higher costs, this has led to inconsistencies in practice among clinicians and hospitals.

Objective: Our aim is to compile and present the most up-to-date nutrition evidence available regarding the provision of IEFs containing Arg, omega-3, and RNA to help clinicians develop an evidence-based nutrition care plan; identify available evidence of whether an esophagectomy patient should receive IEF; determine the cost-effectiveness and safety of such nutrition; and determine appropriate administration quantity and timing (pre-, peri-, or postesophagectomy).

Methods: This review will include RCTs involving the use of IEFs enriched with Arg, omega-3 polyunsaturated fatty acids, and RNA in the pre-, peri-, or postoperative period (for at least 5-7 days) given orally or via enteral feeding tube, in adult cancer patients undergoing esophageal resection. Lower gastrointestinal, gastric, or head cancer surgery with parenteral nutrition or non-IEF or use of isolated immunonutrient (Arg vs omega-3 vs RNA) will be excluded. Primary outcome comprises postoperative infectious complications. Secondary outcomes (pre/postoperatively) consist of cost-effectiveness, length of stay, survival/mortality, quality of life, nutritional status, percentage of weight loss, and biochemical changes. The risk of bias will be independently assessed by the reviewers, using a domain-based evaluation tool. Blinding will be assessed for subjective and objective outcome measures. Publication bias will be visually assessed by funnel plots. A meta-analysis will be generated by the Review Manager 5.3 software and represented in forest plots.

Results: The first results are expected in 2018. Outlining the protocol will ensure transparency for the completed review.

Conclusions: This protocol for a systematic review and meta-analysis will enable a comprehensive appraisal of the literature to help determine whether overall institutional savings are associated with this approach. Findings will form a knowledge base relevant to stakeholders across the health system and researchers who are involved in decision making on evidence-based nutrition care plan pathways for patients undergoing esophagectomy, as well as the use of IEF, timing, and administration quantity.

Trial Registration: PROSPERO Registration Number: CRD42017056908; http://www.crd.york.ac.uk/PROSPERO/display_record.asp? ID=CRD42017056908 (Archived by WebCite at http://www.webcitation.org/6rLyeqaD6)

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KEYWORDS

immunonutrition; nutritional support; esophagectomy; postoperative infectious complications; immune-enhancing formula

Introduction

Description of the Condition

Adult patients with an esophageal cancer or intractable strictures often require resection of the esophagus with complex anastomoses that can potentially be compromised with postoperative leaks or fistulae if patients' nutritional status is in a vulnerable stage [1,2]. Additionally, pulmonary complications, especially pneumonia, are a major component of morbidity after an esophagectomy [3].

Although it is challenging to define and measure nutritional status in oncology, cancer-associated malnutrition seems to affect this population even in those overweight or well-nourished patients with a recent diagnosis [4]. Up to 85% of patients develop cancer-associated malnutrition, in which individual susceptibility depends on several factors such as the type, grade, and stage of cancer as well as the side effects of treatment modalities [5,6]. These factors may have a negative impact causing systemic anorexia combined with altered absorption of nutrients, unintentional weight loss, and depletion of lean body mass [4]. Moreover, pre-existing poor dietary habits, socioeconomic status, functional performance, nutritional impact symptoms, requirements for fasting, and inadequate nutritional therapy may affect nutritional intake as well, causing a progressive and widespread sarcopenia [6]. Because of this nutritional depletion, the risk of morbidity and mortality increases as well as the length of hospitalization and health care costs [7].

Currently in Australia, there is a growing need for clinicians to know whether the use of immune-enhancing formulas (IEFs) containing arginine (Arg), omega-3, and ribonucleic acid (RNA) is a cost-effective approach compared with isonitrogenous-isocaloric formula to reduce postoperative infectious complications (POIC) in esophagectomy patients [8]. Since these IEFs may carry higher costs, selective and cautious use with patients has led to inconsistencies among practitioners or hospitals, possibly because of insufficient targeted evidence-based guidelines advocating or supporting enteral immunonutrition (IN) in esophageal resection patients [9].

Thus, this systematic review will enable a comprehensive appraisal of the literature to assist in determining whether overall institutional savings are associated with this approach. This review also seeks to compile and present the most up-to-date available evidence on the provision of IEFs containing Arg, omega-3, and RNA, to help clinicians develop an evidence-based nutrition care plan. Furthermore, we aim to identify available evidence of whether an esophagectomy patient would be the ideal case to receive IN, and a cost-benefit analysis to determine appropriate administration quantity and timing (pre-, peri-, or postesophagectomy).

We aim to address the following research questions. In cancer patients undergoing esophageal resection and requiring postoperative nutritional support: (1) Is there sufficient quality evidence on perioperative IEF enriched with omega-3, Arg, and RNA to recommend it as routine practice among clinicians?, (2) Do IEFs enriched with omega-3, Arg, and RNA confer additional clinical benefits such as reducing the risk of POIC and improving patients' health care outcomes compared to standard enteral nutrition?, and (3) Are IEFs enriched with omega-3, Arg, and RNA a cost-effective strategy to be considered by clinicians?

Methods

Types of Studies

This review will include randomized controlled trials (RCTs) on National Health and Medical Research Council level II intervention and use of IEFs in esophagectomy patients. The trials selected should contain IEFs (containing Arg, omega-3, and RNA) compared with standard enteral formulas (SEFs) either pre-, post-, or perioperative. Non-RCT intervention studies such as cohort studies will be excluded, since the potential risk of bias is higher. Likewise, we will exclude observational studies, abstracts, review papers, conference proceedings, and studies that are not English, Spanish, or Portuguese language.

Ethical approval is not required for the proposed systematic review and meta-analysis because the data used in this review will not involve the privacy of individual patients. Findings will be reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [10]. As well, the manuscript will be submitted for publishing in a peer-reviewed journal or the findings presented at a relevant conference.

Types of Participants

All patients 18 years or over undergoing surgical procedure for esophageal cancer will be included. Also, those included should be receiving IEF (containing a combination of Arg, omega-3, and RNA) pre-, peri-, or postoperatively for at least 5-7 days. Moreover, we will include all inpatient and outpatient/ambulatory patients in the health care facility where patients are having surgery (Textbox 1).

Types of Interventions

The intervention will be the use of IEFs containing the immunonutrients Arg, omega-3 polyunsaturated fatty acid, and RNA provided either orally or via an enteral feeding tube. To be included, studies will have IEF given pre-, peri-, and/or postoperatively as an intervention. Co-intervention with other oral or parenteral substances will not be included. The control group should be receiving the traditional isonitrogenous-isocaloric SEF or polymeric nutritional supplements either orally or via enteral feeding tube.

Primary and Secondary Outcomes

Primary Outcomes

The primary outcome will be POICs including wound infections or fistulae formation, bacteremia, sepsis, anastomotic leakage, abscess and pulmonary complications, especially pneumonia or bronchopneumonia within the first 2 weeks of surgery and during the whole stay in hospital [3]. The measure will be as defined by trial authors (categorical: present/absent or yes/no or continuous as number of cases or percentage of people with POIC).

Textbox 1. Participant inclusion and exclusion criteria.

Inclusion criteria:

- Adult patients (≥18 years) undergoing an elective surgical procedure for esophageal cancer; perioperative patients
- Adult patients in various stages of the disease including I, II, III, and IV
- All patients (inpatient and outpatient) undergoing surgery
- Receiving perioperative IEF (Impact/other similar formulation: combination of Arg, omega-3, and RNA for at least 5-7 days)

Exclusion criteria:

- Lower GI cancer surgery, gastric, or head cancer surgery
- Patients with cancer having parenteral nutrition or enteral feeding with non-IEF or IEF with only one isolated nutrient (Arg vs omega-3 vs RNA)

Secondary Outcomes

We will consider the following secondary outcomes measured pre- and/or postoperatively:

- Health-related costs/cost-effectiveness/cost-benefit: defined by the authors
- Health care use: length of stay (LOS) measured in number of days; readmissions to acute care, subacute care or intensive care unit; re-operations measured in number of cases
- Survival/mortality: number/proportion of deaths related to treatment 18 months (long-term survival) [11]; number/proportion of deaths (≤30 days and/or in-hospital postoperatively) [11]
- Quality of life: health-related quality of life measures via a validated diagnostic tool such as the European Organisation for Research and Treatment of Cealth-related quality of life questionnaires (within the first 3, 6, and 24 weeks postoperatively [12]; including symptoms such as eating difficulties, reflux, dysphagia, and trouble with coughing [13]
- Nutritional status: classified as well-nourished or malnourished and measured by validated nutrition assessment tool within 2 weeks pre-operatively
- Percentage of weight loss: 5% weight loss in past month (1/12) and 1 week and/or 3 weeks postoperatively
- Biochemical changes: as per trial authors, including C-reactive protein levels (from ≤7 days prior surgery and first 2 weeks postoperatively)

Searches

Searches for RCTs will be conducted systematically by the reviewers, with no publication year restriction. Non-English/Spanish/Portuguese studies might be excluded unless translations were provided or arranged. Also, original authors may be contacted for clarification and request of further data if trial reports seem unclear. Computerized searches will be performed for relevant published studies on the following databases from their inception until July 2017: the Cochrane Central Register of Controlled Trials (CENTRAL-The Cochrane Library), PubMed, EMBASE, CINAHL, LILACS, ClinicalTrials.gov, and the Trip (Turning Research into Practice) database. Subject strategies for databases in the search strategy will be modeled and designed for CENTRAL, CINAHL, and PubMed (Multimedia Appendix 1), which can be adjusted for other databases. Where appropriate, subject strategies will be combined with adaptations of the highly sensitive search strategy for identifying RCTs as described in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [14]. Additionally, during the searching process, consideration will be given to the different terminology used and the spelling of keywords as they may influence the identification of relevant studies.

The reference lists of identified publications will be scanned for further trials, and some trial authors may be contacted if required. Additional searches with Google Scholar, Google, and Bond University Library online will be conducted to retrieve remaining systematic reviews and meta-analyses pertinent to this review, in order to scan their reference lists for additional existing trials. A search of gray literature may be performed using the and .

Data Collection and Analysis

Selection of Studies

The results of the searches will be combined as indicated in Multimedia Appendix 1. The titles and abstracts identified from the search will be screened and assessed independently by the reviewers against the inclusion criteria to remove those that are inappropriate. If the title or abstracts are inconclusive, further in-depth screening and evaluation against the inclusion criteria will be undertaken. The reviewers will record independently the reasons for study exclusion and will report them in a flow diagram according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) format [10]. Disagreements over study selection will be resolved by discussion, and an external person may arbitrate if needed. Trial investigators shall be contacted if further information is required. All eligible references will be entered/collected into the bibliographic software package EndNote.

Data Extraction and Management

Data such as study design and setting, number of participants, outcome measure, and timing of IN initiation, route feeding, and total duration of IN will be autonomously extracted and organized on a matrix table (Multimedia Appendix 2). The meta-analysis data will also be pooled and organized on a matrix table (Multimedia Appendix 3). Reviewers will reach a consensus view by discussion. If further information is needed from an RCT, one of the reviewers may contact the nominated

trial investigator/author. A plan of how data will be pooled and organized for the outcome measures analysis is shown in Multimedia Appendix 4.

Assessment of Risk of Bias

The risk of bias in the eligible studies will be independently assessed by the reviewers. Any disagreements will be resolved through discussion with an external arbitrator if required. Risk of bias assessment will be performed using the domain-based evaluation tool described by the *Cochrane Handbook for Systematic Reviews of Interventions* [14].

Every RCT will be appraised according to the quality of 6 domains: (1) random sequence generation and allocation concealment (selection bias), (2) blinding of participants and personnel (performance bias), (3) blinding of outcome assessment (detection bias), (4) incomplete outcome data (attrition bias), (5) selective reporting (reporting bias), and (6) any other potential concerns to validity [14]. Blinding will be assessed separately for subjective (eg, nutritional status, LOS, quality of life) and objective (eg, percentage of weight loss, biochemical/immunological changes, mortality) outcome measures as the latter are less likely to be affected by knowledge of the treatment allocation group. Publication bias will be visually assessed by funnel plots as indicated by PRISMA [10].

Based on study reports, preliminary information will be collected in matrix tables to inform the risk of bias assessments (Multimedia Appendix 2). Trial authors shall be contacted to provide a study protocol or to clarify uncertainties where inconsistencies or unclear methodology were present during the risk of bias assessment.

A low risk of bias RCT will be considered if all or the majority of domains were gauged as adequate. RCTs will be considered as having a high risk of bias when one or more of the assessed domains within that trial were unclear or inadequate (unless original authors answer queries otherwise). The “risk of bias or internal validity” will be reported as part of the “characteristics and outcomes of identified studies” matrix (Multimedia Appendix 2) as well as a “risk of bias summary figure” presenting detailed judgments or explanations for all included studies in this review [2].

Data Analysis and Synthesis

Categorical data will be presented as risk ratio and risk difference or odds ratio including their 95% confidence intervals (CI), which will be calculated/extracted for the analysis of most of the outcome measures apart from health care use (ie, LOS) and biochemical/immunological changes that are exclusively represented as continuous variables (Multimedia Appendix 4). Also, numbers needed to treat for benefit or harm could be calculated as needed. Continuous data will be presented as mean, mean difference, or standardized mean difference with 95% CI, as applicable, excluding the nutritional status outcome measure, as it is represented exclusively as dichotomous variable. If a specific study does not report standard deviations, these will be calculated from the standard error and the sample size or the 95% CI. Finally, a P value of <.05 for both continuous and dichotomous variables will be considered statistically significant (Multimedia Appendix 4).

Assessment of Heterogeneity

Heterogeneity must be considered from both a clinical and statistical perspective. On one hand, clinical expertise will be used to decide whether it would be meaningful to combine the studies based on the potential sources of heterogeneity for each outcome measure. The potential sources where the RCTs may not show the exact same result could depend on factors such as the patients’ demographics (eg, age: adult vs elderly), nutritional status baseline, type of surgery (invasive or less invasive), different doses and timing of pre- versus peri- versus postoperative IEF, definition of the outcome measures, as well as the timing for measuring those outcomes (Multimedia Appendix 5). Hence, clinical heterogeneity will be reported using subgroup (pre-, peri-, and postoperative subgroups using IEF; well-nourished vs malnourished patients’ subgroups). Sensitivity analysis might also be calculated by restricting the analysis to trials classified as having an overall low risk of bias, which will help determine whether excluding studies at high risk of bias affects the results of the meta-analysis [13,15,16].

On the other hand, statistical heterogeneity, which quantifies the variation due to heterogeneity and not due to chance across the RCTs, will be also checked through the statistical calculation of an I^2 test [2]. Hence, values of 25%, 50%, or 75% will denote low, moderate, or high levels of heterogeneity respectively [2].

After that process, if the degree of clinical and statistical heterogeneity of studies are not excessive, a quantitative summary measures (meta-analysis) will be generated by the Review Manager (RevMan) 5.3 software and represented in forest plots [14]. Thus, the meta-analysis will characterize the effect of the dichotomous and continuous outcomes.

Where statistical pooling is not possible, the findings will be presented in narrative form or a table to describe the outcomes, different tools used to assess the outcomes listed for this review, or continuous data that can be pooled for meta-analysis.

Confidence in Cumulative Estimate

The quality of evidence for all outcomes will be judged using the Grading of Recommendations Assessment, Development and Evaluation working group methodology. Therefore, the quality of evidence will be assessed across 5 domains: risk of bias, consistency, directness, precision, and publication bias. Additional domains may be considered where appropriate. High-quality evidence will be adjudicated when further research might be very unlikely to change the reviewer’s confidence in the estimate of effect; moderate quality if further research is likely to have a significant impact on the confidence and may change the estimate; low quality if further research is needed and is very likely to have an important impact and likely to change the estimate; and very low quality if there is considerable uncertainty about the estimate of effect.

Results

The first results are expected in 2018. Outlining the protocol will ensure transparency for the completed review.

Discussion

Principal Considerations

Given the nature of esophageal cancer and the significant potential for nutritional deficiencies prior to resection as compared with other gastrointestinal (GI) pathologies, it seems appropriate that there should be a specific focus on the role of perioperative nutritional supplementation [17]. Research has shown that IEFs enriched with a combination of Arg, omega-3 fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), RNA, and antioxidants [18], can act pharmacologically on the immune system and potentially improve the patient's immune response [9]. Furthermore, providing patients with peri-operative IEF has shown to favorably modulate the inflammatory, metabolic, and immune response after upper GI surgery [19,20]. These effects generated on the immune system modulated through specific nutrients are called immunonutrition.

IEFs enriched with a combination of immunonutrients (Arg, omega-3, and RNA) are well known to Australian clinicians. However, IN is not consistently used with cancer patients undergoing esophageal resection as standard practice [21]. Since this IEF offers the combination of immunonutrients in one product, it has been implemented in a wide range of surgical and trauma patients [22] to significantly reduce POICs by 39%-61%, LOS by 2 days [23], antibiotic use, and health-related costs [18]. Several studies have shown positive outcomes among GI surgical patients, where anastomotic leaks were 46% less prevalent when these IEFs were part of the pre-operative nutrition care plan [3,18,21,23,24]. Additionally, it has been found that LOS and POIC in malnourished (upper and lower) GI cancer patients significantly decreased when a "5-7-day peri-operative approach" was implemented with IEF over SEF [18,25,26]. Thus, nutrition support of surgical patients with malnutrition should not only include the adequate quantity but also the nutrient quality, type, and prescription timeframe to support the patient's recovery, postoperative outcomes, and reduce health care costs [20,27-29]. In terms of health care cost-benefit analysis, the implementation of IN in surgical patients resulted in savings of US $3300 per patient based on the reduction of POIC rates [22] and reported savings of up to US $6000 per patient, based on the shortening of LOS [16], showing that enteral IEFs are a beneficial and cost-effective intervention.

Conclusion

To date, there have been several systematic reviews and meta-analyses of RCTs undertaken to determine the effectiveness of IN in elective upper and lower GI surgical practice [7,16,21,30]. However, the effect of a particular combination of immunonutrients (Arg, omega-3, and RNA) and its overall effect on postesophagectomy outcomes have not been systematically reviewed. Hence, there is a lack of sufficient, recent clinical evidence supporting the use of IEFs in esophagectomy patients. Evaluation of the studies identified in this review has merit because the review will aim to provide the most up-to-date evidence-based nutrition statements regarding pre-, peri-, and postoperative enteral IN effects on postesophagectomy outcomes.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Search terms and results of the search strategy.

[PDF File (Adobe PDF File), 46KB - resprot_v6i11e214_app1.pdf]

Multimedia Appendix 2

Characteristics of studies including immunonutrition for esophagectomy.

[PDF File (Adobe PDF File), 43KB - resprot_v6i11e214_app2.pdf]

Multimedia Appendix 3

Characteristics of RCTs included in meta-analysis of immune-enhancing formula versus standard enteral formula.

[PDF File (Adobe PDF File), 42KB - resprot_v6i11e214_app3.pdf]

Multimedia Appendix 4

Outcome measures analysis table.

[PDF File (Adobe PDF File), 56KB - resprot_v6i11e214_app4.pdf]

Multimedia Appendix 5

Table of the planned statistical analysis for the meta-analysis.

[PDF File (Adobe PDF File), 59KB - resprot_v6i11e214_app5.pdf]

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Abbreviations

Arg: arginine
CI: confidence intervals
GI: gastrointestinal
IEF: immune-enhancing formula
IN: immunonutrition
LOS: length of stay
POIC: postoperative infectious complication
RCT: randomized controlled trial
RNA: ribonucleic acid
SEF: standard enteral formula

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Protocol

Should Medical Assistance in Dying Be Extended to Incompetent Patients With Dementia? Research Protocol of a Survey Among Four Groups of Stakeholders From Quebec, Canada

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Abstract

Background: Alzheimer's disease and related disorders affect a growing number of people worldwide. Quality of life is generally good in the early stages of these diseases. However, many individuals fear living through the advanced stages. Such fears are triggering requests for medical assistance in dying (MAiD) by patients with dementia. Legislation was recently passed in Canada and the province of Quebec allowing MAiD at the explicit request of a patient who meets a set of eligibility criteria, including competence. Some commentators have argued that MAiD should be accessible to incompetent patients as well, provided appropriate safeguards are in place. Governments of both Quebec and Canada are currently considering whether MAiD should be accessible through written requests made in advance of loss of capacity.

Objective: Aimed at informing the societal debate on this sensitive issue, this study will compare stakeholders' attitudes towards expanding MAiD to incompetent patients with dementia, the beliefs underlying stakeholders' attitudes on this issue, and the value they attach to proposed safeguards. This paper describes the study protocol.

Methods: Data will be collected via a questionnaire mailed to random samples of community-dwelling seniors, relatives of persons with dementia, physicians, and nurses, all residing in Quebec (targeted sample size of 385 per group). Participants will be recruited through the provincial health insurance database, Alzheimer Societies, and professional associations. Attitudes towards MAiD for incompetent patients with dementia will be elicited through clinical vignettes featuring a patient with Alzheimer's disease for whom MAiD is considered towards the end of the disease trajectory. Vignettes specify the source of the request (from the patient through an advance request or from the patient's substitute decision-maker), manifestations of suffering, and how close the patient is to death. Arguments for or against MAiD are used to elicit the beliefs underlying respondents' attitudes.

Results: The survey was launched in September 2016 and is still ongoing. At the time of submission, over 850 respondents have returned the questionnaire, mostly via mail.

Conclusions: This study will be the first in Canada to directly compare views on MAiD for incompetent patients with dementia across key stakeholder groups. Our findings will contribute valuable data upon which to base further debate about whether MAiD should be accessible to incompetent patients with dementia, and if so, under what conditions.

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KEYWORDS

euthanasia; dementia; decisional incapacity; advance directive; attitude; survey; Canada

Introduction

Medicine aims to relieve patient suffering and cure illness [1]. When patients can no longer be cured, palliative care aims to improve quality of life by relieving suffering [2]. Palliative care has expanded over the past decades, although accessibility gaps remain, notably for patients with Alzheimer's disease and related disorders whose illnesses are still too often not recognized as terminal [3,4]. Moreover, despite quality palliative care, some patients (with and without dementia) experience treatment-refractory symptoms that may lead to medical assistance in dying (MAiD) requests as a last resort to alleviate suffering [5,6]. Whether MAiD should be accessible to incompetent patients with dementia raises complex ethical and practical issues. We designed a study to investigate the views of stakeholders on these issues in Quebec, Canada. In this paper, we summarize current knowledge on these issues, state the objectives of our study, describe its methodology, and discuss its strengths and limitations.

Legal Landscape on MAiD Internationally in Canada, and in Quebec

Outside of Canada, euthanasia and/or physician-assisted suicide have now been legalized in four countries (The Netherlands, Belgium, Luxemburg, and Colombia), four US states (Oregon, Washington, Vermont, and California) and the District of Columbia. In the scientific literature, *euthanasia* commonly refers to, "the administration of drugs with the explicit intention of ending the patient's life at his or her explicit request" and *physician-assisted suicide* refers to, "the prescription or supply of drugs with the explicit intention of enabling the patient to end his or her own life" [7]. An *explicit request* can be made contemporaneously or previously (ie, in advance of incapacity). Physician-assisted suicide is also allowed by operation of a court decision in Montana. In Switzerland, euthanasia is illegal but assisted suicide (whether by a physician or nonphysician) is only prohibited when done for a "selfish motive" [8-11]. Between 0.1% and 4.6% of all deaths involve MAiD in countries where it is legal [12,13].

In most permissive jurisdictions, MAiD is not available to individuals with dementia. Patients are either still capable but not near enough to the end of life, or they are close enough to the end of life but no longer capable. However, in the Netherlands, where being at the end of life is not a condition of eligibility for MAiD, 109 euthanasia requests from competent patients in the early stages of dementia were granted in 2015 [6]. Furthermore, the Dutch legislation allows a physician to comply with a euthanasia request made by a formerly competent patient through an advance request, as long as all of the "criteria of due care" are met (notably including unbearable suffering). To date, four cases have been reported regarding Dutch patients who requested euthanasia while competent via a written request, and whose requests were granted after they had become incompetent [6,14]. Similarly, the law in Belgium does not require patients to be at the end of life or terminally ill, and does permit some access to MAiD through written requests made in advance of loss of capacity. However, in these cases the patient must be unconscious. In Luxembourg, a patient must be in a terminal condition, and access to MAiD is permitted through an advance request (provided the patient is unconscious). These requirements mean that many patients with dementia will not qualify for MAiD, but some will.

Until recently, MAiD was prohibited in Canada under several provisions of the *Criminal Code*. There have been court challenges to these provisions over the last 25 years, the most notable being *Rodriguez v. British Columbia (Attorney General)* in 1993 [15] and, more recently, *Carter v. Canada (Attorney General)* in 2015 [16]. In the first case, the Supreme Court of Canada dismissed the appeal of Sue Rodriguez, a woman living with amyotrophic lateral sclerosis who had challenged the validity of the *Criminal Code* prohibitions on MAiD [15]. This decision was overturned on February 6, 2015 by a unanimous decision of the Supreme Court in *Carter v. Canada* [16] . The judges ruled that the prohibitions violate section 7 of the *Canadian Charter of Rights and Freedoms*.

The Court's ruling catalyzed the Government of Canada to engage in consultation and draft legislation specifying the eligibility criteria and procedural safeguards for access to MAiD. Bill C-14 came into force on June 17, 2016 [17], enacting exemptions from criminal liability for physicians and nurse practitioners who provide MAiD, and for others who assist them. Eligibility is restricted to a competent adult who makes a voluntary and well-considered request for MAiD and has a, "grievous and irremediable medical condition" [17]. Canada Bill C-14 defines *medical assistance in dying* as:

> *The administering by a medical practitioner or nurse practitioner of a substance to a person, at their request, that causes their death, or the prescribing or providing by a medical practitioner or nurse practitioner of a substance to a person, at their request, so that they may self-administer the substance and in doing so cause their own death [17]*

MAiD thus encompasses both euthanasia and physician-assisted suicide, as defined above. A person has a grievous and irremediable medical condition only if all of the following criteria are met:

> *(a) they have a serious and incurable illness, disease, or disability; (b) they are in an advanced state of irreversible decline in capability; (c) that illness, disease, or disability or that state of decline causes them enduring physical or psychological suffering that is intolerable to them and that cannot be relieved under conditions that they consider acceptable; and (d) their natural death has become reasonably foreseeable, taking into account all of their medical circumstances, without a prognosis necessarily having been made as to the specific length of time that they have remaining [17]*

Contrary to recommendations made by a Provincial-Territorial Expert Advisory Group on Physician-Assisted Dying [18] and a Special Joint Committee of the House and Senate on Physician-Assisted Dying [19], the federal legislation does not allow a person to access MAiD through a request made in advance of loss of capacity. However, the legislation mandated an independent review and reporting back to Parliament on several issues, including advance requests. The government has commissioned the Council of Canadian Academies to independently manage the review and report to Parliament by December 2018.

On June 10, 2014, eight months before the Supreme Court's ruling in *Carter v. Canada*, the Quebec National Assembly adopted *An Act respecting end-of-life care* (Bill 52) which codifies recommendations made by the Quebec College of Physicians [20] and the province's Select Committee on Dying with Dignity [21]. Briefly, Bill 52 first affirms the right of everyone to end-of-life care that is appropriate to their needs. The bill also regulates continuous palliative sedation, establishes an advance medical directives regime, and permits MAiD under strictly defined circumstances [22]. In Quebec Bill 52, MAiD is defined as:

> *Care consisting in the administration by a physician of medications or substances to an end-of-life patient, at the patient's request, in order to relieve their suffering by hastening death [22]*

This definition corresponds to euthanasia, as defined above. Nurse practitioners are not authorized to administer aid in dying under the Quebec legislation. The legislation became effective on December 10, 2015. Eligibility for MAiD is restricted to competent adults from Quebec who are at the end of their lives, have made persistent explicit requests for MAiD, and:

> *Suffer from a serious and incurable illness, are in an advanced state of irreversible decline in capacity, and experience constant and unbearable physical or psychological suffering which cannot be relieved in a matter the patient deems tolerable (article 26) [22].*

For greater clarity, article 51 specifies that MAiD may not be requested by means of an advance medical directive.

Quebec Bill 52 has drawn both opposition and support, with some supporters recommending that access to MAiD be extended to incompetent patients, provided appropriate safeguards are in place [23]. Proposed safeguards for MAiD, should it be accessible to incompetent individuals, have included: an explicit request made in an advance directive by the patient while competent; consent from the patient's legal representative; and prior authorization of a local or provincial body, where relatives and health professionals could be heard [24]. Ultimately, Quebec decided not to give incompetent patients access to MAiD through Bill 52, noting a lack of societal consensus on this issue [25]. However, recently the Minister of Health and Social Services announced that an expert group will be tasked with studying whether access to MAiD should be permitted through requests made in advance of loss of capacity. This initiative has obvious implications for patients with dementia.

In both Canada and the province of Quebec, eligibility criteria for MAiD currently exclude patients who have become incompetent due to Alzheimer's disease or other forms of dementia. These are serious incurable conditions that progressively and irreversibly erode patients' abilities to perform basic activities of daily living. Additionally, many affected individuals develop serious clinical complications (eg, eating problems, pneumonia) and distressing symptoms (eg, pain, dyspnea) that are difficult to manage [26-29]. However, by the time a patient satisfies these criteria, he or she is unlikely to be competent. Strong opinions have been voiced in support of, and in opposition to, the exclusion of patients with advanced Alzheimer's disease and other forms of dementia. The issue of respecting MAiD requests that are to be carried out after the patient has lost capacity is a complex health care issue that brings diverse societal values and beliefs into relief and conflict; these are briefly reviewed below.

Arguments For and Against MAiD, in General and for Incompetent Patients With Dementia

Arguments in favor of MAiD generally include individual autonomy and freedom of choice, the inability to relieve suffering in some cases, the absence of a moral distinction between withholding/withdrawing potentially life-sustaining treatment and MAiD, and the claim that permitting MAiD allows the establishment of stronger safeguards and oversight for the entire spectrum of end-of-life medical care through carefully-designed regimes. Arguments against MAiD include: the sanctity of life; the need to protect socially vulnerable populations from abuse and social discrimination; concerns about the *slippery slope* which (depending on the interpretation) could lead to more abuse, or to the legislation being extended to incompetent patients; the risk of impeding the development of palliative care; and ethical tensions faced by physicians who object to MAiD on moral grounds, but could feel or be obliged to carry out the request [11,30-33].

Other arguments are raised against MAiD when referring specifically to patients rendered incompetent by advanced dementia: patients' potential to adapt to their disease, which may change previously expressed wishes (the so-called "disability paradox"); the impossibility of health care providers

and families engaging in meaningful conversations with the patient to confirm the wish to die; and practical difficulties in assessing suffering, balancing current preferences against earlier wishes laid down in a now-forgotten request, and choosing the right moment to carry out the request. Complying with an advance request for MAiD also raises the philosophical question of whether a request made by a previously competent person should have any authority over the life of a person who now has severe dementia [34-44].

Attitudes of Stakeholders Towards MAiD

Major groups of stakeholders likely to be impacted by extending MAiD to incompetent patients include older adults, relatives of patients with dementia, physicians, and nurses. Systematic reviews of quantitative studies from several countries, including Canada, show increasing support from these groups of stakeholders for MAiD in cases of competent terminally-ill patients experiencing severe pain who make an explicit request [10,11,45-47]. Far fewer studies have investigated opinions of stakeholders on MAiD for patients with dementia [48-58]. None of these studies were conducted in Canada and only two have focused exclusively on this issue [53,56]. As shown in Table 1, support was found to be higher in the general population and lower among physicians, with nurses' opinions falling in between. Support for advance requests for MAiD is also stronger among the general public than among health care practitioners, who raise numerous issues regarding their use [37,39].

In conclusion, growing knowledge of possible clinical complications of advanced dementia, and current access to MAiD for competent adults, will likely trigger advance requests for MAiD from Canadians diagnosed with dementia [11,59,60]. To date, no study has investigated the attitudes and beliefs of Canadians on this complex and sensitive issue. Similarly, no study has examined whether Canadians support other end-of-life medical practices in advanced dementia, such as the withholding of antibiotics for a life-threatening pneumonia or continuous deep sedation for agitation refractory to treatment. This study will shed light on these specific issues, providing much-needed evidence to support future health care policy development on end-of-life care for Canadians with advanced dementia.

Table 1. Studies that have elicited attitudes towards assistance in dying for incompetent patients (mostly due to dementia).

First author (year of publication)	Country	Age of sample, years (standard deviation)	Sex of sample, male (%)	Response rate (%)	Sample size	Percent judging the practice (or its legalization) acceptable[a]
General Public						
Koenig (1996) [49]	United States (Durham, NC)	61% over 75 years	23	86	168	14
Van Holsteyn (1998) [50]	The Netherlands	18 or older	unspecified	46	911	45
Ryynänen (2002) [51]	Finland	18 to 70	42	59	587	48
Rietjens (2005) [52]	The Netherlands	20 to 93	39	78	1388	62
Williams (2007) [53]	United Kingdom (London)	43 (17)	46	71	725	57 to 59
Lindblad (2010) [54]	Sweden	20 to 84	50	52	625	60 to 65
Kouwenhoven (2013) [55]	The Netherlands	53 (15)	54	78	1960	77
Relatives of patients with dementia						
Rurup (2006) [56]	The Netherlands	57	38	72	136	89
Physicians						
Ryynänen (2002) [51]	Finland	24 to 87	48	62	506	8
Rietjens (2005) [52]	The Netherlands	63% aged 40 to 55	76	81	391	6
Rurup (2006) [56]	The Netherlands	41	51	96	107	16
Lindblad (2010) [54]	Sweden	32 to 79	69	56	667	13 to 15
Kouwenhoven (2013) [55]	The Netherlands	51 (8)	65	41	793	33
Nurses						
Ryynänen (2002) [51]	Finland	20 to 63	6	73	582	23
Rurup (2006) [56]	The Netherlands	34	17	94	148	57
Gielen (2009) [57]	Belgium (Flanders)	44 (9)	12	70.5	415	52 to 56
Inghelbrecht (2009) [58]	Belgium (Flanders)	42% aged 36 to 45	12	62.5	3321	57
Kouwenhoven (2013) [55]	The Netherlands	44 (11)	10	unspecified	1243	58

[a]Range reported when several items were used to measure acceptability

Research Objectives and Hypotheses

Restricted to Quebec with plans for extension to other Canadian provinces, this study will elicit and compare the attitudes of four groups of stakeholders (seniors, relatives of persons with dementia, physicians, and nurses) towards MAiD for incompetent patients with dementia, the beliefs underpinning stakeholders' positions on this matter, and their opinions as to whether proposed safeguards can adequately protect incompetent patients. Based on findings in other countries [11,31], we expect that: (1) support for MAiD for incompetent patients with dementia will be higher among seniors and relatives than among health care practitioners; (2) support among health care practitioners will increase with additional safeguards, without reaching the level of support found in the two other groups; (3) religiosity, *slippery slope*, autonomy, and dying-with-dignity arguments will affect respondents' permissiveness toward MAiD for incompetent patients with dementia; and (4) the relative weight of these arguments in shaping opinions will vary across the four groups of stakeholders.

Methods

Study Design, Target Groups, and Sampling

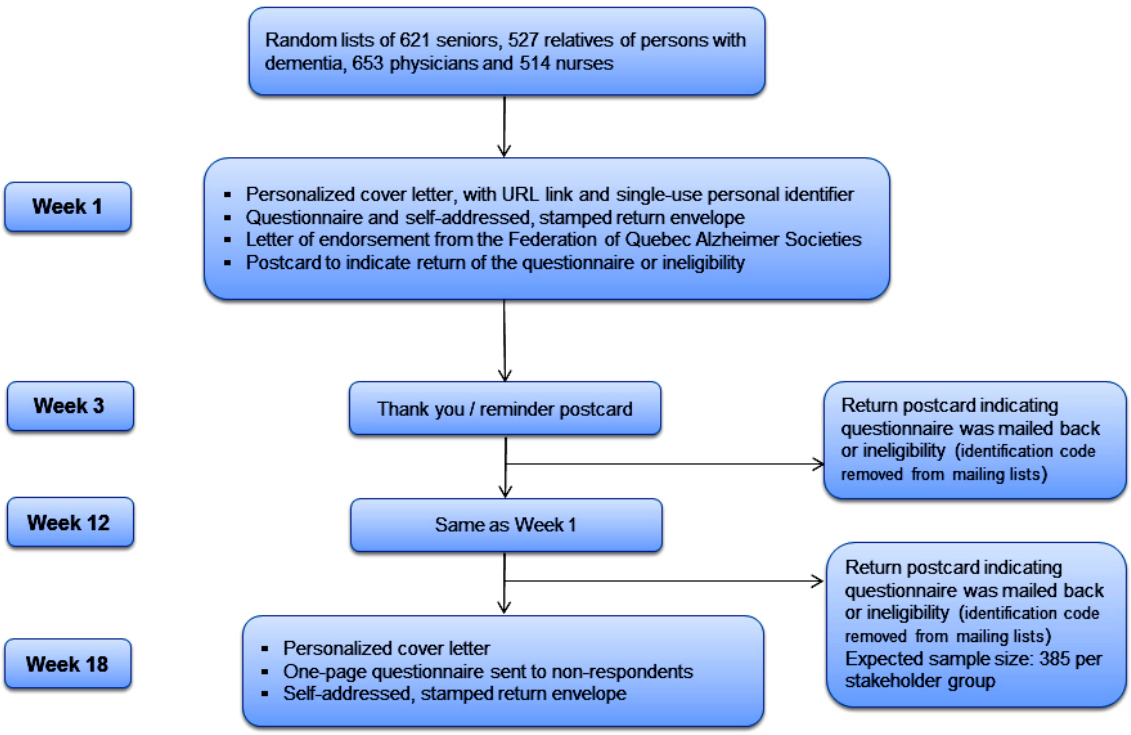
An anonymous province-wide postal survey using clinical vignettes will be conducted on random samples of French-speaking Quebec residents belonging to one of four groups of stakeholders: (1) community-dwelling seniors aged 65 years or older, (2) relatives of persons with dementia, and (3) physicians and (4) nurses likely to be involved in end-of-life decision making. In Quebec, 94% of the population speaks French [61].

The random sample of community-dwelling seniors will come from the Quebec health insurance database. Relatives of patients with dementia will be reached through regional Alzheimer Societies. To protect their members' right to privacy, participating Societies will randomly select a predetermined number of potential participants (proportional to the size of their memberships) and distribute the survey package directly to them per our instructions. Assistance in managing the survey will be provided by our research staff to any Society that expresses the need. Practicing physicians and nurses will be recruited through their respective professional bodies, excluding those in full-time administrative, teaching, or research positions due to their limited direct contact with patients. Specialties for physicians will be restricted to family medicine, geriatrics, internal medicine, neurology, psychiatry, and intensive care; for nurses, specialties will be restricted to geriatrics/gerontology and end-of-life care.

Postal Survey

The survey and questionnaires were designed using strategies shown to maximize response rates and data quality [62]. As depicted in Figure 1, randomly sampled individuals receive a personalized cover letter and accompanying materials in week 1, and a thank-you/reminder postcard in week 3. Nonrespondents are mailed a second survey package in week 12. The personal letter states the aim of the survey, explains how recipients were chosen, mentions that completing the questionnaire requires 20 minutes on average (based on pretesting), and addresses issues of privacy and anonymity. The letter also provides the Internet link (website address) to the online version of the questionnaire as well as the recipient's single-use personal identifier. A self-addressed and stamped return envelope is enclosed in the survey package for those who prefer to complete the printed questionnaire.

Figure 1. Outline of the postal survey.



A letter of endorsement from the Federation of Quebec Alzheimer Societies is also included, with a postcard bearing the respondent's name, to be returned separately from the questionnaire. Returned postcards make it possible to identify sampled individuals who have returned the questionnaire–either by mail or electronically–while preserving the anonymity of their answers. The postcard also serves the purpose of identifying sampled individuals who are no longer eligible (eg, seniors who are now institutionalized or too cognitively impaired to participate). The names of those who return the postcard are immediately removed from the mailing list to prevent further reminders. At the close of the postal survey, nonrespondents receive a 3-item questionnaire asking: (1) for their reasons for not participating (eg, felt questions were biased, lack of time, or doubt that anonymity can truly be preserved); (2) how comfortable they are with the current Quebec legislation that gives competent patients access to MAiD if certain conditions are met; and (3) whether they favor or oppose allowing physicians to administer MAiD to incompetent patients, with proper safeguards in place. The latter two questions will be used to assess nonresponse bias.

Questionnaires

After stating the eligibility criteria for MAiD as defined in Quebec's *Act respecting end-of-life care*, the 3-part questionnaire presents a series of multiple-choice questions, with space for the respondent's comments. Part 1 elicits attitudes towards MAiD and other end-of-life practices. Two sets of clinical vignettes are used for that purpose. The first vignette features a cancer patient who is eligible for MAiD. Using a 5-point Likert-type scale, respondents are asked to what extent they find it acceptable for a physician to sedate the patient continuously until death to relieve suffering, or to comply with the patient's request for MAiD. The second set, containing 7 interrelated vignettes, features a woman moving along the dementia trajectory, from the early stage when she is diagnosed with Alzheimer's disease to her final days of life. End-of-life practices (besides MAiD) for which support or opposition is investigated include withholding antibiotics for a life-threatening infection and continuous deep sedation for refractory agitation. Vignettes specify the source of the request for MAiD (an advance request made in writing by the patient while she was still competent, or her family), whether the patient appears to be suffering (eg, showing signs of distress, crying regularly), and whether death seems imminent. Vignettes are kept as nontechnical as possible to be easily understood, regardless of the respondent's medical knowledge. A sensitive and neutral tone is used throughout the questionnaire to prevent response bias. Part 1 ends with a list of statements designed to capture respondents' reasons for supporting or opposing MAiD, generally and for incompetent patients in particular. Reasons include, for example: religious and moral objections, respect for patient autonomy, practical difficulties in ascertaining whether an incompetent patient is suffering unbearably, and concerns about the *slippery slope*.

Part 2 explores related issues, such as whether respondents have filled out an advance directive for themselves, personally know someone with dementia, or have ever accompanied a dying relative or friend. Respondents are also asked the likelihood that they would request MAiD in advance of loss of capacity, should they be diagnosed with Alzheimer's disease, or ask a physician to comply with such a request drafted by a loved one under similar circumstances.

Part 3 collects sociodemographic data from all respondents (eg, age, gender, ethnicity, degree of religiosity) and contains additional group-specific questions. For seniors, these questions include educational attainment and self-rated health. Relatives are asked how long ago the person with dementia was diagnosed and their current level of cognitive functioning. Questions for physicians and nurses explore their experience in caring for dying and dementia patients, training in palliative care, and exposure to MAiD requests from patients or patients' relatives. Physicians are also asked whether they would be willing to provide such assistance, were it legal. Few physicians currently administer MAiD in Quebec, and to preserve their anonymity, surveyed physicians are not asked whether they have in fact provided such assistance in the past.

Questionnaires were developed in English with input from renowned English-speaking content experts from countries where assisted dying is legal or not criminalized. The questionnaires were then translated into French and pretested through cognitive interviews performed by a research assistant with representatives of the four groups of stakeholders (n=20). Interviews were aimed at assessing the length of the questionnaires, clarity of the questions, uniformity in comprehension, and respondent comfort with the content [63]. Following these interviews, minor modifications were made to some questions, which aimed at emphasizing differences between vignettes (eg, advanced vs. terminal stage of Alzheimer's disease, presence vs. absence of a written request). Questionnaires were then converted to a Web format. The Web questionnaires were developed using the latest version of LimeSurvey [64], a free open-source online survey application that allows assigning a single-use password to each sampled individual. The server hosting the LimeSurvey software uses proven encryption methods (Transport Layer Security) to transmit survey answers to a secure server and export collected data into a statistical package for analysis. Before launching the survey, the Web version was tested in-house and with several remote participants on different operating systems, browsers, and platforms, and for different types and speeds of Internet access. Systematic troubleshooting was performed to uncover unforeseen technical problems.

Data Analyses

The data will be analyzed in four consecutive steps. First, we will compare nonrespondents, respondents to the one-page questionnaire only, and late versus early respondents to the full questionnaire, to detect response bias and establish sample weights where needed. Response rates will be reported as recommended by the American Association for Public Opinion Research. In Step 2, we will study patterns of item nonresponse and determine whether imputing missing data would be appropriate [65]. Next, we will summarize participant answers to the questionnaire, and compare distributions of answers within respondents, as well as within and between the four groups of stakeholders. Within-respondent comparisons will require

multilevel analyses, since answers to different questionnaire items will be correlated [66]. For instance, the proportions of respondents who support MAiD at the advanced versus terminal stages are not independent and hence cannot be compared using the usual Chi-square test. Estimations of model parameters will be based on maximum likelihood with adaptive quadrature, which outperforms other methods in terms of bias and efficiency of the estimates when the number of study participants is large, as is typical of survey research [67]. Respondent characteristics will subsequently be added to the models in a stepwise fashion to identify additional correlates of response patterns in addition to group membership. Residual analyses will be conducted to assess the tenability of the assumptions underlying the statistical models, and to identify influential observations and outliers. Multilevel modelling will be conducted with SAS Proc NLMIXED [68], which offers a wide choice of integral approximations and optimization techniques.

Sample Size

The data from our four samples will first be summarized with proportions and associated confidence intervals. In the worst-case scenario of equal proportions for and against a given end-of-life practice, two-sided 95% confidence intervals for proportions require 385 respondents per sample when the semiinterval width is set at 5% (nQuery Advisor, version 7.0). The sample size required for reliably fitting multilevel models depends on several factors, including sample size at each level of the analysis, number and type of predictors included in the model, intraclass correlation, and model complexity. Recent Monte Carlo simulation studies on multilevel models for binary and continuous outcomes suggest that 100 to 200 level-2 units (ie, survey respondents) with 5 to 10 level-1 units (ie, questionnaire items) ensure model convergence and provide adequate power for testing fixed and random effects [69]. To determine the number of questionnaires to mail out to achieve the target of 385 respondents per group, we applied response rates derived by averaging those reported in Table 1 with our own [70,71]. The resulting numbers are: 621 seniors, 527 relatives of persons with dementia, 653 physicians, and 514 nurses, for a total of 2315 potential participants.

Ethical Considerations

This study will investigate views on sensitive issues. While there are no physical risks to participants, psychological risks must be acknowledged. Questionnaires may trigger emotional distress in some participants or revive painful memories of the death and suffering of a loved one. In an effort to minimize these risks, the cover letter that accompanies the questionnaire includes contact details for a support resource, if needed. Participation in the survey is voluntary and answers are anonymous. Signed consent is not required; in anonymous surveys, implicit consent is inferred from respondents who return the questionnaire [72]. All information needed for informed consent is provided in the cover letters, including a toll-free telephone number and email address for those who have questions or concerns about the survey. Personal information on sampled individuals is coded, and access to password-protected lists of codes is restricted to the research team. Sampling lists will be destroyed five years after the end of the study. The Research Ethics Board of the University Institute of Geriatrics of Sherbrooke granted ethical approval of the survey design and questionnaires (file # 2016-623).

Results

The survey was launched in September 2016 among relatives of patients with dementia, physicians, and nurses, and is still ongoing. The survey will be launched among older adults as soon as we receive a random list of names extracted from the Quebec health insurance database.

Discussion

To the best of our knowledge, this study will be the first to uncover Quebec stakeholders' attitudes towards MAiD for incompetent patients with dementia, which is a vulnerable and rapidly expanding population of patients. Dementia affects more than 37 million people worldwide, with a projected increase to over 115 million by 2050 [73]. The Alzheimer Society of Canada has estimated that 564,000 Canadians were living with dementia in 2016, and this number is expected to rise to 937,000 by 2031, representing an increase of 66% [74]. Life expectancy after a dementia diagnosis is believed to lie between 3 and 12 years [75]. Because no cure is foreseen in the near future, many people will die with or from dementia. Over the last decade, deaths attributed to Alzheimer's disease rose by 39% in the United States [76]. Although quality of life can be good in the early stages, dementia still ranks among the most feared clinical conditions in modern societies [77]. Indeed, some perceive this syndrome as a "fate worse than death" and dread the prospect of living through the advanced stages of dementia [78,79]. People are apprehensive about the progressive loss of decisional capacity and control, prolonged dependence upon others for their most basic needs, inability to report physical and psychological suffering, and lengthy periods of institutionalization before death. As the prevalence of dementia continues to rise, a growing number of individuals who do not want to experience the full course of dementia might request MAiD.

Do stakeholders believe that MAiD should be made available to patients who have reached an advanced stage of dementia? Under what circumstances? Are other end-of-life practices viewed as more appropriate? Can proposed safeguards on MAiD adequately protect vulnerable individuals from abuse and coercion? Do views on these issues vary markedly within and between groups of stakeholders? By using a proven research methodology and identical questions across stakeholder groups, this study will provide answers to these questions, which have yet to be explored in Canada, and have only been partially investigated in other countries.

Strengths and Limitations

The current study has strengths and limitations. Strengths include: the timeliness of the survey, which will inform ongoing legislative activities; random selection of potential respondents from four highly relevant groups of stakeholders; the anonymity of answers, which decreases bias due to social desirability; the care taken in designing and testing the questionnaires with input

from international content experts; and our decision to administer a common set of questions to all four groups of stakeholders, enabling direct comparison of their views on MAiD for incompetent patients with dementia. The presence of investigators on the research team who support, and others who oppose, extending MAiD to these patients is another strength, as it minimizes the risk of biased questions and increases uptake of research findings [80].

Although not without limitations, surveys contribute invaluable data to inform ethical debates, public policy development, and future research on sensitive issues such as whether MAiD should be extended to incompetent patients with dementia [81]. Postal surveys offer many advantages over other data collection methods. First, such surveys are relatively inexpensive for surveying large and geographically dispersed populations, provide greater flexibility for the respondents, maintain anonymity, and yield higher response rates than telephone surveys [62]. In our survey, sampled individuals have the option to complete a paper or online version of the questionnaire, which is a strategy shown to yield even higher response rates [82,83]. Second, earlier studies conducted abroad provide a solid basis for the design of high-quality clinical vignettes featuring incompetent patients, MAiD requests, and end-of-life practices [49-58]. Additionally, the practical problems and moral dilemmas created by advanced MAiD requests, and the arguments for and against MAiD for incompetent patients with dementia, have been thoroughly reviewed [34-44]. These reviews have provided ample materials from which to formulate questionnaire items for exploring beliefs underlying attitudes.

Low response rates threaten the external validity of findings from attitude surveys. To counter this problem, both the survey and the questionnaires were designed using strategies that comprehensive reviews have shown to be effective [84,85]. Response rate is an imperfect indicator of survey quality, however. Empirical assessments over the past decade have concluded that response rates may not be as strongly associated with survey quality as was generally believed [86]. The degree to which respondents differ from the target population is the central issue. Well-recognized approaches to assess nonresponse bias and minimize its effect are part of our analytical plan and include: inviting initial nonrespondents to complete a shorter questionnaire with only key measures of interest, comparing respondents with nonrespondents using information available in the sampling frame, comparing early versus late respondents on personal characteristics and answers to survey questions, and weighting analyses of the variables of primary interest.

One limitation is the restriction of the survey to the province of Quebec. We plan to extend the survey to the rest of Canada in the near future, using the same questionnaires to enable provincial/territorial comparisons. Short case descriptions with a limited number of possible answers fall short of capturing the complexity of end-of-life decision making [52]. Our upcoming pan-Canadian survey will include a qualitative component aimed at gaining deeper insight into respondents' thought processes and the reasons behind their support for, or opposition to, MAiD for incompetent patients with dementia [43]. Opinions are elicited using specific vignettes. Whether opinions extend to other clinical contexts involving MAiD requests from incompetent patients with dementia will remain unknown. We chose not to elicit attitudes towards extending MAiD to patients at earlier stages of dementia who are still competent. Including cases of early and late stage dementia in the same questionnaire would increase its length and possibly lower response rates. We also chose not to recruit in long-term care facilities, where most residents would be too cognitively impaired to provide reliable and valid answers to the survey questionnaire. We do not purposefully target seniors with dementia, even though those at an early stage of the disease would likely have the cognitive abilities to participate in the survey. We felt that a self-administered questionnaire was not ethically appropriate for this subpopulation, given the sensitive nature of the subject under investigation [81]. However, as the views and concerns of this population regarding end-of-life practices in advanced dementia are highly relevant yet currently unknown, we are simultaneously conducting a qualitative study in this population. The data from persons with early dementia will be collected during face-to-face interviews, allowing the interviewer to respond promptly should questions trigger negative emotions in some participants. Combining findings from our survey with those from the in-depth interviews will allow more nuanced recommendations as to whether MAiD should be expanded to incompetent patients with dementia.

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Authors' Contributions

GB is the principal investigator and lead author. As coinvestigators, MA, JD, MFD, and SK contributed to the development of the study protocol and grant application to the Alzheimer Society of Canada. CR implemented the study and is managing the postal survey under the close supervision of the principal investigator. As part of his Master's degree in health sciences, and under the cosupervision of GB, VT designed and is currently running the qualitative study exploring attitudes of persons with early dementia towards MAiD. All authors except VT were actively involved in designing the questionnaires, with special input from CMH, SP, and LVDB. All authors read and approved the final version of the paper.

Conflicts of Interest

None declared.

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Abbreviations

MAiD: medical assistance in dying

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Original Paper

Web-Based Intervention to Teach Developmentally Supportive Care to Parents of Preterm Infants: Feasibility and Acceptability Study

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Abstract

Background: Preterm birth affects 8% to 11% of the population and conveys a significant risk of developmental delays. Intervention programs that support child development have been shown to have a positive impact on early motor and cognitive development and on parental well-being. However, these programs are often difficult to implement in a real-life setting due to lack of resources. Hence, our multidisciplinary team developed Mieux Agir au Quotidien (MAQ) to teach developmentally supportive care to parents of preterm infants with the goal of improving child development and parental outcomes. Our intervention included 3 in-person workshops that occurred prior to hospital discharge and a Web-based platform with written and videotaped materials that addressed 5 main themes: (1) infant behavioral cues, (2) flexion positioning; (3) oral feeding support, (4) parent-infant interactions, and (5) anticipation of developmental milestones.

Objective: This study aimed to test the feasibility and acceptability of the intervention by parents of preterm infants and assess clinical benefits on child neurodevelopment and parental outcomes during the first year of life.

Methods: A total of 107 infants born at <30 weeks and admitted to Sainte-Justine Hospital neonatal intensive care unit and their parents were enrolled in a nonrandomized controlled before-and-after interventional study (intervention n=55, comparison n=52). Acceptability of the program was assessed with a user satisfaction questionnaire. When the infants were at 4 months' corrected age, all parents completed questionnaires on infant temperament, parenting stress, sense of competence, and parenting satisfaction. At 12 months' corrected age, neurodevelopmental testing was performed on infants using the Alberta Infant Motor Scale and the Bayley Scales of Infant and Toddler Development, Third Edition. Comparisons between the 2 groups were done using independent *t* tests, Wilcoxon rank-sum tests, and Fisher exact tests.

Results: The majority of parents (43/45) were satisfied with the intervention program and all would recommend MAQ to others. MAQ met their need for evidence-based information that proved useful to support their child development. No difference in parental or child neurodevelopmental outcomes was detected in this pilot study for most outcomes except for higher median scores for parental coercive behaviors in the intervention group, although proportions scoring in the coercive range did not differ.

Conclusions: Acceptability of the program was high among parents thus supporting the relevance of such intervention. A larger study using a randomized controlled trial design is needed to better document impact on parent and children and investigate how Web-based technologies can efficiently complement individualized intervention to alleviate the burden on health care resources.

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KEYWORDS

early intervention; developmental intervention; preterm infants; neurodevelopmental outcomes; Web-based intervention; Internet

Introduction

Preterm Birth: Risk Factor for Neurodevelopmental Impairment

Medical progress has led to an increase in preterm birth (occurring <37 weeks of gestation) along with improvement in survival of the sickest and most immature babies. However, rates of neurodevelopmental impairment remain high, with half of preterm children born <32 weeks of gestation exhibiting a spectrum of morbidities affecting motor, cognitive, language, socioemotional, and behavioral development [1].

Although prematurity-related medical complications account for some of the variability in neurodevelopmental outcomes [2], the preterm child's physical and social environment also significantly influences brain development [3]. After the preterm infant is born, exposure to various noxious sensory stimulations (loud noise, bright light, pain, invasive oral stimulation, prolonged restrictive positioning) occurs in the neonatal intensive care unit (NICU). The infant's immature neuronal circuitry is not ready to process these overwhelming physical stressors, which may affect normal brain development [3]. In addition, the quality of parent-infant interaction is challenged after preterm birth due to unanticipated separation [4]. Together, these environmental and social factors may hinder healthy brain development in preterm infants.

Developmental Intervention to Improve Neurodevelopmental Outcome

Developmental interventions aim to support infant development through educational strategies or techniques that promote the emergence of new skills and competences while preventing delays and disabilities [5]. These interventions take advantage of infant brain plasticity which is thought to be maximal between 28 and 32 weeks postconception to 2 years of age [6]. Developmental interventions in preterm infants commonly address adaptation of the physical environment to improve sensory inputs, enhancement of parent-infant interactions, and infant stimulation through, for example, neurodevelopmental therapy [7]. Existing developmental interventions for preterm infants are numerous and all differ in terms of timing, intensity, setting, structure, and resources.

Meta-analyses suggest that developmental interventions in preterm infants enhance cognitive and motor outcomes during the early years [7-9], although sustainability of these improvements has only been shown in one study [10]. Benefits on maternal anxiety, depressive symptoms, and self-efficacy have also been documented [11]. Moreover, individual intervention programs have shown positive effects on parent-infant interactions [12-14] and child behavior [14-18]. Developmental interventions with the most promising results share the following key components: parent-mediated intervention, parenting education, adaptation of the environment to reduce stressful stimuli, enhancement of parent-infant interactions, and psychosocial support [9,11,19].

Despite the benefits of developmental interventions, human and financial resources required to implement such endeavors often hinder implementation in a real-life setting [20]. In recent years, Web-based technologies have emerged as an alternative to deliver self-management or parenting interventions with proven effectiveness in chronic health conditions such as asthma and traumatic brain injury [21,22]. Web-based interventions have a high potential for outreach at lower costs. To our knowledge, there are no such programs for parents of preterm infants.

Mieux Agir au Quotidien: Multimodal Approach Using Web-Based Technologies to Deliver a Developmental Intervention

Overview

Mieux Agir au Quotidien (MAQ) is designed to empower parents to create an enriching physical and social environment for their infant using developmentally sound practices. It targets parents of preterm infants at risk of developmental delays. To improve efficiency of program delivery with a minimum of resources, MAQ uses a multimodal approach that combines educational support from a developmental intervener along with a Web-based platform that serves to provide and consolidate acquired knowledge [23]. The program is divided into 5 task-oriented teaching-learning modules readily available at all time in the NICU and at home through the Internet (Textbox 1). The 5 modules address (1) interpretation of behavioral cues and environmental adaptation, (2) adapted flexion positioning, (3) oral feeding support, (4) enhancement of parent-infant interactions through play, and (5) anticipatory guidance of preterm infant development and stimulation activities. All modules are structured similarly and explain the relevance of each theme to child development, provide some theoretical background, and teach developmental and behavioral activities that can be easily replicated in everyday life to consolidate knowledge acquisition. The program can be initiated when the infant reaches 32 weeks of postmenstrual age (Table 1). While the baby is still in the NICU, parents are introduced to developmentally supportive care through 3 hour-long in-person workshops that cover interpretation of behavioral cues, adapted flexion positioning, and parent-infant interactions. These workshops are delivered by the developmental intervener and use the Web-based platform as a visual support. Parents are encouraged at each session to go through the first 4 Web-based modules, which contain both written and visual contents illustrating hands-on activities that can be readily applied in the NICU (pictures, videos). Moreover, posters illustrating key concepts (behavioral cues and flexion positioning) are placed in the NICU as an additional reminder.

Textbox 1. Overview of the Web-based teaching modules of Mieux Agir au Quotidien.

Reading my child's behavior:

- Understanding sensory development
- Recognizing the different sleep-arousal states and the importance of sleep protection
- Interpreting infant behavioral cues (stress and self-regulatory behaviors)

Bringing the infant to an organized and stable state (control of environmental stimuli, skin-to-skin holding, nonnutritive sucking)

Positioning my child in the right position:

- Understanding muscle tone and motor development in preterm infants
- Recognizing abnormal postures that can lead to muscle and bone deformities

Promoting adapted flexion positioning and optimal posture during sleep, play time, and daily activities

Supporting oral feeding:

- Understanding developmental milestones related to oral feeding
- Understanding feeding challenges in preterm infants

Facilitating oral feeding (nonnutritive sucking, flexion positioning, pacing)

Playing and interacting with my child:

- Understanding attachment development
- Understanding how an infant temperament can influence parent-infant relationships
- Promoting play time

Creating an environment that will facilitate interactions and fun play

Foreseeing my child's developmental milestones:

- Understanding child developmental milestones and diversity of developmental trajectories
- Recognizing developmental red flags

Promoting neurodevelopmental stimulation

Table 1. Timing of intervention.

Schedule	In the neonatal intensive care	Home
Timing	Starting at 32 weeks of gestational age.	From term-equivalent age to 1 year of age.
Number of sessions	Three in-person workshops: (1) infant behavioral cues, (2) flexion positioning, (3) parent-infant interactions. Four Web-based modules: (1) infant behavioral cues, (2) flexion positioning, (3) oral feeding support, (4) parent-infant interactions.	Consolidation of first 4 Web-based modules. Fifth Web-based module on anticipation of developmental milestones.

After hospital discharge, parents can continue to go through all 5 Web-based modules containing educational material with new stimulation activities that can be done at home and are applicable throughout the first year of age. At all times, they can reach the developmental intervener through email.

MAQ is guided by 2 principles: early developmental care and enhancement of parent-infant interactions.

Early Developmental Care

Early developmental care is the cornerstone of many developmental interventions. Early developmental care aims to reduce stress and optimize developmentally appropriate stimulation [24,25]. Different strategies are employed to promote infant well-being and include control of external stimuli (adjusting ambient light, reducing noise), clustering of care and sleep protection, appropriate flexion positioning and handling (such as skin-to-skin holding), oral feeding support (including nonnutritive sucking), and parent involvement. By tailoring care to the infant's needs and behavioral state, his or her energy expenditure is kept at a minimum and can be redirected to optimize growth and development [24]. MAQ provides parents with specific modules that teach these evidence-based techniques of early developmental care.

Enhancement of Parent-Infant Interactions

Child developmental outcomes are shaped by the continuous dynamic interactions of the child and the immediate social experience provided by the family [26]. This transactional model

of development highlights how the child influences his or her environment (including caregivers), which in turn affects the child, and so on. Preterm birth can significantly alter parent-infant interactions. On one hand, preterm infants often display poorly regulated behaviors that are exacerbated by noxious stimuli (bright light, pain, noise, etc). This will interfere with social interactions, notably with parents [27]. On the other hand, parents of preterm children have been shown to be at increased risk of psychological distress and report higher levels of parenting stress, especially when faced with an infant with difficult temperament [28,29]. This can impede nurturing behaviors and negatively shape the infant's experience. MAQ teaches parents about interpretation of infant behavioral cues (stress/avoidance vs approach/self-regulatory behaviors) and how to sensitively respond to them during key moments such as sleep and feeding. In addition, a module is dedicated to techniques during play time to enhance shared positive parent-child experiences and promote bonding.

MAQ is novel for its key combination of parents' active involvement and developmentally supportive care using an easily accessible Web-based interface. However, before we launched MAQ in practice, we conducted a study whose objectives were to examine feasibility and acceptability of our pilot educational intervention and assess its clinical benefits on infant development and parental well-being. This study was granted approval by the Sainte-Justine Hospital Research and Ethics Committee.

Methods

Study Design and Population

This was a nonrandomized before-and-after intervention feasibility study that compared a historical group to an intervention group that received the program. All families with preterm infants born <30 weeks of complete gestation from 2010 to 2013, admitted at Sainte-Justine Hospital NICU, Montreal, Canada, and surviving to 32 weeks' postmenstrual age were eligible for participation. Exclusion criteria were: (1) chromosomal anomalies and major congenital malformation, as the pathophysiology for neurodevelopmental impairment is different, (2) documented parental history of recent illicit drug use, alcoholism, severe mental illness, intellectual disability, or domestic violence, given the added adverse effects on brain development and for adherence and consent issues, (3) foster care placement, for consent issues, (4) no family member speaking French (English translation had not taken place at that time), or (5) patients doomed to die within a few days, as estimated by the attending physician.

Procedure

The historical nonexposed comparison group comprised 52 infants born from 2010 to 2011 who were recruited after discharge from the hospital. Before implementation of MAQ in the NICU at Sainte-Justine Hospital, standardized protocols of developmentally supportive care were scarce and included nonmandatory workshops on skin-to-skin holding. After neonatal discharge, families were seen for routine neurodevelopmental assessment at the neonatal follow-up clinic where referrals for medical or early intervention services could be made depending on needs.

The intervention group consisted of 55 infants born from 2012 to 2013, enrolled when they reached 32 weeks of gestational age, prior to hospital discharge. Upon recruitment, parents received a unique identifier that allowed them to access the Web-based platform to start the educational intervention program. A computer was made available to parents at all time in the NICU. We also printed the written material available on the Web as requested by some parents. In-person workshops were then scheduled with the developmental intervener who was a board-certified occupational therapist trained in developmental care. After the infant was discharged, the developmental intervener maintained contact through phone or email to encourage parents to access the Web-based modules (around 4, 8, and 12 months' corrected age [CA]). Of note, all families had home access to a computer and an Internet connection. Families were also seen when possible at the neonatal follow-up clinic as part of standard of care (1-2, 4, and 8-9 months' CA).

For this study, participants were seen at 4 and 12 months' CA for outcome assessment at Sainte-Justine Hospital.

Outcome Measures

Measures of Feasibility and Acceptability

For families enrolled in the MAQ intervention program, compliance and use of the different modules were monitored by attendance records at workshops and self-reported access to the Web-based platform. Parental satisfaction regarding the contents and structure of the Web-based component of the educational program was appraised using an adapted version of the User Satisfaction Questionnaire [30], in which parents were asked to rate on a 4-item scale their opinion on 15 statements. An overall mean score of 45 indicates user satisfaction with the Web-based application. Parental concerns and beliefs regarding the program were also addressed through open-ended questions, specifically (1) what they generally thought about the workshops and Web-based platform, (2) what were perceived barriers and facilitators to access the Web-based platform, (3) what were their suggestions for improvements.

Measures of Parental Outcomes

When the child was 4 months' CA, parents were asked to complete the Parental Cognitions and Conduct Toward the Infant Scale (PACOTIS) [31] that measures parental perceptions and behavioral tendencies toward a recently born infant. There are 4 subscales: parental self-efficacy and perceived parental impact center on parents' beliefs about their role as a parent, whereas parental coercive behaviors and parental overprotection reflect behavioral tendencies toward the infant. A higher score indicates greater endorsement of a given parenting dimension.

Parents also filled the Parenting Stress Index–Short Form (PSI) [32], a well standardized and validated questionnaire that yields a total stress score from 3 scales: parental distress, parent-child dysfunctional interaction, and difficult child. The PSI identifies dysfunctional parenting and predicts the potential for parental behavior problems and child adjustment difficulties.

Measures of Infant Neurodevelopmental Outcome

Child temperament was assessed at 4 months' CA using the Bates' Infant Characteristic Questionnaire [33], a self-administered questionnaire in which parents indicate the level of perceived difficulty of their child in dealing with specifically described behaviors.

At 12 months' CA, cognitive, language, and motor development was assessed by a trained occupational therapist using the Bayley Scales of Infant and Toddler Development (BSITD), 3rd edition [34], a widely used norm-referenced and standardized instrument. The BSITD yields 3 scales—cognitive, language, and motor—with a mean of 100 and a standard deviation of 15. Finally, the Alberta Infant Motor Scales [35], an observational and standardized measure of motor development, was performed by physical therapists.

Statistical Analyses

As this was a pilot study to primarily test the feasibility and acceptability of our educational intervention program, with 50 infants per arm, the power to detect a difference in developmental scores of 0.3 to 0.5 standard deviations between the intervention and comparison groups at a 2-sided alpha level of .05 was between 38% and 70%.

Qualitative comments from questionnaires were analyzed by 2 independent reviewers (TML, PP) using thematic analysis and coding. To summarize the study population characteristics, descriptive statistical analysis was performed on baseline perinatal and sociodemographic factors using means and standard deviations, medians and range, and proportions. Comparisons were made using independent *t* tests (normally distributed continuous variables), Wilcoxon sum-rank tests (continuous variables not normally distributed), and chi-square or Fisher exact tests (categorical variables). Statistical analyses were performed with SPSS 24.0 (IBM Corp).

Results

Participant Characteristics

Overall, 107 infants and 96 mothers (45 in the comparison group, 51 in the intervention group) were recruited to the study (see study flow diagram in Figure 1). Table 2 describes sociodemographic and neonatal characteristics. Infants in the intervention group, compared to the historical cohort, were of higher gestational age and birth weight and were less likely to have severe retinopathy of prematurity. Therefore, their baseline risk of adverse neurodevelopmental outcomes was lower [36].

Participation in the intervention program was high with 44/51 mothers attending workshops and 45/51 going through the Web-based educational modules. In total, 48/51 parents (94%) participated in the program.

Figure 1. Flow diagram of study population.

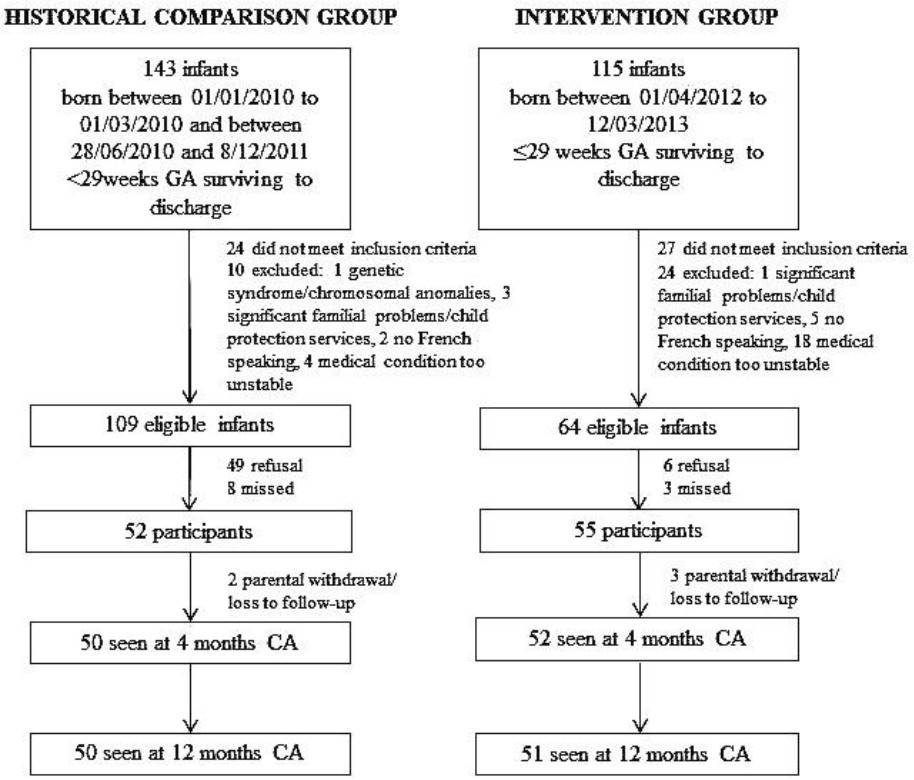

Table 2. Sociodemographic and neonatal characteristics of the study population.

Characteristics	Comparison N=45 parents N=52 infants	Intervention N=51 parents N=55 infants
Parent		
Maternal education, n (%)		
High school and less	5 (11)	12 (24)
Some college	20 (44)	15 (29)
University	20 (45)	24(47)
Single parent household, n (%)	4 (9)	4 (8)
White, n (%)	36 (80)	35 (69)
Paternal education, n (%)		
High school and less	11 (27)	12 (26)
Some college	14 (33)	14 (30)
University	16 (38)	20 (44)
Infant		
Gestational age, weeks, mean (SD[a])	25.6 (1.5)	27.5 (1.4)
Birth weight, g, mean (SD)	917 (207)	1088 (233)
Male, n (%)	28 (54)	34 (62)
Multiple gestation, n (%)	12 (23)	10 (18)
Small for gestational age, n (%)	6 (12)	4 (7)
Bronchopulmonary dysplasia, n (%)	33 (63)	28 (51)
Sepsis, n (%)	20 (38)	21 (38)
Surgical necrotizing enterocolitis, n (%)	2 (4)	0
Severe retinopathy of prematurity, n (%)	10 (19)	2 (4)
Severe brain lesions on ultrasound, n (%)	2 (4)	6 (11)
Duration of neonatal hospitalization, days, mean (SD)	102 (41)	89 (31)

[a]SD: standard deviation.

Overall Satisfaction With the Intervention Program

The User Satisfaction Questionnaire was completed by 45 parents in the intervention group (Multimedia Appendix 1). Satisfaction with the Web-based component was good with an overall mean score of 51 (minimum 44 and maximum 60). The majority of parents (43/45) rated the Web application above the acceptable range (≥45), with 2 parents giving a score of 44. All parents agreed (24/45, 53%) or strongly agreed (21/45, 47%) with the statement on overall satisfaction with the Web-based tutorials, and all would recommend them to other parents of preterm infants. A small number of parents reported that the amounts of examples and illustrations were insufficient (3/45) and disagreed with the statement that "technology was as effective as traditional teaching methods in helping them learn the material" (5/45). Narrative comments were provided by 10 mothers about the entire intervention program. Parents invoked 3 main themes: (1) information (ie, intervention responded to their need for information), (2) complementarity (ie, using different teaching approaches [workshop, Web-based modules, posters] was important), (3) concrete examples (ie, more day-to-day examples of problems and solutions should be provided). With regard to the latter, parents notably enjoyed the module on "Positioning my child" as it was problem-based and practical, whereas the module on "Supporting oral feeding" was deemed to be too theoretical. In relation to information, it was considered important that teaching material be presented in a nonjudgmental and nondirective way (eg, "Don't say that we should, but rather that we could").

Parental Outcomes

In total, 43 parents of 48 infants in the comparison group and 42 parents of 45 infants in the intervention group responded to questionnaires when their infants reached 4 months' CA (Table 3). Parents in the intervention group had a higher median score on the coercive behavior scale, but there was no difference in proportion scoring in the coercive range. Moreover, no difference was detected on the other scales of the PACOTIS or on the Parenting Stress Index.

Table 3. Parental outcomes at infant's 4 months corrected age.

Outcome	Comparison (N=43)	Intervention (N=42)	*P* value
PACOTIS[a]			
Self-efficacy			
Parental self-efficacy, median (IQR[b])	8.8 (7.8-9.3)	8.8 (8.2-9.2)	.57
Low self-efficacy, n (%)	11 (26)	8 (19)	.47
Impact			
Perceived parental impact, median (IQR)	9.0 (7.2-10.0)	8.1 (7.0-9.8)	.59
Low parental impact, n (%)	6 (14)	7 (17)	.73
Coercion			
Parental coercive behaviors, median (IQR)	0.4 (0-1.4)	1.3 (0.3-2.1)	.04
Coercive parenting, n (%)	6 (14)	10 (24)	.25
Overprotection			
Parental overprotection, median (IQR)	5.2 (3.0-6.4)	4.3 (3.0-6.8)	.33
Overprotection, n (%)	9 (21)	8 (19)	.83
Parenting Stress Index			
Total stress score, median (IQR)	63 (54-70)	62 (50-82)	.82
Parental distress, median (IQR)	24 (19-28)	26 (19-31)	.82
Parent-child dysfunctional interaction, median (IQR)	18 (14-21)	16 (14-21)	.39
Difficult child, median (IQR)	22 (16-25)	20 (16-26)	.82

[a]PACOTIS: Parental Cognitions and Conduct Toward the Infant Scale.

[b]IQR: interquartile range.

Table 4. Infant neurodevelopmental outcomes at 12 months of corrected age.

Outcome	Comparison (N=50)	Intervention (N=51)	*P* value
Alberta Infant Motor Scales			
Total score, median (min-max)	47 (33-56)	49 (6-58)	.53
Score <10th percentile, n (%)	22/49 (45)	21/51 (41)	.71
BSITD[a]			
Cognition score, mean (SD[b])	96 (9)	97 (13)	.77
Motor composite score, mean (SD)	92 (11)	89 (13)	.22
Gross motor scale, mean (SD)	9 (3)	8 (3)	.78
Fine motor scale, mean (SD)	9 (2)	9 (2)	.18
Language composite score, mean (SD)	90 (12)	96 (13)	.74
Expressive language scale, mean (SD)	8 (2)	9 (3)	.27
Receptive language scale, median (min-max)	9 (4-11)	9 (1-15)	.16
Cognition score <85, n (%)	3/50 (6)	6/48 (13)	.20
Motor composite score <85, n (%)	10/49 (20)	10/48 (22)	.76
Language composite score <85, n (%)	13/50 (26)	7/48 (15)	.26

[a]BSITD: Bayley Scales of Infant and Toddler Development.

[a]SD: standard deviation.

Infant Neurodevelopmental Outcomes

At 4 months' CA, there was no difference in mean scores on parental perception of infant temperament (comparison: 23 [SD 6], intervention: 23 [SD 7]). In the comparison group, 38/46 (83%) infants were described as fussy versus 34/47 (73%) infants in the intervention group. We did not find any difference on motor, cognitive, and language development between the 2 groups at 12 months' CA (Table 4).

Discussion

Principal Findings

This study aimed to assess feasibility and acceptability of this new multimodal educational program of developmentally supportive care for parents of preterm infants. This program is unique for its Web-based platform, and is, to our knowledge, one of the first to offer such educational material. The majority of parents participated into the educational program, and the majority were also satisfied with the clinical contents and format, thus supporting feasibility and acceptability of such intervention. However, parents in the intervention group reported more coercive tendencies toward their infant when compared to the historical cohort, although proportion scoring in the abnormal range did not differ. Analysis of preliminary results did not reveal any difference on parenting stress or infant neurodevelopmental outcomes at 12 months' CA.

Existing developmental intervention programs for infants born preterm require substantial human resources, which can represent a challenge with regard to implementation. For example, promising programs such as the Mother-Infant Transaction Program and modified versions [14,37,38], the Infant Behavioral Assessment and Intervention Program [39] and the Victorian Infant Brain Studies Plus [40], to name a few, include from 7 to 10 individual sessions, some of which are conducted during home visits. Although ideal, this may not be feasible due to shortage of qualified personnel or geographical reasons, when long distances need to be covered for home visits. We attempted to bridge this gap by combining in-hospital face-to-face sessions with a Web-based tutorial for parents of preterm infants. Indeed, all parents in our study endorsed the Web-based component of the program and would recommend it to others as it responded to a need for scientifically sound information about developmentally supportive care.

Limitations

However, some weaknesses were identified. Although 44/51 parents attended workshops, great efforts from our developmental intervener were required to plan these sessions. Indeed, flexibility in the schedule was crucial to accommodate parents' visiting hours. In addition, workshops often ended as individual bedside sessions as parents were understandably reluctant to leave their preterm infant. Therefore, in a real-life setting, significant resources and time would still need to be allocated to ensure in-person delivery of program contents with compliance likely to be well below the observed 86% in our study.

Another limitation was that most parents accessed the Web-based platform during their neonatal stay when they had more spare time and not at home as they became busier and started forgetting about the available resource. To improve uptake of the program at home, parents need to become more familiar with the Web-based component prior to discharge, which can only occur with increasing use. Barriers to use included easy access to a computer and Internet connection at our hospital at the time of the study (2012-2013). Although a computer was available, it could not be used at bedside. Nowadays, wireless Internet access is becoming more widespread in hospitals in industrialized countries. The website has also been made compatible with mobile phones and tablets. Furthermore, we addressed parents' feedback to improve the contents and formats of the Web-based component of MAQ to make it more appealing. All written material has been re-edited so messages would be clearer and less directive. More tables, figures, and videos have been created to facilitate learning and understanding of the material (Multimedia Appendices 2 and 3). Translation to English has been completed to broaden the audience. It has also been suggested that personalized reminders be sent by emails or text messages with links directing parents to age-appropriate learning material. This is in our long-term goals to improve MAQ.

Preliminary results on parent and infant outcomes must be interpreted with caution, especially the finding of higher scores for parental coercive behavior in the intervention group. However, proportions with coercive tendencies did not differ between groups. Our exploratory study used a nonrandomized design which made it vulnerable to selection bias. Indeed, infant and parent characteristics were not balanced across groups. Infants in the historical comparison cohort were of lower gestational age and birth weight and more likely to have severe retinopathy of prematurity, whereas their parents were more likely to have completed higher educational levels. The small sample size limited our ability to adjust for all these factors in our analyses. Second, we did not examine parents' behavioral characteristics at study entry, and it is possible that parents in the intervention group differed in terms of their baseline personal traits, which could have influenced their answers to the parental questionnaires. This can only be addressed with a pilot randomized controlled trial. We did not find any difference between groups in motor development as measured by the Alberta Infant Motor Scales nor did we detect cognitive, language, or motor improvements on the BSITD following the intervention. As this was a feasibility and acceptability study, it was underpowered to find small or even moderate differences between groups. Moreover, other studies suggest that the greatest benefits may be on behavioral outcomes [17,18]. A future study would therefore need to assess child behavior at later ages. In addition, it would also require assessment of improvement in parental knowledge at different time points as a first step in the application of the educational material. Finally, current results are only applicable to the subset of very preterm infants without other medical risk factors such as chromosomal abnormalities or social risk factors including parental mental health issues and foster care placement.

Conclusions

We have shown the feasibility and acceptability of using a multimodal approach including Web-based applications to

deliver an educational intervention on developmentally sound practices for parents of preterm infants. Parental input regarding weaknesses of the Web-based component of the program has been since carefully considered to significantly improve contents and format. With increasing use of the Internet as a source of knowledge, the *Mieux Agir au Quotidien* website is highly relevant to respond to parents' needs for reliable and evidence-based information. Results from this preliminary study can now serve to inform a future pilot randomized controlled trial.

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Authors' Contributions

TML and JG contributed equally to the entire study. TML drafted the initial manuscript. LFX and PP contributed to data collection and data analysis. PP contributed to development of the Web-based intervention. SC reviewed the protocol and contributed to data analysis and interpretation. CDW reviewed the protocol. TK reviewed the protocol and contributed to development of the Web-based intervention. All authors reviewed the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

User Satisfaction Questionnaire (n=45).

[PDF File (Adobe PDF File), 26KB - resprot_v6i11e236_app1.pdf]

Multimedia Appendix 2

Examples of material on the Web-based component of Mieux Agir au Quotidien.

[PNG File, 184KB - resprot_v6i11e236_app2.png]

Multimedia Appendix 3

Examples of material on the Web-based component of Mieux Agir au Quotidien.

[JPG File, 166KB - resprot_v6i11e236_app3.jpg]

Multimedia Appendix 4

Peer review and funding report from SickKids Foundation and the Institute of Human Development, Child and Youth Health.

[PDF File (Adobe PDF File), 439KB - resprot_v6i11e236_app4.pdf]

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Abbreviations

BSITD: Bayley Scales of Infant and Toddler Development
CA: corrected age
MAQ: Mieux Agir au Quotidien
NICU : neonatal intensive care unit
PACOTIS: Parental Cognitions and Conduct Toward the Infant Scale
PSI: Parenting Stress Index

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Protocol

Patient Transfers and Risk of Back Injury: Protocol for a Prospective Cohort Study With Technical Measurements of Exposure

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Abstract

Background: More than one third of nurses experience musculoskeletal pain several times during a normal work week. Consistent use of assistive devices during patient transfers is associated with a lower risk of occupational back injuries and low back pain (LBP). While uncertainties exist regarding which type of assistive devices most efficiently prevent LBP, exposure assessments using technological advancements allow for quantification of muscle load and body positions during common work tasks.

Objective: The main objectives of this study are (1) to quantify low back and neck/shoulder muscle load in Danish nurses during patient transfers performed with different types of assistive devices, and (2) to combine the exposure profile for each type of assistive device with fortnightly questionnaires to identify the importance of muscle load (intensity and frequency of transfers) and body position (degree of back inclination and frequency) on LBP intensity and risk of back injury during a patient transfer.

Methods: A combination of technical measurements (n=50) and a prospective study design (n=2000) will be applied on a cohort of female nurses in Danish hospitals. The technical measurements will be comprised of surface electromyography and accelerometers, with the aim of quantifying muscle load and body positions during various patient transfers, including different types of assistive devices throughout a workday. The study will thereby gather measurements during real-life working conditions. The prospective cohort study will consist of questionnaires at baseline and 1-year follow-up, as well as follow-up via email every other week for one year on questions regarding the frequency of patient transfers, use of assistive devices, intensity of LBP, and back injuries related to patient transfers. The objective measurements on muscle load and body positions during patient handlings will be applied to the fortnightly replies regarding frequency of patient transfer and use of different assistive devices, in order to identify risk factors for back injuries related to patient transfers and intensity of LBP.

Results: Data collection is scheduled to commence during the winter of 2017.

Conclusions: The design of this study is novel in its combination of technical measurements applied on a prospective cohort, and the results will provide important information about which assistive devices are associated with intensity of LBP and risk of back injury related to patient transfers. Furthermore, this study will shed light on the dose-response relationship between intensity, duration, and frequency of patient transfers and the intensity of LPB in Danish nurses, and will thereby help to guide and improve electronic health practices among this population.

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KEYWORDS

nurse; low back pain; electromyography; assistive devices; pain; hospital

Introduction

Musculoskeletal disorders (MSDs) represent a widespread occupational disease as well as a major socioeconomic burden on public health systems in Europe and North America [1,2]. Low back pain (LBP) and neck/shoulder disorders are the main culprits of a physically demanding job, often leading to increased sickness absence and loss of productivity [2-4]. A number of work-related risk factors for developing MSDs have been highlighted in the literature. For example, heavy lifting as well as frequent bending and twisting of the spine have repeatedly been associated with increased risk of developing LBP [2,5,6]. Additionally, a meta-analysis from 2014 showed that both intensity and frequency of lifting tasks predict the occurrence of LBP [7]. Therefore, even though the development of MSDs has a complex etiology comprised of individual physical and psychosocial factors, it is clear that certain occupations and job tasks pose an inherent risk of developing MSDs.

One occupation that is commonly associated with MSDs as a result of physically demanding job tasks is the health care profession. The annual prevalence of MSDs among nurses and nurses' aides is high (ie, 55% for LBP [8]). Furthermore, more than 36% of Danish nurses experience musculoskeletal pain several times during a normal work week [9]. These numbers not only reflect serious and broad-ranging health issues for the nurses in question, but will also have the potential to pose significant negative consequences for their patients. For example, as an inherent component of persistent pain, it is likely that nurses will decrease the number and quality of patient handlings (with and without assistive devices) due to LBP, which effectively diminishes the services of the hospital.

It is well-known that the utilization of various assistive devices during patient transfers decreases the risk of back injuries and intensity of LBP [10,11]. Furthermore, both ergonomic interventions [12] and the application of a "no lifting policy" [13] have proven effective in reducing work-related back injuries in hospitals. Despite these developments, most health care personnel report that they do not use appropriate assistive devices when moving patients [14]. A recent Danish cohort study showed that staff members performing daily patient transfers were more prone to back injuries one year later (odds ratio [OR] 1.56-1.81) compared with their counterparts who did not move patients on a daily basis [10]. An equally important finding from this cohort study was that the staff members who used assistive devices during patient transfers experienced a markedly lower risk of back injuries related to patient transfers one year later (OR 0.59-0.62) [10]. However, despite the clear indications that utilizing appropriate assistive devices during patient transfers in hospitals has a positive effect on the number of back injuries and prevalence of LBP, it is still unknown which assistive devices are most effective in terms of LBP prevention.

Previous research has used biomechanical measurements to identify peak loading during various job-related tasks among health care workers [15-19]. For example, muscular load has been shown to be significantly lower during patient transfers when using a ceiling-attached lift compared to traditional manual lifts from the floor [18]. Following this study, laboratory research by Schibye et al [20] illustrated the effect of lifting technique, showing that a self-chosen technique results in higher levels of spinal loading compared with the recommended patient transfer technique. This finding was further confirmed by another laboratory study showing that low back compression forces were influenced more by the health care worker's technique and use of appropriate assistive devices than the weight and disability of the patient being repositioned in bed [21]. From the literature cited above, it appears that the appropriate use of assistive devices is of great importance when the goal is to decrease the prevalence of MSDs and the accompanying high amount of sickness absence in this population of nurses. However, only a small number of studies have measured work-related muscular load during a full real-life work day [22-24], and no study has investigated this among health care personnel.

The primary aim of this project is therefore to quantify muscular loads during different patient transfers. By following Danish nurses during a full work day, this study seeks to obtain real-life measurements during patient transfers. The key aspect of this project is the measurement of muscle load and body positions during a number of patient transfers, with and without the use of assistive devices. These technical measurements, using surface electromyography (EMG) and accelerometers to quantify muscle activity and body movements, respectively, will allow for identification of the biomechanical characteristics of various patient transfers. As preparatory work to ensure high quality data collection, the most common types of patient transfers in Danish hospitals have been identified and a pilot-study that primarily served to test the EMG and actigraphy equipment has been performed (manuscript in preparation). Furthermore, another novel aspect of this project will combine the technical measurements described above with the results from fortnightly emails received from nurses in Danish hospitals. These emails will include answers to a short questionnaire regarding the weekly intensity, frequency, and duration of patient transfers, as well as the number of back injuries (defined as a sudden and unexpected accident during a patient transfer) and the intensity of LBP (Visual Analogue Scale 0-10).

The combination of technical measurements (EMG and actigraphy) and the prospective aspect of this project will allow for the development of a detailed exposure profile [25]. Therefore, by combining the individual strengths of technical measurements and epidemiological research methods, this project seeks to answer important questions regarding the implications of utilizing technical equipment/assistive devices in Danish hospitals, and to improve electronic health (eHealth) practices among Danish nurses.

Methods

Study Design

This study follows a cross-sectional (technical measurements) design as well as a prospective cohort design (questionnaires and fortnightly electronic follow-up). The technical measurements will be performed on full-time nurses from hospitals in Denmark. Therefore, by following nurses during a

work day, the measurements will reflect real-life patient transfer scenarios with and without the use of appropriate assistive devices. Data collection is expected to take place from autumn 2017 to spring 2018, and baseline questionnaires were sent out in March 2017. Figure 1 shows an overview of the study design.

Ethics

Referring to the Helsinki Declaration, all participants will be informed about the content of the study before providing written informed consent. This information will be given both written and verbally. The study (ie, the use of technical measurements) is approved by the Danish National Committee on Biomedical Research Ethics (the local ethical committee of Frederiksberg and Copenhagen; H-3-2010-062) and the Danish Data Protection Agency (j.nr. 2015-41-4232).

Study Population and Recruitment

Approximately 50 female nurses will be recruited from Danish hospitals. To achieve a sufficient number of measurements of patient transfers during each individual work day, prospects will be approached by the lead nurse who knows the schedules. The generalizability of this study will therefore only apply to female nurses, as this constitutes a homogenous group and represents the vast majority of health care personnel in Denmark. Inclusion criteria will be an expected number of 10 or more patient transfers during the work day. Exclusion criteria are life-threatening diseases, pregnancy, and hypertension. The two former criteria will be evaluated by asking the nurse prior to the day of testing, whereas the latter will be measured on the day and is defined as readings >160/100 mmHg.

Electromyography and Actigraphy

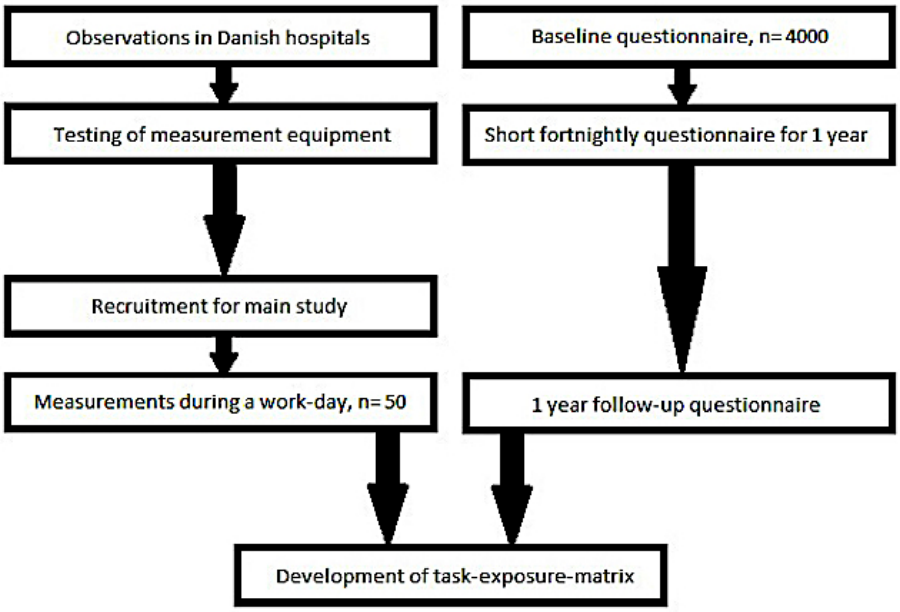
Each participant will be equipped with wireless surface EMG equipment (Noraxon, Arizona, USA), allowing for continuous measurements. Before electrode placement, the skin will be prepped and cleaned. EMG signals will be recorded using a bipolar EMG configuration (Blue Sensor N-00-S, Ambu A/S, Ballerup, Denmark) with an interelectrode distance of 2 centimeters [26-28]. The electrodes will be connected directly to wireless probes that will preamplify the signal (gain 400), and transmit data in real-time to a 16-channel personal computer-interface receiver (Telemyo DTS Telemetry, Noraxon, Arizona, USA). The sampling rate will be set to 1500 Hertz with a bandwidth of 10-500 Hertz to avoid aliasing. Joint angles will be continuously measured and synchronized with live EMG recordings, using two electronic accelerometers (3D DTS 24G accelerometer, Noraxon, Arizona, USA). Previous research has found strong correlations between actual loading and normalized EMG amplitude [29], making EMG measurements a valid methodology to accurately detect differences in muscle load of the magnitude we expect to see in this project.

Data Collection

Before the beginning of a work day, the participant will enter the room designated for equipment application and testing. The EMG electrodes will be positioned bilaterally on: (1) the upper trapezius, 2 centimeters lateral from the middistance between the C7 vertebra and the acromion; (2) on the lower trapezius, 2/3 on the line from the trigonum spinea to the eighth thoracic vertebra; (3) on erector spinae longissimus, two finger widths lateral from L1; and (4) on erector spinae iliocostalis, one finger width medial from the line from the posterior spinae iliaca superior to the lowest point of the rib, at the level of L2 [30,31]. The erector spinae muscles are of primary interest, whereas the trapezius muscles will constitute a future secondary analysis in relation to the high prevalence of neck/shoulder MSDs seen among nurses.

The two accelerometers will be positioned on the lower back (just above the sacroiliac joint) and on the upper back (just below C7 vertebra). The equipment listed will be fixated with adhesive tape (Fixomull, BSN medical GmbH, Hamburg, Germany), and the strength of the signal will be confirmed. After successful application, normalization procedures will be performed.

Figure 1. Overview of study design.



These procedures will consist of: (1) maximal isometric voluntary contractions (MVICs); and (2) submaximal isometric contractions, which will be performed in the morning and again in the afternoon. We will include both procedures as the latter has recently shown greater reliability for the erector spinae muscle [32]. Two trials within each procedure will be performed for all muscles. For the erector spinae muscles, both the MVICs and the submaximal isometric contractions will be performed in the prone Biering-Soerensen test-position [33,34]. Likewise, in this position, a muscle endurance test for the erector spinae muscles will be performed in the afternoon. For the upper trapezius, both normalization procedures will be performed in a standing position with 90-degree arm abduction, whereas the MVICs for the lower trapezius muscles will be performed in a prone position with 130-degree shoulder abduction [35]. Likewise, the accelerometers will be calibrated in known positions prior to fixation, as well as when positioned on the subject during (1) upright standing position, (2) bending forwards to a horizontal torso position with flexed knees, (3) maximal forward bending with straight legs, (4) arching forwards, and (5) arching sideways. The accelerometer normalizations will be performed in the morning and again in the afternoon.

Following the initialization and normalization procedures described above, the participant will start her work day. The test leader will follow the participant as she is performing various patient transfers. Given the nature of the wireless equipment, the test leader will be able to visually monitor the live EMG signals on a laptop. To ensure an adequate level of detail of all patient transfers using this setup, the test leader will observe and note the type of patient transfer and associated assistive devices, the number of nurses involved, as well as patient characteristics (age, body mass, height, and level of self-reliance). Using this methodology, it will be possible to differentiate each patient transfer into its partial lifts that together constitute the whole. This approach will provide a level of detail novel to this field and will allow for more precise measurements of exposure during patient transfers. After finishing her shift, the nurse will return to the test room for end-day normalizations. By using the average value from the standardized normalizations performed before and after the work day, as well as EMG temporal and spectral changes [36], we aim to document the potential effects of fatigue on the EMG measurements.

Outcomes

The main outcomes of this project will be the association between low back muscle activity intensity (normalized EMG and frequency of patient transfers) and body position (position and frequency), on the risk of back injury related to patient transfer and change in intensity of LBP during a one-year period.

The first article will be descriptive in terms of muscle load and body position while using different assistive devices. The following articles will apply the results of technical measurements to the cohort (n=2000) with main outcomes, which are LBP intensity and risk of back injury during patient transfers.

Statistics

All statistical analyses will be performed using SAS statistical software for Windows (SAS Institute, Cary, NC). Poisson regression (injury) and linear regression (LBP) models will be performed using generalized estimating equations (Proc Genmod) and linear mixed models (Proc Mixed). An alpha level of 0.05 will be accepted as significant.

Results

Data collection is scheduled to commence during the winter of 2017.

Discussion

This is the first project to investigate the effect of using assistive devices during patient transfers via a combination of technical measurements and a prospective cohort design. Whereas previous research has either used biomechanical measurements to identify musculoskeletal loads during work or questionnaire-based designs to quantify work-related MSDs, this combination of research methodologies enables us to create exposure matrices regarding the dose-response relationship and importance of load, intensity, frequency, and type of patient transfer, in addition their individual associations with LBP back injuries related to patient transfers. In contrast to the job-exposure matrix commonly used in epidemiological studies, this exposure matrix will provide much greater detail as it assigns job exposure according to the specific tasks performed by the nurse. Furthermore, this is the first study to perform real-life measurements on nurses during a work day and will undoubtedly result in more realistic identification of potential risk factors, which can be made readily available as part of the electronic learning material currently used by nurses. Therefore, the present study has the potential to provide essential and detailed knowledge regarding the use of assistive devices during patient transfers in hospitals, and (via improved eHealth practices) to better guide the workplaces' efforts to reduce the number of back injuries and the occurrence of MSDs among female nurses.

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Conflicts of Interest

None declared.

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Abbreviations

eHealth: electronic health
EMG: electromyography
LBP: low back pain
MSD: musculoskeletal disorder
MVIC: maximal isometric voluntary contraction
OR: odds ratio

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Protocol

The Association of Health Literacy and Electronic Health Literacy With Self-Efficacy, Coping, and Caregiving Perceptions Among Carers of People With Dementia: Research Protocol for a Descriptive Correlational Study

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Abstract

Background: In the last decade, electronic health (eHealth) literacy has attracted the attention of the scientific community, as it is associated with the self-management of patients with chronic diseases and the quality and cost of care. It is estimated that 80% of people with chronic diseases are cared for at home by a family member, friend, or relative. Informal carers are susceptible to physical and mental health problems, as well as social and financial hardships. Nevertheless, there seems to be a research gap in terms of carers' needs, skills, and available resources in the age of new technologies, with the vital role of eHealth literacy of the carers remaining unexplored.

Objective: The aim of this study was to investigate the level of eHealth literacy and health literacy of primary and secondary carers of people with dementia, to explore the association between health and eHealth literacy, as well as their association with the caregiving variables: self-efficacy, coping, and caring perceptions.

Methods: A sample of 200 primary carers (the carer who supports the people with dementia in everyday living) and 200 secondary carers (family member, friend, or other person in the social network assisting the primary carer in their role) will be recruited from dementia day care centers and Alzheimer's associations in Greece and Cyprus. The study will be a cross-sectional correlational descriptive study. Tools to be used include the eHealth Literacy Scale adapted for carers to measure eHealth literacy, European Health Literacy Survey Questionnaire 16 (HLS-EU-Q16), Single Item Literacy Screener, Revised Scale for Caregiving Self-Efficacy, Carers of Older People in Europe (COPE) index for caregiving perceptions, and COPE brief to measure selected coping strategies. Descriptive statistics will be reported, and correlations between different variables will be explored with parametric and nonparametric measures.

Results: As a preliminary study, the HLS-EU-Q16 has been validated in 107 older people. The internal consistency of the scale as estimated using Cronbach alpha coefficient was .77, somewhat lower than other validation studies. Recruitment of pilot study participants started in May 2017.

Conclusions: Carers' eHealth literacy is a new field. Whereas previous studies have focused on the role and impact of low eHealth literacy and health literacy among older adults, the eHealth literacy of carers, and in fact carers of people with dementia, has not been explored. We hypothesize an association between eHealth literacy and health literacy level with carers' perceptions about caregiving role, self-efficacy, and coping strategies. A possible moderator in these associations is the secondary carers'

eHealth and health literacy level, which will also be explored. By confirming the above hypotheses, tailored eHealth literacy interventions for carers of people with dementia and their families will be developed as a direct outcome of this research.

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KEYWORDS

health literacy; carers; dementia; ehealth

Introduction

Carers and Internet Use

In the new digital era, new technologies are developed to support carers in their everyday role. However, most of the time, this is done without taking into consideration carers' health literacy, digital skills, and electronic health (eHealth) literacy level. According to Eurocarers Association, "a carer is the person who provides unpaid care to someone with chronic illness, disability, or other long lasting health and care needs, outside a professional or formal framework." People who provide care at least once or twice per week are those in the age range of 50 to 64 years, followed by the 35 to 49 age group according to the third European Quality of Life Survey [1]. In the case of carers of people with dementia, the age range is almost certainly older, as spouses and children older than 64 years are likely to become carers [2].

Older adults are considered to be the population group with the most difficulty in using new technology. In recent years, many studies have investigated the eHealth literacy of older adults, providing evidence that increased age and lower educational level are good predictors of lower eHealth literacy level and low Internet use [3-7]. Although there is vast literature about eHealth literacy in older adults **,** the level and the role of eHealth and health literacy among carers and, in particular, carers of people with dementia is very limited. There is, nevertheless, abundant information, mainly of descriptive nature, with regard to the type of Internet use among carers of people with different chronic diseases, without any further exploration or recommendation.

In a recent study in the United States, Kanthawala et al [8] investigated the type of questions and replies that people with diabetes and their carers post on the Web in the WebMD online diabetes website. People usually search information on their suggested treatment, questions that doctors have not replied to, and information on health habits. Most people consider the information on the Internet of good quality. Kanthawala et al classified questions searched into three categories: questions of fact, those related to policy or action, and those of value. Furthermore, they tried to address which type of resource is more adequate and clinically relevant for carers, concluding that community resources provided better quality results than search results of a common search engine such as Google.

In another study in the United Kingdom, Blackburn et al [9] explored the Internet use among 3014 carers. The study provided an overview of the digital gap among carers, which relates to both age as well as socioeconomic position. Half of the sample had never used the Internet. Of those using the Internet, 61% were frequent users (accessing the Internet once or more per week). Internet access by carers seems to be influenced by demographic and socioeconomic factors. Specifically, the age of the carer and the age of the patient, gender, employment status, living conditions, and hours of care are factors associated with Internet use. Similar findings have been reported by Kim [10] for a sample of carers of people with dementia. Specifically, younger carers (children and grandchildren), more educated, with a higher income, and fewer hours of caregiving are most likely to be health-related Internet users. Li [11] provided similar results for a sample of 812 carers of older adults.

According to Lam and Lam [12], the most common use of Internet among carers in Australia included chat sites and emails, indicating carers' need to communicate. However, carers also used the Internet to retrieve information, as well as to access governmental services, for example, to pay bills. Interestingly, the study reported that carers who had been using the Internet 12 months before the study had better mental health in comparison with carers who had not used the Internet during that period. This is also supported by Kinnane and Milne [13] who have reviewed the literature for carers of cancer patients and have found that carers mostly use the Internet for information search for themselves or at a request by the cared for person for support group activity and email usage.

In a qualitative study, carers visiting a caregiving website mostly looked for health information and practical, legal, and financial issues. These preferences were directed by the type of caregiving. Kernisan et al [14] categorized replies in four categories: caring for parent, caring for self only, other caregiving situation, and unknown caregiving situation. In the case of carers of older people, practical issues were most frequently searched.

There is also a large number of studies looking at the effectiveness and the usability of Web-based support programs such as online communities, fora, and psychoeducational programs that aim to improve education and communication of carers [15]. A recent scoping review by Wasilewski et al [15] found that most studies mainly discuss carers' experiences from participating in the programs or interventions, generally suggesting a positive attitude toward Web-based services. However, commonly no follow-up studies report either the usage and/or effectiveness of the specific interventions.

Key Concepts and Their Associations Within the Proposed eHealth Literacy and Carers' Research Framework

eHealth Literacy

As a term, eHealth literacy has gained considerable attention in recent years with the increased use of new technologies in health. Nevertheless, there is accumulating evidence that

available technologies provided to people with chronic diseases or their carers are not properly used, or people are not using them because of lack of digital skills. In 2006, Norman and Skinner [16] presented the Lily model in an attempt to describe the different dimensions of eHealth literacy, defining the term as "the ability to seek, find, understand, and appraise health information from electronic sources and apply the knowledge gained to addressing or solving a health problem." The Lily model refers to six basic types of eHealth literacy and categorizes them in two central types of skills: analytic- and context-specific skills. The analytic type includes:

1. Traditional literacy, which includes basic skills to read, understand, write, and speak language.
2. Information literacy, which describes the skills needed by a person to find, select, and use information available of any type.
3. Media literacy, which is defined as a process of metacognitive reflective strategies to place the information from several media sources in a social and political context.
4. Health literacy, for which several definitions have been used in the literature. One of the most frequently cited definitions is the one proposed by Ratzan and Parker [17], which refers to "The degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions." More recently, the construct of health literacy was explored in a cross-national European Health Literacy Survey among 8000 people from eight countries: Austria, Bulgaria, Germany, Greece, Ireland, the Netherlands, Poland and Spain. As a result, a new definition and conceptual framework was derived that incorporated elements from previous definitions, namely, "Health literacy is linked to literacy and entails people's knowledge, motivation and competences to access, understand, appraise, and apply health information in order to make judgments and take decisions in everyday life concerning healthcare, disease prevention and health promotion to maintain or improve quality of life during the life course" [18].

In the context-specific type of skills, Norman and Skinner include (5) computer literacy, which is the ability to use computers, and (6) scientific literacy, which is the skill to understand the aims, methods, implementation, limitations, and politics of creating knowledge. As part of this theory, Norman and Skinner [19] developed the eHealth Literacy Scale (eHeals), one of the few and most frequently used tools to measure eHealth literacy.

Chan and Kaufman [20] have proposed a methodological and theoretical framework to analyze and measure eHealth literacy based on the Lily model and Bloom's taxonomy. Bloom's taxonomy describes the cognitive dimensions that are a prerequisite for any type of literacy and includes remembering, understanding, applying knowledge, analyzing, evaluating, and creating a coherent meaning. Furthermore, in their model, Chan and Kaufmann separated traditional literacy into three types: reading, writing, and numeracy.

Norman [21] discussed the need for eHealth literacy to be revised, taking into consideration the latest progress in Internet tools and environment with Web 2.0 and the use of social media and mobile Internet. Norman discusses the eHeals scale that had a good correlation with Web 1.0 and was tested with youth and youth workers, who were the frequent users during that period from 1990 to 2000. In 2011, the study of Van der Vaart et al [15] made the first critique to the model and the weak correlation between eHeals and Web 2.0, suggesting the revision of the tool.

After the revision of the Lily model, which actually included the cognitive factors of users, additional attempts to expand the model have taken place [22,23]. Gilstad [22] redefined eHealth literacy as "...the ability to identify and define a health problem, to communicate, seek, understand, appraise and apply eHealth information and welfare technologies in the cultural, social and situational frame and to use the knowledge critically in order to solve the health problem." Four new dimensions were included to the Lily model: bodily experience (the ability to identify a health problem), procedural literacy (the "how" dimension of knowledge), contextual and cultural literacy (knowledge of a social situation: norms, values, rules, and regulations), and communicative expertise (the ability to convey personal health issues). Additionally, identifying the age bias toward young adults inherent to the Lily model and the eHeals questionnaire of Norman and Skinner, Koopman et al [23] considered dimensions that are relevant for older adults. The result was the Patient Readiness to Engage in Health Internet Technology instrument to measure the eHealth literacy of older adults.

More recent suggestions are the ones proposed by Norgaard et al [24] and Bautista [25]. Norgaard et al [24] have used concept mapping workshops with relevant stakeholders: information technology (IT) users, nonusers, patients, health care providers, and IT experts to update the dimensions contained in the eHealth literacy framework. Core dimensions that have been identified are the ability of info processing, a person's motivation and interest in health and in using the digital services, feeling of safety and control, accessibility, sustainability, and appropriateness of Web-based services. Bautista [25] tried to redefine eHealth literacy as a term that "...involves the interplay of individual and social factors in the use of digital technologies to search, acquire, comprehend, appraise, communicate and apply health information in all contexts of healthcare with the goal of maintaining or improving the quality of life throughout the lifespan."

Carers' Self-Efficacy, Coping Strategies, and Social Support

Considering the important role that carers play for the national health systems, both the scientific community and policy makers alike have become more interested in maintaining carers' health in recent years. Carers experience more stress than the general population, and they report higher use of antidepressants, are more susceptible to infections and cognitive decline, and have high mortality rates [26-28]. Furthermore, there are 3 close relatives for every person with Alzheimer disease [29]. For the purpose of this protocol, we will define the supporter relative or friend to the primary carers as the secondary carer. The term secondary carer is not a term regularly used; however, it has

been previousy used in studies with carers of traumatic brain injury and cancer [30-32].

The stress process model [33] includes the core dimensions that influence carers' well-being, mental and physical health, including concepts such as carers' personality, primary stressors related to the severity of disease and perceived burden, secondary role strains, and secondary intrapsychic strains, including self-esteem, mastery, competence, and loss of self. According to Pearlin et al [34], self-esteem is influenced by four dimensions: role captivity, loss of self, competence, and gain. In caregiving, competence refers to the person's ability to cope with the caregiving demands, and gain refers to the satisfaction that the carer might receive from caregiving tasks. Self efficacy and competence are often used interchangeably. Self-efficacy determines the various characteristics of a coping behavior; for example, when and if the coping strategy will be initiated, how long will it last, and the coping resources that will be used. Self-efficacy is influenced by "performance accomplishments, vicarious experiences, verbal persuasion, and psychological states" [35].

The coping strategies and the social support of the carer in combination with the different types of the stressors, according to Pearlin's model, act as mediators of the mental and physical health of the carer [34].

Social support is included in Pearlin's stress process model as part of the personal resources that are important to cope with life stressors [34]. The model has been subsequently adapted by Pearlin to conceptualize stress as a dynamic process with its origins in the social world. Economic and social position, as well as the neighborhood context plays a crucial role [36]. According to the convoy model of social relations, four types of networks are available: the diverse, family-focused, friend-focused, and restricted. The social convoy is actually the protective base of each person and is differentiated according to the specific structure (size, frequency, proximity of members, marital status, and participation in social organizations) and the quality of the relationships [37].

In the initial model by Pearlin [29], as part of the personal resources, aside from social support, there are also the coping strategies, including problem-focused, emotion-focused, and meaning-focused. According to Pearlin and Schooler [38], when a person has control over a role (ie, a family role), it is more effective to follow a problem-focused strategy. Where personal control over a role is lower (work and finances), the person may adopt emotion-focused or meaning-focused strategies when reappraising the situation. In some cases, there is the so-called compensatory coping, when after reappraisal, the person may proceed to a problem-focused strategy to reinvest [36].

Additionally, Lazarus and Folkman [39] distinguish within the transactional framework between coping processes and coping styles: the relationship between person and environment and the traits of the person, respectively. Part of the transactional framework is the appraisal theory **,** discussing the primary and secondary appraisal. In primary appraisal, the person focuses on the importance of the event, if it is irrelevant to their own well-being, benign, positive, or stressful. In the secondary appraisal, we encounter the contextual factor and the ability of the person to cope with the stressor.

There is limited research on the associations between the abovementioned concepts, with research especially limited in terms of the role of eHealth literacy. Figure 1 connects the concepts in an effort to conceptualize the associations of health and eHealth literacy of primary and secondary carer and social support provided to the primary carer with self-efficacy, coping strategies, and perception of carer role.

In Figure 1, eHealth literacy is associated with health literacy, as described by Norman [16]. Taking into consideration the new definition provided by Soerensen et al [18], health literacy "entails people's knowledge, motivation and competences to access, understand, appraise, and apply health information."

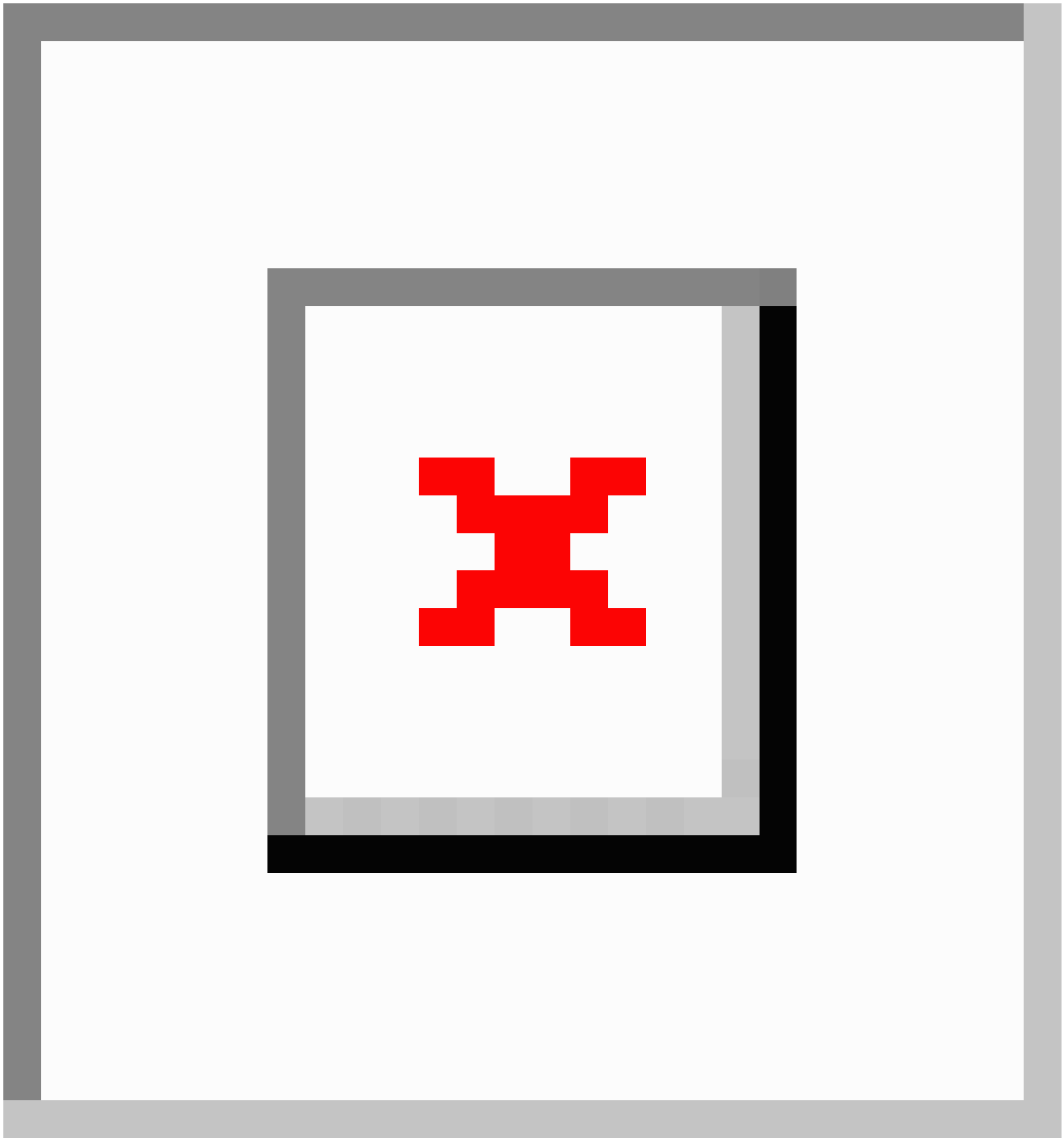
Concerning the selected caregiving variables, self-efficacy is related to cognitive appraisal and acts as a motivator of action and selection of coping strategies [35]. Perceptions of carers' role are related to coping strategies [40]. A person with enhanced self-efficacy is more likely to search for health awareness opportunities and feel empowered (being in control of one's own health).

We presume the effect of health and eHealth literacy of the secondary carer and primary carer's perceived social support on the health and eHealth literacy of the primary carer and the selected caregiving variables.

Social support is also a concept connected with health literacy, acting as a possible moderator in the relationship between low health literacy and poor health and is defined as "the degree to which individuals have access to social resources, in the form of relationships, on which they can rely" [41,42]. The support of social networks seems to play a role in the management of a person's health problem and acts as a coping behavior. We can distinguish two types of social support: structural and functional. The structural support refers to the actual support network and as such the sources and extent of support as a result of the different roles that a person may have in the community (professional role, volunteering role, family role, and other roles). The social network a person belongs to may facilitate the communication of a health problem without directly improving health literacy but instead decrease the feeling of shame and possible stigma because of the inability to read and write about health information or seek medical advice for a health problem. Family and friends may also be facilitators in a decision about health or may take the decisions for the patient. This also may work in the opposite direction, where family and friends with low health literacy have a negative influence on the person's health decisions [41].

The second dimension of social support, which may possibly interact with the level of health literacy, includes the emotional, informational, health reminder support, and tangible aspect of support and is referred to as functional support [41,43]. According to Lee [43], older adults with low health literacy had higher support concerning medical information and health reminder support. However, tangible support was rather low in this population with low health literacy, probably because of a lack of social networks [41,43].

Figure 1. Health literacy and electronic health (ehealth) literacy of primary and secondary carer in association with primary carer's perceived social support and the selected caregiving variables.jpg.



Aim of This Study

According to a recent review [15], we find a large number of Web-based support services for carers of people with dementia. Carers and new technologies is a topic of interest, so we consider it important to identify any issues related with carers' health and eHealth literacy. Although there is some literature for older people or for carers of people with other chronic diseases, health and eHealth literacy have not been explored in carers of people with dementia. Furthermore, other than the primary carer, the role of health and eHealth literacy of the secondary carer will be assessed in this study. In addition, this study aims to explore the associations between health literacy, eHealth literacy and self-efficacy, coping strategies, social support, and caregiving perceptions of dementia carers, taking into consideration the role and support provided by the secondary carer.

As part of the study, health and eHealth literacy tools, as well as the Revised Scale for Caregiving Self-Efficacy will be validated in the Greek language for use among this population group.

The main research questions are

- RQ1a: What is the level of health literacy and eHealth literacy of dementia patients' primary carers?
- RQ1b: What is the level of health literacy and eHealth literacy of dementia patients' secondary carers?

- RQ2: Is there a difference between health literacy and eHealth literacy level of dementia patients' primary and secondary carers, given the generation gap?
- RQ3: What is the association between health literacy and eHealth literacy of dementia patients' primary and secondary carers?
- RQ4: What is the association (if any) between health literacy and eHealth literacy of dementia patients' carers and caregiving self-efficacy?
- RQ5: What is the association (if any) between health literacy and eHealth literacy of dementia patients' carers and their ability to cope with the stressors of caring?
- RQ6a: What is the association (if any) between health and eHealth literacy of dementia carers and their perceptions toward the caregiving role?
- RQ6b: What is the association (if any) of the health literacy and eHealth literacy of the dementia patients' secondary carer and the primary carers' self-efficacy, coping, and caregiving perceptions, and to what extent does the observed association between health literacy or eHealth literacy and caregiving variables in the primary carer differ according to the health and eHealth literacy of the secondary carer?
- RQ7: What is the association (if any) between social support and caregiving variables and to what extent the observed association between health literacy or eHealth literacy and caregiving variables in the primary carer differ according to the levels of social support?

Methods

Study Design

The study will be a cross-sectional correlational descriptive study design to explore the level of health literacy, eHealth literacy, and their association with caregiving self-efficacy, coping strategies, social support, quality of support, positive value, and negative impact of caregiving in Greece and Cyprus.

Pilot Phase

Before the full scale research study, a pilot phase will be conducted to assess the appropriateness of selected questionnaires, the mode of data collection and length of interview, the acceptance of the research material by the primary and secondary carer, and expected challenges in sample recruitment. According to Connelly [44], the adequate number of people for a pilot study design is 10% of the total sample. Other researchers [45,46] suggest a number of 10 to 30. The minimum number of pilot participants in this case was set to a minimum of 17 to 30 primary carers.

Sample

Carers of people with dementia will be recruited from dementia centers and Alzheimer's associations in Greece, (Athens, Thessaloniki) and Cyprus. They will be invited to participate in the study following informed, signed consent. The sample will include primary carers (the carers who support the people with dementia in activities of daily living) and secondary carers (named family member, friend, or other person in the social network assisting the primary carer in their role). For each primary carer, a secondary carer who provides support to the primary carer will be identified. The secondary carer will be named by the primary carer as the closest person who supports the primary carer in his or her caring role. Selected questions will assist the primary carer to identify the supporter carers.

As there are many social cultural similarities related to caregiving between Greece and Cyprus, given the common language and historical and sociocultural background of both countries, it was decided to recruit one sample from both countries. Carers in both countries have the most important role in the care of people with dementia substituting for gaps in the national health care systems. The non-for-profit associations have undertaken the role of supporting and providing services to carers in Greece and Cyprus. In Greece, a number of services provided to carers by the not-for-profit associations are funded by the Ministry of Health through the mental health reform program [47].

Furthermore, the inclusion of two metropolitan cities from Greece, Athens and Thessaloniki, offers the opportunity to involve very active Alzheimer's associations in Greece with both a high as well as more heterogeneous number of users, in an effort to achieve the inclusion of as wide as possible set of members from the target population in terms of their sociodemographic characteristics, as well as the variables of interest. As this is a correlational study, the multicenter convenience sampling aims to increase the observed variability in the variables of interest.

The sample size was calculated considering carers in Greece and Cyprus as one sample according to the above requirement The minimum required sample size with 95% power to detect a statistically significant correlation of the aforementioned variables of the magnitude of r=.25 (type I error 5%) is 168 primary carers and 168 secondary carers. To account for issues with possible inconsistencies in data, incomplete questionnaires, and missing values, it was decided to increase the recruitment to a sample of 200. Moreover, in this way, we ensure that the number of the secondary carers (and thus primary-secondary carers dyads) will not fall under the minimum required sample size, as it is likely that not all secondary carers may agree to participate. Estimated duration of the recruitment period will be 12 months.

Recruitment Process

In Cyprus, prospective participants will be recruited from the Pancyprian Association of Alzheimer's Disease and from the Alzheimer's day centers, Ithaki, which are located in the city of Limassol and Pafos. We have selected these two day centers as they are currently the only services for carers. In Athens and Thessaloniki, recruitment will be done through the Alzheimer's association. In Athens, there are currently six dementia day care centers: in the municipalities of Marousi (1), in Halandri (1), in the city of Athens (3), and in Ilioupoli (1). In Thessaloniki, there are two dementia centers. Furthermore, a sample will also be selected during the events on Carers' day, which is usually organized by the associations annually.

Inclusion criteria for the primary carer include being a self-appointed carer of a person with dementia; supporting the person in activities of daily living, irrespective of the

relationship with the person (spouse, children, sibling, friend, or neighbor); being over 18 years of age; and able to read and write in Greek.

The carers will be first approached by the manager of the centers and/or associations who will explain to them the aims of the study. If a carer fulfills the inclusion criteria and is willing to participate, she or he will be referred to the researcher for data collection.

Secondary carers will be nominated by the primary carer and will also be invited to participate in the study. The primary carer will initially contact the secondary carer asking if they are interested in participating, and the researchers will follow this communication to arrange the face-to-face or telephone survey interview.

The face-to-face surveys will be conducted at a place and time convenient for the primary carer. In the case of the secondary carer, an effort will be made to collect the data in face-to-face survey interviews, but the option for a telephone survey interview will be provided to reduce the likelihood of nonparticipation by the secondary carers. The primary carers will respond to the full questionnaire pack, whereas the secondary carers will be asked to respond to the health literacy and eHealth literacy scales (using the same tools as in the case of the primary carers), as well as providing information with regard to sociodemographic characteristics.

Study Questionnaires

Information on sociodemographic characteristics will be collected from both the primary and secondary carers, as well as for the people with dementia they are caring for. Primary and secondary carers information will include age, gender, education, employment status, living situation, hours of care per week (primary carer), years of care (primary carer), number of care recipients (primary carer), relationship with the person with dementia (primary carer), care professional help (primary carer), relationship with primary carers (secondary carer), and type of support provided to primary carers (secondary carer). Information of the person with dementia will include age, gender, diagnosis, stage of the disease, and functional level.

Health Literacy Measures

eHealth Literacy: eHeals Adapted for Dementia Carers in the Greek Language

eHeals, a self-report tool measuring eHealth literacy based on the Lily model, will be used [19]. The scale consists of 8 questions, and it assesses the users' perceived skills at using health technology. In the original study, the scale showed good internal consistency with Cronbach alpha=.88. The eHealth scale taps into the usefulness, importance, perceived knowledge, and evaluation of Web-based health information, with a theoretical range for the overall score from 8 to 40. To date, the tool has been validated in Dutch [48], Italian [49], Chinese [50], and German [51] among varied population groups as school children, university students, and chronic disease patients. In the Dutch, Italian, and Chinese version, the questionnaire was treated as a unidimensional tool. In the German version, there were two dimensions (information-seeking and information appraisal). In all versions, the tools showed high internal consistency with Cronbach alpha ranging from .82 to .92 across the aforementioned studies. Only in the Dutch study were the participants people with rheumatic diseases, whereas the scale has not been previously used among carers of people with dementia.

For this study, the eHeals will be translated into the Greek language using backward-forward translation of the original English version. The questionnaire items will be adapted accordingly where necessary to address carers based on a review by an expert panel. The metric properties of the Greek version will be assessed using the Content Validity Index (CVI) based on the responses of an expert panel in the field of eHealth and health care to assess its content validity. Furthermore, the construct validity of the scale will be assessed in exploratory and confirmatory factor analyses as necessary. The internal consistency of the scale will be assessed using Cronbach alpha coefficient. The validation will be part of the analysis of data derived from the final sample.

The Internet Use Carers Profile

The Internet use carers profile will be measured using a series of 10 questions that assess the frequency and type of use, for example, use of websites, emails, e-learning, social media, interactive services, forums, blogs, mobile, and the Internet. It was deemed important to supplement the eHeals scale with these profile questions, as there has been much criticism with regard to the lack of relevant questions in the eHeals scale, given the Web evolution during the last decade [21,48].

European Health Literacy Survey Questionnaire 16 (HLS-EU-Q16) Short Form

In addition to eHealth literacy, the health literacy of the primary and secondary carers will be assessed using the European Health Literacy Survey Questionnaire 16 **(**HLS-EU-Q16) [52,53]. The long form of the questionnaire consists of 47 questions, whereas there are also two shorter forms, one with 16 and one with 6 questions. Due to the large number of questionnaires included in this study, it was decided to use the 16-item short form of the scale. The short form was developed based on Rasch modeling and is considered one-dimensional and discriminates three levels of literacy: sufficient health literacy, problematic health literacy, and inadequate health literacy. The tool has been validated in German [54,55], Bulgarian [53], Dutch [53], Israeli [56], and Swedish [57]. As far as we are aware, there is no published validation in Greek, even though Greece participated in the original cross-national survey.

Single Item Literacy Screener (SILS)

Single Item Literacy Screener (SILS) assesses inadequate health literacy and together with the HLS-EU-Q16 provides the information on the health literacy level of the study participants. SILS has been part of 16 questions developed by Chew et al [58]. Initially, 3 questions were identified as better predictors of low health literacy and difficulty in reading printed material. Chew et al [59] proceeded in selecting the single item (SILS) that had better sensitivity (ie, 39% at a score <2) and specificity (93%) than the other 2 questions in predicting inadequate health literacy. The question "How often do you need to have someone

help you when you read instructions, pamphlets, or other written material from your doctor or pharmacy?" is replied with a 5-point Likert scale from 1=never to 5=always. A score of 2 and above is considered adequate health literacy level. SILS according to Brice et al [60] does not assess marginal literacy accurately, as it is defined based on the Short Test of Functional Health Literacy in Adults (S-TOFHLA): the person "has difficulty in reading and interpreting health texts." SILS is easy to use in a clinical setting for a quick screening of health literacy, can discriminate between inadequate and adequate reading ability, and predicts well S-TOFHLA scores of low health literacy. For this specific study, SILS will be validated in Greek to assess the sensitivity and the specificity of the question and adjust the selected cut-off score for this specific population.

Other Constructs (Dependent Variables)

Revised Scale for Caregiving Self-Efficacy

The scale assesses the self-efficacy of carers [61]. It consists of 15 items organized in three subscales, namely, (1) self-efficacy for obtaining respite, (2) self-efficacy for responding to disruptive patient behaviors, and (3) self-efficacy for controlling upsetting thoughts about caregiving. Internal consistency of the three scales was high with Cronbach alpha over .80. The Revised Scale for Caregiving Self-Efficacy has high correlation with depression, anxiety, anger, and social support scales [57]. This scale will be validated in Greek.

Perceptions Toward Caring: COPE Index

COPE index measures carers' perceptions toward positive and negative values of caring [62]. It consists of 15 items and is part of a study protocol realized in five countries: Italy, Greece, Poland, Sweden, and the United Kingdom. Positive value of caring includes five items, and negative values includes six items. Furthermore, three additional items measure the quality of support, and one item taps into the financial hardships. Negative values items had high internal consistency (Cronbach alpha=.88) in comparison with positive values items with a more modest internal consistency (Cronbach alpha=.67). The criterion validity of the scale was assessed with the use of General Health Questionnaire, Hospital and Depression Scale, and World Health Organization Quality of Life-BREF [62]. Negative values items had significant association with all measures in all countries. Positive values of caring items demonstrated significant association with all measures but was restricted to certain countries (Sweden and Greece).

Brief COPE

Brief COPE assesses the coping strategies adopted by carers [63]. It consists of 28 items organized in pairs in 14 groups of strategies, namely, acceptance, active coping, positive reframing, planning, use of instrumental support, use of emotional support, behavioral disengagement, self-distraction, self-blame, humor, denial, religion, venting, and substance use.

Multidimensional Scale of Perceived Social Support—MSPSS

Multidimensional scale of perceived social support consists of 12 items measuring social network support, including three factors: significant other, family, and friends. The items are scored on a Likert scale from 1 (very strongly disagree) to 6 (very strongly agree) [64,65]. The higher score is 84 and, commonly, a cut-off score of 65 is used. The scale has been tested among different population groups from students to older adults, including patients with chronic diseases. High internal consistency was reported for overall scale (Cronbach alpha=.88), as well as for the subscales (significant other Cronbach alpha=.72, family Cronbach alpha=.85, and friends Cronbach alpha =.75) [63].

Statistical Analysis

Descriptive statistics will be reported, and bivariate correlations between all variables of interest will be explored with parametric and nonparametric measures. Sociodemographic correlates associated with health literacy will also be assessed. Additional data analysis (eg, *t* test, analysis of variance) will be used as needed, for example, to investigate differences in eHealth and health literacy according to sociodemographic characteristics of the participants. The association between dependent variables (coping, self-efficacy, and caregiving perceptions) and independent variables (health literacy, eHealth literacy of primary and secondary carers) will be assessed in multiple regression models before and after adjusting for sociodemographic variables. The extent to which the observed association between health literacy and coping and caregiving perceptions among primary carers differs according to self-efficacy, social support, and the secondary carer's eHealth and health literacy (moderators) will also be explored.

Concerning the adaptation and validation of the health literacy questionnaire, SILS, and Revised Scale of Caregiving Self Efficacy, face and content validity will be assessed by an expert panel. The metric properties (construct validity and internal consistency) will be assessed using exploratory and confirmatory factor analyses and internal consistency reliability analysis. Analysis will be performed by Statistical package for the Social Sciences (SPSS) version 22 (IBM Corp) and exploratory factor analyses with SPSS AMOS.

Ethics Approval

Permission to conduct the study was granted by the National Committee of Bioethics in Cyprus on January 10, 2017, according to the National Law (ΕΕΒΚ ΕΠ 2016.01.151). The commissioner of personal data protection in Cyprus has been notified accordingly and confirmed notification on December 19, 2016 (study number 3.28.460). In Greece, the scientific committee of the Athens Association of Alzheimer's Disease and Related Disorders have also been notified and approved the study on March 17, 2017, with a decision by the Executive Board. This process will be repeated for the Alzheimer's association in Thessaloniki.

All participants will be fully informed about the purpose and the requirements of participation in the study. Consent forms will be signed, and participants will have the right to withdraw at any time. Confidentiality of the participants will be respected. Researchers will safeguard the well-being of the participants during the data collection.

Participants who are interested in receiving feedback will be contacted by email or telephone as soon as the results are

analyzed and drafted. Researchers will try to make the participants feel comfortable and resolve any kind of conflict concerning the time, the place of the meetings, and the way that the secondary carers will be contacted.

To safeguard personal sensitive data, a database protected by a password will be developed and will be stored by the research team university computers. Only members of the research team will have access to the database. Hard copies of all measurements will be stored and locked in the Office of the Scientific Supervisor.

Results

The pilot phase of the study is in progress. In the following section, we report some preliminary results of the validation of HLS-EU-Q16 in Greek for the purposes of this protocol.

A convenience sample of 107 older people from an outpatients' eye clinic in Cyprus and open clubs for leisure activities for older people in Athens, Greece, participated in the validation of the scale (Table 1).

The internal consistency of the scale as estimated using Cronbach alpha coefficient was .77 and was adequate, even though it was somewhat lower that the respective figure observed in validation studies elsewhere. CVI for each item, as well as the overall scale was also calculated with a panel of experts (N=6) and a panel of health professionals (N=20), providing high scores for item-level CVI and scale-level CVI/average (S-CVI/Ave) in both groups. S-CVI/universal agreement (S-CVI/UA) was lower among health professionals compared with the group of experts (Table 2).

In-depth analysis of the results derived by the validation of HLS-EU-Q16 will be presented in a subsequent paper. The data collection of the pilot study started in May 2017, and the data collection for the main study is projected to start in October or November 2017.

Table 1. Sociodemographic characteristics of the participants to Health Literacy Scale-Europe-Questionnaire 16 (HLS-EU-Q16) validation.

Characteristics	n (%)
Gender	
Women	62 (57.9)
Men	45 (42.1)
Total	107 (100)
Age in years	
<60	9 (8.4)
61-80	80 (74.8)
>81	18 (16.8)
Education	
No primary education	9 (8.4)
Primary education	47 (43.9)
Secondary education	40 (37.4)
Tertiary education	11 (10.3)
Profession	
Pensioner	84 (78.5)
Employed	12 (11.2)
Unemployed	2 (1.9)
Other (eg, housekeeping)	9 (8.4)
Family status	
Married	82 (76.6)
Single	3 (2.8)
Divorced	2 (1.9)
Widowed	18 (16.8)
Other	1 (0.9)
Comprehensive health literacy level	
Sufficient	49 (45.8)
Problematic	49 (45.8)
Inadequate	9 (8.4)
Health perception	
Good	77 (72)
Neither good or bad	26 (24.3)
Bad	4 (3.7)
Quality of life perception	
Good	84 (78.5)
Neither good or bad	20 (18.7)
Bad	3 (2.8)
Chronic illness	
Yes	58 (54.2)
No	49 (45.8)
Country	
Cyprus	69 (64.5)
Greece	38 (35.5)

Table 2. Content validity index analysis of the European Health Literacy Survey Questionnaire 16 (HLS-EU-Q16).

Panel	Mean I-CVI[a]	S-CVI/Ave[b]	S-CVI/UA[c]
Group of experts (N=6)	.96	.96	.81
Group of health professionals (N=20)	.97	.97	.69
Total	.93	.97	.63

[a]I-CVI: item-level content validity index.

[b]S-CVI/Ave: single-level content validity index/average.

[c]S-CVI/UA: single-level content validity index/universal agreement.

Discussion

Principal Findings

In this study protocol, we have presented the preliminary results of the HLS-EU-Q16 validation. The validation was carried out among 107 older people in Greece and Cyprus, providing information for the comprehensive health literacy level of older people in these two countries. The main study will investigate the relationship of eHealth literacy and health literacy with caregiving self efficacy, coping strategies, and care management perceptions of carers of people with dementia. Previous studies have explored the associations between health literacy and coping strategies, health literacy and self-efficacy, coping strategies and care management, caregiving and self-efficacy, social support and self-efficacy, and social support and health literacy in different target groups. However, no previous study has adopted a unified approach or explored these issues in carers of people with dementia [36,66-69]. Furthermore, studies commonly focus on the primary carer. In this study, information will be also collected from the supporter carer (or secondary carer). The support provided by the secondary carer to the primary carer may influence the primary carer's self efficacy, coping strategies, and/or caregiving perception. Furthermore, the health and eHealth literacy of the secondary carer may influence both the health and eHealth literacy of the primary carer, as well as acting as a moderator in the association between health literacy and caregiving variables in the primary carer.

eHealth literacy is a rather underresearched concept among this population, taking into consideration the age of the majority of carers (above 50 years). The idea of connecting eHealth literacy with caregiving becomes more challenging. New technologies are a core part of everyday life for a large percentage of the population worldwide, but still there are specific groups with low access to technological advances. Low income, low socioeconomic status, and racial or ethnic minorities are considered a predictor of Internet nonuse [5].

Carers and especially spouses could be considered to be a minority in the use of technology. On the other hand, several projects are funded to develop technological innovations to support carers in their role, including Web-based psychoeducational programs and support groups [70-73], interactive services (forums, online communities) [74-76], interventions for depression and stress management [77], e-learning courses and carer platforms or websites [76,78-81], telemedicine, and telehealth (global positioning system, sensor technologies) [82,83]. The need to investigate the level of eHealth literacy and related skills and resources in this population becomes more important considering the possible discrepancy between the development of new technologies for carers on the one hand and the actual frequency of use, and thus benefit, of such technology.

This is also confirmed by the systematic review by Chi et al [84]. Six types of technology-based interventions for carers were identified:

1. Education using mainly telephone-based, Web-based, and video interventions
2. Consultation using videoconferencing
3. Psychosocial or cognitive behavioral therapy intervention using telephone and videoconferencing tools
4. Social support using videoconferencing tools
5. Data collection or monitoring, including response center, sensors, and fall detectors
6. Clinical care delivery using videoconferences

Taking into consideration the large amount of research available on the usability and feasibility of this type of research, it is interesting that there is little focus on the skills required by this target population to use the aforementioned services.

Limitations and Strengths

The challenges of this study concern the recruitment of carers, both in terms of access (hence a convenient sample of people in contact with services), as well as the time requirements and other elements of the recruitment procedure, mainly the survey completion time (estimated at 60 min) and potential difficulties in contacting and recruiting secondary carers. We expect that the majority of secondary carers will be the children or friends of the primary carer, making the arrangement of the survey interview challenging both in terms of time and location but also in terms of motivation to participate.

This study presents numerous strengths. Even though a convenience sample will be recruited, the recruitment will be from a variety of settings to increase the heterogeneity of the sample in terms of their sociodemographic characteristics, as well as the variables of interest. Furthermore, the eHeals questionnaire will be adapted to the needs of carers, and the HLS-EU-Q16 will be used and validated for the first time in this specific population. More importantly, the study will assess the level of health and eHealth literacy of Greek and Cypriot carers of people with dementia for the first time, as well as explore the role of these constructs in the caregiving process. This has important implications about the services provided.

Moreover, screening tools will be available to measure health and eHealth literacy levels for this specific population, and future research on eHealth literacy training of carers in Greece and Cyprus will follow.

Conclusions

Taking into consideration the fast technological progress, the demand for Web-based training and eHealth literacy training is only a matter of time. More and more resources are being developed to support carers on the Web, and the use and assessment of this type of technologies by carers are becoming essential skills that in future years will become obligatory. Focusing on training and developing, training classes and e-learning courses could facilitate the development of these specific skills among this population. Furthermore, the usage of new technologies and the Internet could act as a facilitator in the caregiving demands of carers.

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Authors' Contributions

AE has written the manuscript. AC and NM have contributed in writing, consultation, and reviewing. EP supervised the writing process, consulted the first author, and reviewed the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

COPE: Carers of Older People in Europe
CVI: content validity index
eHeals: eHealth Literacy Scale

eHealth: electronic health
HLS-EU-Q16: European Health Literacy Survey Questionnaire 16
I-CVI: item level content validity index
IT: information technology
S-CVI/Ave: scale level content validity index/average
S-CVI/UA: scale level content validity index/ universal agreement
SILS: Single Item Literacy Screener
S-TOFHLA: Short Test of Functional Health Literacy in Adults

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Protocol

Development and Usability Testing of a Computer-Tailored Decision Support Tool for Lung Cancer Screening: Study Protocol

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Abstract

Background: Awareness of lung cancer screening remains low in the screening-eligible population, and when patients visit their clinician never having heard of lung cancer screening, engaging in shared decision making to arrive at an informed decision can be a challenge. Therefore, methods to effectively support both patients and clinicians to engage in these important discussions are essential. To facilitate shared decision making about lung cancer screening, effective methods to prepare patients to have these important discussions with their clinician are needed.

Objective: Our objective is to develop a computer-tailored decision support tool that meets the certification criteria of the International Patient Decision Aid Standards instrument version 4.0 that will support shared decision making in lung cancer screening decisions.

Methods: Using a 3-phase process, we will develop and test a prototype of a computer-tailored decision support tool in a sample of lung cancer screening-eligible individuals. In phase I, we assembled a community advisory board comprising 10 screening-eligible individuals to develop the prototype. In phase II, we recruited a sample of 13 screening-eligible individuals to test the prototype for usability, acceptability, and satisfaction. In phase III, we are conducting a pilot randomized controlled trial (RCT) with 60 screening-eligible participants who have never been screened for lung cancer. Outcomes tested include lung cancer and screening knowledge, lung cancer screening health beliefs (perceived risk, perceived benefits, perceived barriers, and self-efficacy), perception of being prepared to engage in a patient-clinician discussion about lung cancer screening, occurrence of a patient-clinician discussion about lung cancer screening, and stage of adoption for lung cancer screening.

Results: Phases I and II are complete. Phase III is underway. As of July 15, 2017, 60 participants have been enrolled into the study, and have completed the baseline survey, intervention, and first follow-up survey. We expect to have results by December 31, 2017 and to have data analysis completed by March 1, 2018.

Conclusions: Results from usability testing indicate that the computer-tailored decision support tool is easy to use, is helpful, and provides a satisfactory experience for the user. At the conclusion of phase III (pilot RCT), we will have preliminary effect sizes to inform a future fully powered RCT on changes in (1) knowledge about lung cancer and screening, (2) perceived risk of lung cancer, (3) perceived benefits of lung cancer screening, (4) perceived barriers to lung cancer screening, (5) self-efficacy for

lung cancer screening, and (6) perceptions of being adequately prepared to engage in a discussion with their clinician about lung cancer screening.

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KEYWORDS

lung cancer screening; informed decision making; shared decision making; patient decision aid; patient education; early detection of cancer; lung neoplasms; decision support techniques; decision making, computer-assisted

Introduction

Lung cancer screening is a US Preventive Services Task Force (USPSTF) grade B recommendation, indicating there is high certainty that the overall benefits are substantial [1]. The National Lung Screening Trial, on which the recommendation is based, found a 20% lung cancer-related mortality reduction for long-term smokers screened annually with low-dose computed tomography (LDCT) compared with chest radiography [2]. However, lung cancer screening with LDCT is a complex issue. Screening has associated risks and potential harms that complicate the decision to screen [1]. Most notable among these are false-positive results and incidental findings, which can lead to a cascade of unnecessary invasive testing [1,2]. Therefore, the USPSTF recommends that the decision to screen for lung cancer should be the result of a shared decision-making process between a patient and their clinician. In addition to shared decision making being incorporated into the lung cancer screening guideline [1], for the first time, it is a requirement for reimbursement of a cancer screening test from Medicare [3].

Our team's preliminary work revealed that most individuals eligible for lung cancer screening are unaware of, or confused or misinformed about (1) how lung cancer screening is performed, (2) the benefits and associated risks of screening, and (3) the causes of and associated risk factors for developing lung cancer [4]. It is critical to increase long-term smokers' awareness of and education about lung cancer and screening. Education is an essential component of the shared decision-making process, and the USPSTF guidelines provide criteria for whom to engage in shared decision making about lung cancer screening [1]. The screening decision should, therefore, be the result of a clinical encounter in which the clinician and patient engage in shared decision making. Patients who are involved in decision making about their health have better outcomes [5], and shared decision making is ideally suited for the complex nature of the decision to screen, or not, for lung cancer. However, awareness of lung cancer screening remains low in the screening-eligible population [6]. In our team's recent study exploring the decision to opt in or out of lung cancer screening, our findings highlighted the prevalence of time-constrained clinical encounters and their negative effect on the shared decision-making process about screening [7]. When a patient visits their clinician and has never heard of lung cancer screening before, engaging in the shared decision-making process to arrive at an informed decision can be a challenge. Methods to effectively support both patients and clinicians to engage in shared decision making are essential. Importantly, to facilitate this process, effective methods to prepare patients to *have* these important discussions with their clinician are needed.

Several decision aids [8-11] have been developed in response to the USPSTF lung cancer screening guideline and Medicare mandate for shared decision making. However, few are theoretically grounded. To our knowledge, 2 theoretically grounded lung cancer screening decision aids have been published in the literature and both are conceptually framed from a perspective of risk [8,9]. Volk and colleagues developed the video *Lung Cancer Screening: Is It Right for Me?* [8]. This 6-minute video provides information about risk factors for lung cancer, and harms and benefits of lung cancer screening, and presents vignettes depicting trade-offs between harms and benefits to clarify values [8]. Initial feasibility showed that this decision aid increased knowledge ($P<.01$) and supported readiness to make a decision to screen for lung cancer as reflected in significantly higher values clarity scores [8]. Lau and colleagues developed a Web-based decision aid guided by the Ottawa Decision Support Framework using an established prediction model to compute baseline lung cancer risk and an individual's chance of benefiting from, and risk of being harmed by, screening [9]. Knowledge of lung cancer and screening increased ($P<.001$) and decisional conflict decreased ($P<.001$) in initial feasibility testing [9]. Other commercially developed lung cancer screening decision aids focus on calculating personal risk for the development of lung cancer with subsequent screening recommendations based on the calculated risk [10,11].

As mentioned, lung cancer screening is a complex issue with associated risks and potential harms that complicate the decision to screen. During phase I with our community advisory board (CAB; described in more detail below), participants expressed concern about messaging for former smokers being similar to that for current smokers and the potential for increased perceived stigma. This highlighted the importance of tailoring a decision support tool based on smoking status. With careful consideration of the messaging, we chose a tailored approach because tailored interventions are more effective than nontailored ones, and have been shown to improve knowledge, change health beliefs, and promote health behavior change in other types of cancer screening such as breast and colorectal cancers [12-17]. Our previous research revealed that perceived risk was not associated with actual screening behavior in lung cancer [18]. Regardless, it is important for any decision support tool in lung cancer screening to include risks for the development of lung cancer; however, to support the shared decision-making process in lung cancer screening, it is critical that lung cancer screening decision aids go beyond assessing risk and that they tailor messages based on multiple salient variables that may be personally relevant to the individual. Lung cancer screening decision aids

should also leverage the previsit time frame (ie, during either the time spent waiting in the clinic before the clinician comes in for the visit or the week leading up to a scheduled well-care appointment, in which patient education can be consumed at home) to prime patients with new knowledge about lung health and the option of screening. Educating patients during the previsit time period has the potential to enhance the subsequent clinical encounter for patient engagement in a shared decision-making process.

It is also important to acknowledge the role stigma may play in lung cancer screening discussions and decisions. Individuals qualify for lung cancer screening based on their history of long-term tobacco use, and smokers are different from populations targeted for other types of cancer screening, which base eligibility on age and sex. Smokers have reported perceiving blame and feeling stigmatized in clinical encounters secondary to their status as a current or former smoker [4,19]. Further, initial focus group discussions with screening-eligible individuals revealed that former smokers did not wish to be addressed as a current smoker. Therefore, patient decision aids for lung cancer screening may benefit from tailoring messages and content by smoking status.

This paper discusses the development and usability testing of a computer-tailored decision support tool called LungTalk. This decision support tool was developed using the USPSTF lung cancer screening guideline and the qualifying and certification criteria of the International Patient Decision Aid Standards instrument version 4.0 as a guide [20]. The purpose of LungTalk is to prepare individuals for the shared decision-making process about lung cancer screening by educating individuals about (1) lung health broadly including the effects of nicotine, (2) risk factors for the development of lung cancer, (3) the option of lung cancer screening with LDCT of the chest, and (4) risks and benefits of lung cancer screening. The content and messages of LungTalk are tailored by smoking status. LungTalk is Web based and can be delivered via email or sent to a patient via a health system's patient portal with an embedded weblink prior to an upcoming clinic visit. LungTalk can also be delivered via a tablet-based device in the clinic.

Methods

We developed a prototype of a computer-tailored decision support tool using user-centered design based on the most recent USPSTF lung cancer screening guidelines and the International Patient Decision Aid Standards instrument version 4.0 checklist. Its aim was to (1) educate individuals about lung health and lung cancer screening, (2) prepare them to engage in a discussion about screening with their clinician, and (3) enhance the shared decision-making process between clinicians and screening-eligible patients. This study was approved by the Institutional Review Board at Indiana University prior to recruitment, and we obtained informed consent prior to study participation. We used a 3-phase process to develop and test the prototype in the target population. We describe the process below by phase.

Phase I: Development

Overview

The computer-tailored decision support tool was developed by a team of researchers and clinicians with expertise in behavioral science, nursing, primary care, oncology, lung cancer screening, and informatics. Informed by a CAB comprising 10 screening-eligible individuals, the computer program was named LungTalk because the program goes beyond educating individuals solely about lung cancer screening to also educate broadly about lung health. We designed LungTalk to increase the users' awareness of potential risks related to long-term nicotine exposure, benefits of and potential harms related to lung cancer screening, and importance of shared decision making in the decision to screen for lung cancer or not, and to prompt users to initiate a discussion with a clinician about lung cancer screening.

LungTalk is unique in that it tailors messages based on smoking status and provides a tailored printout to help patients initiate a discussion with their clinician about their lung health and the option of screening. Our prior qualitative research with screening-eligible individuals revealed that many former smokers perceived stigma in clinical encounters where their long-term tobacco use was a focus [4,7]. This highlighted the importance of considering the framing of messaging based on smoking status in the development of the content of the decision support tool, as well as the importance of providing support for a discussion through a tailored printout.

Recruitment of Community Advisory Board Members

Our target population for LungTalk was lung cancer screening-eligible individuals based on the USPSTF lung cancer screening criteria [1]. These included persons who are aged 55 to 80 years, and current smokers or former smokers who had quit within the past 15 years with a minimum 30-pack-year tobacco smoking history [1]. We recruited CAB members from the local community using newspaper advertisement and through the Indiana University Health Lung Screening Clinic, Indianapolis, Indiana, USA, to ensure equal representation of individuals who had recently been screened for lung cancer and individuals who had not been screened.

Development of LungTalk With the Community Advisory Board

In phase I, we assembled the CAB to provide critical input and feedback during the initial development of LungTalk. We held 3 CAB meetings over the course of 6 months under the direction of 2 researchers (LCH and SMR) to discuss individual components of the computer program. Guided by user-centered design and in consultation with the study's design team (consisting of experts in informatics, user experience design and engineering, and visual communication), we asked members of the CAB to provide iterative feedback on the design and prototypes, preferences for how the program should "look and feel," and expectations of how the program should work when used in real-world settings. More specifically, the CAB provided feedback on what should and should not be included; development of, and specific wording for, messages to constitute the content library for LungTalk; specific graphic components

of the program; and the tailored printout. Each CAB meeting was audiotaped in order to accurately capture feedback from CAB members and facilitate prototype revisions with the design team. Digital audio recordings and field notes from the CAB meetings were reviewed by a researcher (LCH) and summarized for the design team.

Description of LungTalk

LungTalk is a computer-tailored decision support tool that is theoretically grounded in the conceptual model on lung cancer screening participation [21]. This model links the health belief model to the precaution adoption process model and includes key psychological variables (eg, stigma, mistrust, fatalism, fear, and worry) as factors that may influence an individual's decision to screen, or not, for lung cancer [21]. The LungTalk prototype is an interactive program that includes audio, video, and animation segments with tailoring algorithms for scripts presented from the master content library. In addition, LungTalk offers the option of saving or printing a tailored printout at the end. This printout highlights key points related to lung health and screening tailored by smoking status, offers question prompts the user can use to initiate the discussion with their clinician, and tailors messages based on questions that remain important to the user that they wish to discuss further with their clinician. Literacy level has been considered in the development of LungTalk and messaging is presented at an eighth-grade level. In addition, in consideration of different ways people like to learn, the content is presented via narration as well as key text on screen.

Phase II: Usability Testing

Overview

Following the initial prototype development of LungTalk, we conducted usability testing with 13 screening-eligible individuals (different from those constituting the CAB). Table 1 presents the sociodemographic characteristics of the CAB and usability testers.

Data Collection

Pretesting took place in the usability testing laboratory at the Indiana University School of Informatics. We used the method for iterative usability evaluation based on the Milano-Lugano evaluation method systematic usability inspection technique [22]. This method enabled us to identify communication breakdowns and recommend design improvements on task support, information architecture, navigation design, and interaction mechanisms.

Table 1. Phase I and phase II participant sociodemographic and health status characteristics.

Characteristics	Community advisory board (n=10)	Usability testing (n=13)
Age (years), mean (SD)	63.3 (6.7)	62.6 (7.2)
Sex, n (%)		
Male	6 (60)	10 (77)
Female	4 (40)	3 (23)
Race, n (%)		
White	4 (40)	10 (77)
Black	6 (60)	3 (23)
Education, n (%)		
Less than high school	1 (10)	1 (8)
High school graduate	4 (40)	0 (0)
Some college	4 (40)	7 (54)
College graduate or higher	1 (10)	5 (39)
Income (US $), n (%)		
<25,000	2 (20)	6 (46)
25,000-50,000	5 (50)	2 (15)
>50,000	3 (30)	5 (39)
Health insurance, n (%)		
Government	6 (60)	5 (39)
Private	4 (40)	8 (62)
Smoking status, n (%)		
Current smoker	5 (50)	4 (31)
Former smoker	5 (50)	9 (69)
Family history of lung cancer, n (%)		
Yes	4 (40)	5 (39)
No	6 (60)	8 (62)

Each usability testing session was facilitated by the researcher and a member of the study design team. The primary purpose of the usability testing session was to identify any programming errors or design issues that would prevent a satisfactory user experience and to curate additional feedback on the overall program.

Usability testing involved the participant using the program twice. First, the participant used the program without interruption. The researcher and study design team member observed how the participant interacted with the program and completed an investigator-developed observer checklist (see Multimedia Appendix 1). The participant was then asked to use the program a second time and was stopped at key points for the researcher to ask questions. The assessment included questions about specific content, messaging, points of potential confusion, opinions on visual, written, and verbal content, and flow design. On completion, the participant completed 2 questionnaires: (1) the 10-item System Usability Scale (SUS; see Multimedia Appendix 2); and (2) the 21-item Acceptability and Satisfaction Questionnaire (see Multimedia Appendix 3) [23,24].

Measures

We measured usability with the 10-item SUS. The SUS comprises 4-point Likert-response option items (1=strongly disagree, 2=disagree, 3=agree, 4=strongly agree). Participants rated items across a variety of specific tasks, including ease of use, consistency of the computer program, perception of how integrated the program felt during use, and perception of how well the computer program was able to prepare the user to discuss lung cancer screening with their clinician. In addition, open-ended questions were provided to allow participants to give feedback on negative and positive impressions of the overall program, as well as specific components. Participants were also asked to provide an overall letter grade rating for the program (ranging from A=excellent to F=unacceptable).

We measured acceptability and satisfaction with a 22-item questionnaire using a 4-point Likert-response option (1=strongly disagree to 4=strongly agree). In addition to overall satisfaction with the computer program, items assessed a variety of acceptability- and satisfaction-related components of the computer program, such as (1) amount of time to complete, (2)

clarity of the messages, (3) enjoyment with use, (4) content relatability, and (5) ability to engage the user.

Analysis and Results

All 13 participants viewed LungTalk twice as previously described. None of the participants experienced any technical difficulties during testing (eg, interruption of Internet service, computer program pausing or ending unexpectedly). However, 3 participants had difficulty recognizing the forward arrow button at the bottom of the screen to advance the program at the beginning. All 3 recommended that this button either be highlighted in green or flashing to indicate that the user needs to click the button to advance the program. Many users also recommended changing the settings of the program to autoadvance forward through the material in different sections to eliminate the need to click a button. We examined usability with the SUS. Reverse-coded items on the SUS were transformed for analysis, and total SUS scores ranged from 62.5 to 85 on a 100-point scale with an overall mean of 75.8 (SD 7.9). Total scores on the Acceptability and Satisfaction Questionnaire ranged from 79.8 to 97.6 on a 100-point scale with an overall mean of 90.2 (SD 6.3). Slightly more than half of the participants gave LungTalk an overall A rating (ie, excellent; n=7, 54%) with the remainder giving LungTalk a B rating (good; n=6, 46%).

Phase III: Community-Based, Web-Based Pilot Randomized Controlled Trial

Overview

Following development and usability testing of LungTalk, we are conducting a pilot randomized controlled trial (RCT) with the goal of obtaining preliminary effect size data for a future fully powered RCT. The pilot RCT will estimate the effect sizes of LungTalk on (1) changes in knowledge, (2) changes in health beliefs, and (3) participant perceptions of being adequately prepared to engage in a discussion with their clinician about lung cancer screening. Since the purpose of LungTalk is to prepare individuals for the shared decision-making process about lung cancer screening, the occurrence of a patient-clinician discussion about lung cancer screening and actual lung cancer screening completion are not the primary focuses in this initial study. However, for exploratory purposes, we will estimate the effect sizes of LungTalk for both.

Data Collection

Based on the overall objective of the pilot study to obtain preliminary effect size data, we need at least 12 participants per group to obtain reasonable effect size estimates to design a larger, well-powered trial [25,26]. To provide for the potential of attrition, 60 lung cancer screening-eligible participants who have not been screened for lung cancer have been recruited from the community using Facebook targeted advertisement [27]. We have randomly assigned participants to 1 of 2 groups after baseline data collection. The intervention group received LungTalk, and the enhanced control group received a nontailored lung screening information sheet compiled using patient education material from the American Cancer Society website [28]. Participants were randomly assigned and stratified by sex to each group. Stratified random assignment will ensure that the 2 groups are comparable in distribution. We are collecting data via REDCap (REDCap Consortium) at 3 time points via telephone: (1) baseline at recruitment, (2) within 1 week of completing the intervention, and (3) 3 months postintervention. REDCap is a secure Web-based app for building and managing online surveys and databases. REDCap provides audit trails for tracking data manipulation and user activity, as well as automated export procedures for secure data downloads to common statistical packages [29].

We are administering a baseline survey to collect data on sociodemographic and health status characteristics, lung cancer and screening knowledge, health beliefs (perceived risk of lung cancer, and perceived benefits of, perceived barriers to, and self-efficacy for lung cancer screening) [18], self-report of perception of preparation to engage in a patient-clinician discussion about lung cancer screening, and stage of adoption for lung cancer screening. We are measuring stage of adoption using an algorithm that is theoretically based on the precaution adoption process model [30]. This model categorizes individuals into 1 of 7 stages: unaware, aware but unengaged, undecided, decided not to act, decided to act, action, and maintenance [30]. At the completion of the baseline survey, each participant has been randomly assigned to either the intervention group or the enhanced control group. A link to either LungTalk or the lung screening information sheet was emailed to the participant based on their random assignment.

We administered a follow-up survey by telephone within 1 week of intervention completion. The survey included items to assess lung cancer and screening knowledge, health beliefs (perceived risk, perceived benefits, perceived barriers, and self-efficacy) [18], satisfaction with the intervention, self-report of perception of preparation to engage in a patient-clinician discussion about lung cancer screening, self-report of the occurrence of a patient-clinician discussion about lung cancer screening, and stage of adoption for lung cancer screening [30].

We will administer a second follow-up telephone survey 3 months after completion of the intervention. The 3-month follow-up survey will include items to assess self-report of the occurrence of a patient-clinician discussion about lung cancer screening, clinician recommendation, and stage of adoption for lung cancer screening [30]. For individuals who self-report completing lung cancer screening, we will verify the screening by mailing an authorization form to the participant to be signed and mailed back to the research office. A trained research assistant will verify the LDCT scan to screen for lung cancer using the information and signed authorization form by contacting the facility to request confirmation.

Analysis

We will compile deidentified data collected via REDCap and export it into a SAS file (version 9.4; SAS Institute). Data completeness will be assessed through descriptive analyses. Means and standard deviations or frequency distributions will be examined to check for coding errors and out-of-range values. All variables will be described with summary statistics appropriate for measurement level. Key analyses will be descriptive; we will calculate means and standard deviations and Cohen *d* effect sizes of study variables by group and for

each study time point. We will calculate 95% CIs for the effect sizes using the nonparametric bootstrap approach based on 2000 bootstrap replications. For exploratory purposes, we will fit linear mixed-effects models with smoking status and race as factors, and a participant-specific random intercept to account for the association between the observations of the same participant. We will also evaluate the feasibility of study procedures. Therefore, we will calculate participation rates and rates of completion and retention of participants at (1) baseline survey, (2) 1-week postintervention survey, and (3) 3-month postintervention survey. For each, we will calculate the proportion of people who were recruited initially and retained at each stage, along with the associated 95% CI. Patterns of missing values will be examined and evaluated for randomness using the method described by Enders [31]. We will evaluate diagnostic plots and inferential tests for tenability of assumptions and apply appropriate remedial methods where required.

For the pilot RCT, we will estimate initial differences between the 2 intervention groups with respect to key study variables. We will recruit 30 participants per group to estimate effect sizes of LungTalk on (1) changes in knowledge, (2) changes in health beliefs, (3) self-report of participant perceptions of being adequately prepared to engage in a discussion with their clinician about lung cancer screening, (4) occurrence of a patient-clinician discussion about lung cancer screening, and (5) stage of adoption for lung cancer screening. Key analyses will be descriptive; we will calculate means and standard deviations of study variables by group. For exploratory purposes, we will also fit 2-way analysis of variance models with smoking status and race as factors.

Results

We are conducting the pilot RCT. Recruitment began on June 15, 2017 using Facebook targeted advertisement. As of July 15, 2017, all 60 participants have been enrolled into the study and have completed the baseline survey, the intervention, and the first follow-up survey. We expect to have final results by December 31, 2017 and to have completed data analysis by March 1, 2018.

Discussion

Results from pretesting LungTalk in the usability laboratory indicate that the computer program is easy to use, is helpful, and provides a satisfactory experience for the user. The pilot RCT will provide preliminary effect sizes of changes in (1) knowledge about lung cancer and screening, (2) perceived risk of lung cancer, (3) perceived benefits of lung cancer screening, (4) perceived barriers to lung cancer screening, (5) self-efficacy for lung cancer screening, and (6) participant perceptions of being adequately prepared to engage in a discussion with their clinician about lung cancer screening. We anticipate that LungTalk will be helpful to screening-eligible individuals as a tool to support those considering the option to screen, or not, for lung cancer. Specifically, LungTalk can help enhance the shared decision-making process in lung cancer screening by priming individuals with essential baseline knowledge for the discussion and decision-making process.

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Authors' Contributions

LCH and SMR conceived of the study and sought funding and ethical approval. LCH and SMR are responsible for the development phase with the community advisory board. LCH, ECV, AG, and RSC are responsible for the usability testing phase of the study. LCH and SMR are responsible for the pilot RCT phase and planned statistical analysis. LCH, ECV, SMR, and RSC assisted in the development of LungTalk and subsequent iterations. NH and DPC provided feedback on the concept of LungTalk at key points in development. ECV assisted with data collection in all phases of the testing. All authors were involved in drafting and revising the manuscript and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Observer checklist.

[PDF File (Adobe PDF File), 29KB - resprot_v6i11e225_app1.pdf]

Multimedia Appendix 2

System Usability Scale.

[PDF File (Adobe PDF File), 47KB - resprot_v6i11e225_app2.pdf]

Multimedia Appendix 3

Acceptability and Satisfaction Questionnaire.

[PDF File (Adobe PDF File), 56KB - resprot_v6i11e225_app3.pdf]

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Abbreviations

CAB: community advisory board
LDCT: low-dose computed tomography
RCT: randomized controlled trial
SUS: System Usability Scale
USPSTF: US Preventive Services Task Force

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Original Paper

Development of a Behavior Change Intervention to Improve Sexual Health Service Use Among University Undergraduate Students: Mixed Methods Study Protocol

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Abstract

Background: University students are at risk for acquiring sexually transmitted infections and suffering other negative health outcomes. Sexual health services offer preventive and treatment interventions that aim to reduce these infections and associated health consequences. However, university students often delay or avoid seeking sexual health services. An in-depth understanding of the factors that influence student use of sexual health services is needed to underpin effective sexual health interventions.

Objective: In this study, we aim to design a behavior change intervention to address university undergraduate students' use of sexual health services at two universities in Nova Scotia, Canada.

Methods: This mixed methods study consists of three phases that follow a systematic approach to intervention design outlined in the Behaviour Change Wheel. In Phase 1, we examine patterns of sexual health service use among university students in Nova Scotia, Canada, using an existing dataset. In Phase 2, we identify the perceived barriers and enablers to students' use of sexual health services. This will include focus groups with university undergraduate students, health care providers, and university administrators using a semistructured guide, informed by the Capability, Opportunity, Motivation-Behaviour Model and Theoretical Domains Framework. In Phase 3, we identify behavior change techniques and intervention components to develop a theory-based intervention to improve students' use of sexual health services.

Results: This study will be completed in March 2018. Results from each phase and the finalized intervention design will be reported in 2018.

Conclusions: Previous intervention research to improve university students' use of sexual health services lacks a theoretical assessment of barriers. This study will employ a mixed methods research design to examine university students' use of sexual health service and apply behavior change theory to design a theory- and evidence-based sexual health service intervention. Our approach will provide a comprehensive foundation to co-design a theory-based intervention with service users, health care providers, and administrators to improve sexual health service use among university students and ultimately improve their overall health and well-being.

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KEYWORDS

sexual health services; university students; sexually transmitted infection; mixed methods research; intervention design; Behaviour Change Wheel; study protocol

Introduction

Progressing from adolescence to adulthood can be a challenging time for young adults who leave home for the first time to start university [1,2]. For most, this transition is uneventful, but for others, newfound independence and campus culture may lead to high-risk behaviors including excessive alcohol consumption [3], casual sex, and inconsistent condom use [4]. It is normal for young adults to explore their sexual identity and sexual relationships throughout their university journey [5]. However, such behaviors can increase students' risk of undesired health consequences, such as sexually transmitted infections (STIs), unplanned pregnancy, and psychological distress and regret [6]. For example, in Canada, university students are in the age group at highest risk for acquiring an STI [7]. In 2014, the rate of chlamydia infection in young adults in Canada, aged 20-24, was 1627.6 per 100,000 [7].

Many university and college campuses offer a range of sexual health services to promote healthy sexual behaviors (eg, health education, condom distribution) [8] and to prevent sexual health related illness (eg, STI/human immunodeficiency virus [HIV] testing and treatment, gynecological exams, pregnancy testing) among students [8,9]. University sexual health services are seen as ideal "health care homes" [8] for students during their studies, as they provide timely, accessible, and convenient services for many students who are away from their primary care provider [8]. However, young adults, including university students, often delay or avoid seeking sexual health care [10-13]. In the United States, only 27% of university students report having ever accessed sexual health services [12].

Based on a review of the literature, Bender and Fulbright [14] identified four categories of perceived barriers to sexual health services among young people in the United Kingdom, United States, and Canada: service access (ie, location, hours, confidentiality), service entry (ie, waiting time, waiting environment, fear of being seen), quality of services (ie, health care provider characteristics), and personal factors (ie, stress associated with seeking sexual health services). Few studies [10,12,13] have examined sexual health service use among the university and college student population specifically, as they begin to explore their sexuality and engage in risky behaviors during their university experience, and found similar results. Enhancing university students' access to sexual health services is important given the need to prevent their risk of STI transmission and associated negative health consequences [12]. However, we lack a clear understanding of the barriers and enablers to sexual health service use among university students and how their help-seeking behaviors can be changed.

One strategy for addressing students' use of sexual health services is to use behavior change theory in the design, implementation, and evaluation of sexual health interventions [15].

Incorporation of theory into the development and evaluation of complex interventions facilitates behavior change and provides an explanation of the mechanisms of change [16]. The Medical Research Council [17] in the United Kingdom suggests that complex interventions are more likely to succeed when theory is used to underpin the design process. Many behavioral theories and frameworks exist and have numerous overlapping theoretical constructs, which makes it difficult for researchers to choose a theory and apply it to their behavioral problem. In an effort to make theory more accessible for intervention designers, Michie et al [15,16] developed the Behaviour Change Wheel (BCW). The BCW is a systematic guide to intervention design that is based on (1) an analysis of the target behavior, (2) the determinants of behavior that need to be addressed in order to create behavior change, and (3) the interventions and policies required to support the change [15]. The BCW uses the Capability, Opportunity, Motivation-Behaviour (COM-B) model and Theoretical Domains Framework (TDF) to obtain a better understanding of the behavior in context, which is known as a behavioral analysis. The COM-B model [15] is a theory of behavior that proposes one needs capability (C), opportunity (O), and motivation (M) to perform a behavior. The TDF [18] is a behavioral framework consisting of 14 domains (knowledge, skills, behavioral regulation, beliefs about capabilities, beliefs about consequences, social/professional role and identity, optimism, reinforcement, intentions, goals, memory, attention, and decision making, emotion, environmental context and resources, and social influence) that is used in combination with COM-B to identify specific behavioral determinants of one's capability, opportunity, and motivation [15]. Based on the behavioral analysis, researchers are guided through a series of systematic steps in the BCW to identify intervention functions, policy categories, and behavior change techniques (BCTs) that are likely to bring about change [15]. The BCW has been used to design interventions in a variety of contexts, such as smoking cessation and alcohol reduction, prescribing behaviors, condom use, and clinician guideline utilization [15].

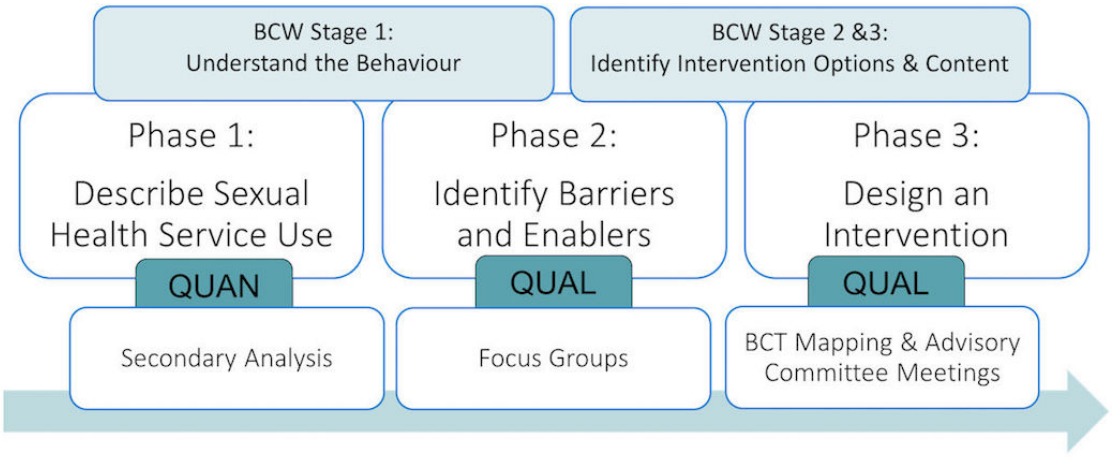
This paper describes the study protocol for using the BCW to design an intervention to address university undergraduate students' use of sexual health services at two universities in Nova Scotia, Canada. The study will address the following four research objectives through three phases. Phase 1 will describe the pattern of university undergraduate students' use of sexual health services at two Nova Scotia universities in 2012 using an existing quantitative dataset. Phase 2 will identify university students', health care providers', and university administrators' perceived barriers and facilitators for student use of sexual health services and will examine how the qualitative data related to the perceived barriers and facilitators to service use help better explain the patterns of student sexual health service use. Phase 3 will identify intervention components and/or strategies that can be used by service providers, university decision makers, policy planners, and students to facilitate the use of sexual health services

Methods

An explanatory sequential mixed methods research design [19] will be used to address the research objectives (Figure 1). The phases will follow the systematic stages outlined in the BCW. Data gathered from Phases 1 and 2 will be used to guide a series of advisory committee meetings in Phase 3 to identify intervention components that could be used to overcome the barriers and enhance the enablers to sexual health service use.

The third phase will culminate in the design of a theory- and evidence-based intervention aimed at improving the use of sexual health services by university students. Future research will pilot test and evaluate this intervention in the university health service setting.

Figure 1. BCW stages and study design diagram.



Phase 1: Understanding the Target Behavior (Quantitative Strand)

Design

To understand the pattern of university students' sexual health service, we will conduct a secondary analysis of data collected during the online Undergraduate Student Sexual Health Survey in the fall of 2012 [20]. This was a cross-sectional survey of a voluntary study population of undergraduate students from eight universities on the east coast of Canada. Data were collected using the Dillman tailored design method [21] through OPINIO, a secure, online surveying service [22]. The survey comprised 49 multiple choice and two open-ended questions. The purpose of this survey was to describe students' substance use, sexual health knowledge, attitudes, and behaviors, and sexual health service use. We will conduct a secondary analysis of these data to identify significant predictors of students' sexual health service use.

Sample

For the purpose of this study, a secondary analysis of a subset of the data collected from sexually active male and female undergraduate students aged 18-25 at two universities in Nova Scotia will be conducted. Both universities provide general health services in addition to sexual health specific services. These two universities were chosen for three reasons. First, University A is a large urban university, with approximately 13,600 undergraduate students (45% male, 55% female) and University B is a small rural university, with about 3500 undergraduate students (42% male, 58% female) [23]. At University A, 70% of first year undergraduate students and 18% of all undergraduate students live on campus, compared to 77% of first year students and 41% of all undergraduate students at University B [23]. The inclusion of a rural and urban university will improve the generalizability and transferability of the study's results to universities in similar contexts. Second, as these universities are in relatively close proximity geographically, the data collection in Phases 2 and 3 will be more feasible. Third, University A and University B yielded two of the highest response rates of the eight participating universities (31.2% and 23.8%, respectively; N=5633) [20].

Measures

Many factors at the individual, social, service, and policy levels influence young adult and university students' use of sexual health services [9,12,24,25,26]. The individual- and social-level variables outlined in Table 1 [27-31] were measured in the Undergraduate Student Sexual Health Survey and will be included in the proposed secondary analysis to identify significant predictors of sexual health service use. Survey questions and possible answers can be found in Multimedia Appendix 1.

Table 1. Variables of interest for Phase 1 secondary analysis.

Variable of interest	Survey item	Psychometric properties	Composite variable for analyses
Age	What is your age in years?	Pearson correlation =.98 [27]	Continuous variable (18-25)
Ethnic/Racial background	What ethnic/racial background do you consider yourself to be?	New question; no retest performed	0=Caucasian descent (white) 1=non-Caucasian Descent (African Descent, Aboriginal, Asian, Middle Eastern, and other)
Residential status	What are your living arrangements?	New question; no retest performed	0=On campus 1=Off campus, with self or peers 2=Off campus with romantic partner 3=Off campus, with parents
Sexual orientation	People have different feelings about themselves when it comes to questions of being attracted to other people. Which of the following best describes your feelings?	Kappa=.8 [28]	0=Heterosexual 1=Non-heterosexual
Sexual health knowledge [28]	Please indicate whether you believe each of the following statements are true or false by checking the appropriate response.	Cronbach α=.71 [28]	Continuous (0-12)
Barriers to help seeking [29]	Please indicate how much you disagree or agree with the following statements by checking the appropriate number on the 5-point scale, where 1 = “Strongly disagree” and 5 = “Strongly agree”	Cronbach α=.93 [29]	Continuous (0-40)
Social support [30]	Please describe how true you believe each of the following statements about your social relationships and support networks, where 1 = “not true at all” and 5 = “completely true”.	Cronbach α=.86 [30]; .71 [31] Kappa=.91	Continuous variable (0-105)
Sexual health service use Males: STI & HIV testing Females: STI, HIV, Pap, & pregnancy testing	Have you ever seen a health professional in order to obtain the following services? If you answer yes for a particular service, please indicate the location where you access that service: University health center or Other	New question; no retest performed	Males: 0=No 1=Yes (STI or HIV testing) Females: 0=No 1=Yes (STI, HIV, Pap, or pregnancy testing)

Data Analysis

Since males and females use sexual health services for different reasons and with different frequencies [6,13,32,33], we will stratify the data by biological sex for all statistical analyses. First, descriptive statistics will be reported to describe the characteristics of the undergraduate students and their use of sexual health services at University A and University B (ie, means/proportions with 95% confidence intervals). Second, to identify factors that are significant predictors of sexual health service use among undergraduate students at the two universities, we will conduct a series of multivariable logistic regressions. We will analyze each of the independent variables using univariable regression to determine significant predictors of sexual health service use at the university health centers. Variables found to be significant predictors (P<.2) [32] will be included in multivariable logistic regression analyses using the enter method [34]. For males, a multivariable logistic regression will be conducted with the STI and HIV testing composite dependent variable. For female respondents, a multivariable logistic regression will be conducted with the STI, HIV, Papanicolaou (Pap), and pregnancy testing composite dependent variable (Table 1). We conducted a power analysis and found that a sample size of 5633 is adequate to detect a minimum odds ratio of 1.2 at 89% power. A significance alpha level of P<.05 will be used as a cutoff for statistical significance. The data will be analyzed using the statistical software program, SPSS (Statistical Package for the Social Science), Version 21 [35].

Anticipated Outputs

Findings from this phase will be used in two ways. First, we will develop a detailed description of the pattern of university undergraduate students’ use of sexual health services on campus. Second, we will incorporate findings into a theory-based semistructured focus group guide to use in Phase 2.

Phase 2: Understanding the Target Behavior (Qualitative Strand)

Design

We will use a qualitative descriptive design [36,37] involving semistructured focus groups and policy document analyses to develop a detailed description of the barriers and facilitators to sexual health service use among university students.

Study Population and Sampling

For the focus groups, we will use a stratified purposive sampling strategy [38] with convenience sampling techniques [39] to recruit university undergraduate students, aged 18-25, as well as health care providers and university administrators (ie, health service directors and managers), from the health centers at the two universities. Based on the descriptive results and significant findings from the Phase 1 analysis, we will divide groups of interest into strata (ie, users and nonusers of sexual health services, males and females) and separately recruit participants from each strata to identify their perceived barriers and enablers to sexual health service use. Due to the sensitive nature of the topic, we will conduct single-sex focus groups to facilitate discussion [40]. We will recruit 6-10 participants per focus group as outlined by Wilkinson's [41] recommendations for conducting focus groups to uncover rich data for health-related phenomena of interest. We aim to recruit 18-30 students from each university (for a total of 36-60) and 6-10 health care providers/university administrators from each university clinic (for a total of 12-20) to participate.

Since the topic of sexual health and use of health services might be a sensitive one for university students [42], recruitment approaches that take place in public places may result in reduced enrollment. As such, we will use recruitment and enrollment mechanisms that allow for discretion. Identical posters and flyers will be distributed across the two university campuses, including libraries and student union buildings. An email describing the study and inviting students to participate will be distributed to student organizations and listservs. For the health care providers and administrator participants, an email will be sent to campus health clinic managers and university administrators with study details and an invitation to participate. Interested participants may contact the research assistant (RA) via email. The RA will respond by sending a study information sheet and a screening questionnaire to student participants to determine eligibility. Once eligibility is confirmed, the RA will send the focus group details and a copy of the consent form. The consent form will be reviewed and completed in person at the focus group meeting. We will provide an option on the consent form for participants to consent to be sent an invitation to participate in the next phase of our research (see Phase 3 below).

Materials

We will conduct separate semistructured focus groups with university undergraduate students, health care providers, and university administrators at each university. We will develop a semistructured focus group guide, informed by the COM-B model and TDF to guide the behavioral analysis and probe participants on their perceived barriers and enablers to sexual health service use among university students [43]. This will allow us to identify key beliefs from the different TDF domains that an intervention could target to improve students' use of sexual health services. As part of the development process, we will review the focus group guide with 3 students and 3 health care providers or administrators. The participants will be asked to read through the guide to identify flaws, uncertainties, concerns about the questions, or need for clarification. The focus groups guides will be refined based on their feedback [44,45].

We chose to conduct semistructured focus groups using a theory-based guide for three reasons. First, focus groups are a useful method for obtaining qualitative data on social and psychological processes [40], as well as social norms and cultural expectations related to sexual health [46]. Second, a semistructured guide will increase the likelihood that participants will cover the topic of interest in an efficient and effective manner [40]. Third, the semistructured guide enables flexibility so the focus group facilitator can explore issues in greater depth [47].

Procedure

The principal investigator, who has been trained in conducting focus groups and using the BCW (COM-B and TDF) to conduct behavioral analyses and design interventions, will facilitate the focus groups using the theory-based focus group guide. The focus groups will take place on the university campus and the research assistant will be present to take notes on group dynamics and nonverbal participant observations. Focus groups discussions will be audiorecorded and are expected to last approximately 45-60 minutes. Participants will be offered a Can $30 grocery store gift card in appreciation of their time.

Data Analysis

Audiorecordings from the focus groups will be transcribed verbatim and coded using directed content analysis [48] in NVivo 11 [49]. Content analysis is a systematic coding and categorization approach to qualitative data analysis used to examine trends and patterns of the data and to identify the frequency and relationships of the words used by participants [48]. Atkins et al [43] recommend a content analysis approach when using the TDF to design interventions. Focus group transcript analysis will involve the following three steps. First, 2 coders will independently code the first two focus groups by categorizing similar statements into the three COM-B categories and further into the 14 TDF domains. Second, the 2 independent coders will use an inductive coding approach to generate subcategories of specific beliefs of the different groups of participants within the initial coding scheme of the 14 TDF domains. Squires et al [50] define a specific belief as a group of similar responses that suggest the belief may influence the target behavior. The coders will compare their results and examine discrepancies. Discussion will be used to achieve consensus and finalize a coding scheme. All subsequent coding will be guided by the coding scheme in an effort to reduce subjective bias [51]. The 2 coders will independently code all remaining transcripts and meet after every two focus groups to review their coding and seek consensus. Third, the coded data will be further inductively examined to identify relevant theoretical domains to our target behavior [43]. The research

team will examine trends, patterns, frequencies, and relationships of the words used by the participants to identify (1) any conflicting beliefs within a domain, (2) the frequency of specific beliefs across the data, and (3) the likely strength of the impact of a belief on the behavior (sexual health service utilization). All three criteria will be considered when examining the relevance of the TDF domains.

Policy Document Analysis

Document analysis is a systematic procedure for reviewing documents that involves skimming, reading, and interpreting the text. It is often combined with other qualitative research methods as a way to seek convergence and corroboration or identify inconsistencies and provide data on the context in which the health system operates [31]. We will contact the health clinic managers at University A and University B via email and request a copy of their STI, HIV, Pap, and pregnancy testing guidelines, as well as any general sexual health service policies. Policies will be compared with the current Public Health Agency of Canada screening guidelines [52] to identify differences and similarities between the documents and barriers identified in the focus groups [39].

Anticipated Outputs

Findings from this phase will be used in two ways. First, we will use the data to provide a detailed description of students', health care providers', and administrators' perceived barriers and facilitators to sexual health service use among university students. Second, we will use the findings in Phase 3 to develop a theory-based behavior change intervention to address the target behavior (sexual health service utilization).

Integration of Quantitative and Qualitative Data

We will integrate the quantitative and qualitative data from Phases 1 and 2 using a triangulation protocol to examine convergence, divergence, and discrepancies from the different data sources [53]. A triangulation protocol is a detailed approach to examine metathemes across findings from different data components that have already been analyzed individually [54]. First, we will create a convergence-coding matrix that will display findings from the quantitative and qualitative phases. Following this, we will evaluate the findings for convergence, divergence, and discrepancies. This approach focuses on explaining the interconnectedness of results between the quantitative and qualitative phases [55]. Overall, by integrating the qualitative and quantitative data, we will generate a clearer understanding of the barriers and enablers to university students' use and nonuse of sexual health services, which will inform the next phase of intervention design.

Phase 3: Designing a Theory-based Behavior Change Intervention (Qualitative Strand)

Using the data obtained from Phases 1 and 2, we will develop a theory- and evidence-based intervention that encompasses BCTs aimed at overcoming the identified barriers and enhancing the enablers to sexual health service use by university students. The intervention will be developed through a series of advisory committee meetings which will be guided by Stages 2 and 3 of the BCW. In each meeting, we will use the nominal group technique to generate ideas, identify potential problems, structure the decision-making process, and achieve consensus [56].

Step One

The research team will meet to review Phases 1 and 2 findings and identify intervention functions and content. The BCW outlines which types of intervention functions are likely to be effective in bringing about behavior change in each COM-B component and TDF domain [15]. Through discussion, the research team will apply the APEASE criteria (affordability, practicability, effectiveness and cost-effectiveness, acceptability, safety, and equity) to each intervention function to explore its appropriateness for the sexual health service context. The APEASE criteria [15] are used to guide decision making during intervention design. Once the intervention functions are identified, the research team will use the BCT taxonomy (BCTTv1) [57] to identify BCTs that would best serve the intervention function. The BCTTv1 uses a standardized language for describing the active ingredients in interventions [57]. Michie et al [15] developed a matrix that maps relevant BCTs to intervention functions and corresponding COM-B and TDF components. The research team will use the APEASE criteria to consider which BCTs would be feasible within the context of university sexual health service delivery and most useful for addressing the identified barriers and enablers to university students' use of sexual health services.

Step Two

We will form an advisory committee at each university consisting of 3-5 students and 3-5 health care providers and university administrators. Participants who provided consent to be followed up in the Phase Two focus groups will be contacted via email and invited to participate in the advisory committee. The objective of the meeting is to review the findings from Phases 1 and 2 and the results from the BCT mapping exercise (Step One) and further refine the intervention design. Through discussion, the advisory committee will identify potential modes of intervention delivery and apply the APEASE criteria to explore its feasibility. The advisory committee will also discuss optimal intervention content, provider, setting, recipient, intensity, duration, and fidelity.

Following the advisory committee meetings, we will collate the meeting results to produce a summary of the final intervention design that could be delivered in the university setting to improve students' use of sexual health services. A copy of the intervention design findings will be sent via email to the participants of each advisory committee.

Anticipated Outputs

Phase 3 will culminate with a co-designed [58], theory- and evidence-based behavior change intervention for improving sexual health service use among university students.

Results

Phases 1 and 2 are complete, and Phase 3 intervention design is ongoing. Results from each phase and the finalized intervention design will be reported in 2018.

Discussion

Principal Considerations

Increasing university students' use of sexual health services is important given the need to prevent their risk of STI transmission and associated negative health consequences. This study will follow a systematic, theory-based approach using a mixed methods research design to develop a behavior change intervention aimed at improving university students' use of sexual health services. The mixed methods approach will allow for an integration of both numerical findings and qualitative text from the perspective of university students, health care providers, and university administrators to enhance our understanding of sexual health service use among university undergraduate students. This study is guided by the BCW, which uses the COM-B model and TDF as theoretical approaches to understanding the target behavior in context and designing theory-based interventions. The BCW has been used extensively in health services research [59-61], including the design of sexual health related interventions for young adults [62,63]. Based on the success of these studies, we anticipate the proposed theory- and evidence-based intervention will be successful at improving university undergraduate students' use of sexual health services.

Limitations

All findings from this study will be interpreted with the following limitations in mind, among others that may arise. First, the two universities included in the Phase 1 secondary analysis had response rates of 31.2% and 23.8%. These response rates are lower than the primary researchers had anticipated, as previous Web-based survey research with Canadian university students had a mean response rate of 40.9%. Further, Web-based sexual health research with US college students yielded response rates that ranged from 24% to 55%. This can result in nonresponse bias that may impact generalizability of the study findings. Second, the Phase 1 data were collected in 2012, which may result in findings that are no longer relevant today. For example, with recent developments in health service technologies (eg, online booking, electronic notification of results, online provision of sexual health information), there may be differences in the accessibility and acceptability of sexual health services among university students. However, our Phase 2 focus groups with students, health care providers, and university administrators will provide an opportunity to follow up on the 2012 data and describe any differences in the accessibility and acceptability of sexual health services during this period of time. Last, a limitation of secondary analyses is that researchers must work with the available data, which may not have been collected to address the research question. The only measures of sexual health service use in the secondary dataset are STI testing, HIV testing, Pap testing, and pregnancy testing. The Phase 2 focus groups will allow for further exploration of a more comprehensive definition of sexual health services, including sexual health promotion initiatives.

Conclusion

Overall, the methods presented in this paper demonstrate a theoretically robust and evidence-based approach to design an intervention to improve university students' use of sexual health services. The BCW will be used to understand the behavior in greater detail, identify intervention options, content, and implementation strategies. Future pilot testing in university settings will be needed to evaluate the effectiveness of the proposed intervention.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Survey questions.

[PDF File (Adobe PDF File), 326KB - resprot_v6i11e217_app1.pdf]

Multimedia Appendix 2

Existing Peer-Review Report.

[PDF File (Adobe PDF File), 318KB - resprot_v6i11e217_app2.pdf]

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Abbreviations

BCT: behavior change techniques
BCTTv1: Behaviour Change Technique Taxonomy Version 1
BCW: Behaviour Change Wheel
TDF: Theoretical Domains Framework

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Protocol

Psychometric Evaluation of a Patient-Reported Symptom Index for Nonmuscle Invasive Bladder Cancer: Field Testing Protocol

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Abstract

Background: Nonmuscle invasive bladder cancer (NMIBC) is a chronic condition requiring intensive follow-up, repeated endoscopic examinations, tumor resections, and intravesical treatments that can occur every 3 months for life. In this clinical context, patient-reported outcomes (PROs) are a critical concern for patients and their managing clinicians. PROs have enormous potential to be integral to treatment assessment and recommendations for NMIBC; however, current PRO measures are inadequate for NMIBC because they lack key NMIBC-specific symptoms and side effects associated with contemporary treatments.

Objective: The overarching aim of this study was to develop and evaluate a patient-reported symptom index (SI) for individuals with NMIBC (the NMIBC-SI) that is acceptable to patients; reliable, valid, and responsive to differences between contemporary treatments for NMIBC; and fit for purpose as an endpoint in clinical trials.

Methods: The NMIBC-SI will be evaluated in 2 field tests across a total of 3 years. Field test 1 is a cross-sectional study design involving 225 adult NMIBC patients recruited while undergoing active treatment or those who completed final treatment within the past week. Data collected include patient demographics, clinical features of the tumor, risk category, treatment type, comorbidity, and PROs. Field test 2 is a prospective longitudinal study involving 225 newly diagnosed NMIBC-SI patients. Clinical data and patient-completed questionnaires will be collected at 4 time points during treatment: before tumor resection, 1 week after resection, end-of-induction intravesical therapy, and 1-year follow-up. Standard psychometric tests will be performed to assess the reliability, validity, responsiveness, and clinical utility of the NMIBC-SI.

Results: Participant recruitment to field test 1 commenced in February 2017. Recruitment for field test 2 is planned to commence in January 2018. Final results are expected to be published in 2019. The NMIBC-SI will be freely available for use via registration.

Conclusions: This study protocol contains detailed methods that will be used across multiple international sites. Phase 2 in the development of the NMIBC-SI will enable a comprehensive evaluation of its reliability, validity, and responsiveness to ensure that the NMIBC-SI is fit for purpose in clinical research and provides an evidence base for the ongoing improvement of future therapies for NMIBC.

Trial Registration: ClinicalTrials.gov NCT03091764; http://clinicaltrials.gov/ct2/showNCT03091764 (Archived by WebCite at http://www.webcitation.org/6umBhQeNX)

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KEYWORDS

quality of life; patient reported outcome measures; cancer; bladder cancer; surveys and questionnaires

Introduction

Nonmuscle Invasive Bladder Cancer Is a Chronic Health Problem

Bladder cancer is the 9th most common cancer diagnosed worldwide and the 13th most common cause of cancer death [1]. Internationally, 430,000 new cases of bladder cancer were diagnosed in 2012, with 165,000 recorded deaths [2]. In Australia alone, in 2014, an estimated 2730 people were diagnosed with bladder cancer [3], and there were 1040 recorded deaths from it [1,4]. Bladder cancer is 3 to 4 times more prevalent in males than in females, and incidence increases with age, with people older than 55 years accounting for 90% of new diagnoses [5]. Around 75% of bladder cancer diagnoses are not muscle invasive at first diagnosis [6]. Because 5-year survival in this group exceeds 80% [7], the prevalence of nonmuscle invasive bladder cancer (NMIBC) is 10 times its incidence, even though the overall rate of recurrence is approximately 60% to 70% and progression is 20% to 30% [8].

Nonmuscle invasive bladder cancer is a chronic disease. Its management depends on the risk of the bladder cancer recurring and progressing [6]: low-risk patients receive frequent cystoscopies, possible tumor resections, and single instillations of postoperative chemotherapy; intermediate-risk patients usually require intravesical therapy, which lasts between 6 weeks and 3 years; and high-risk patients require intravesical Bacillus Calmette–Guérin (BCG; immunotherapy), which starts with 6-week induction treatment and continues with maintenance for 1 to 3 years. The higher the risk, the more the requirement for intravesical therapy. Follow-up is mandatory, with repeated endoscopic examinations, radiological imaging, biopsies, and tumor resections as frequent as 3-monthly and life-long. This makes the cost per patient from diagnosis to death the highest of all cancers [9], contributing a major economic and resource burden on health care systems [9].

Guidelines for the management of NMIBC are based on evidence for the effectiveness of treatments in reducing risk of bladder cancer progression and recurrence. Evidence for reductions in health-related quality of life (HRQoL) and associated side effects with each treatment are not incorporated into the decision-making process because they have been poorly documented (see section below on Critical Gaps in Knowledge About HRQoL and Patient-Reported Outcomes [PROs] in NMIBC). This is despite the fact that these treatments can cause substantial side effects and local and systemic toxicity. For example, the commonly used BCG has proved effective in reducing recurrences in patients with high-grade tumors and carcinoma in situ, but it can cause moderate to severe local and systemic side effects, and only 16% are able to complete their full treatment schedule [10].

Why Patient-Reported Outcomes Are Important

A PRO is any report that comes directly from patients about how they feel in relation to their health condition and its therapy, without interpretation by others [11]. PROs can include symptoms, function, HRQoL, and perceptions of treatment. These patient reports are captured and quantified by patient-reported outcome measures (PROMs) in the form of questionnaires.

PROs are beneficial for improving patient-clinician communication, prioritizing patient-centered care, and improving service provision [12,13]. In contrast to life-threatening conditions where survival endpoints may dominate HRQoL considerations, PROs should be key considerations in chronic conditions [14]. For example, a treatment found to be effective in improving survival in a clinical trial may fail in the real world because of toxicity and reduced HRQoL, which could compromise compliance and subsequently its effectiveness [15]. Similarly, the inconvenience of repeated clinic visits for monitoring or treatment can compromise compliance [16]. The acceptance of PROM-based evidence by regulatory bodies is reflected in the US Food and Drug Administration's (FDA) approval of PROs to support product labeling claims [17].

Critical Gaps in Knowledge About HRQoL and PROs in NMIBC

The primary goal in managing NMIBC in patients is to completely remove the tumor and control the unpredictable risk of recurrence and progression to muscle invasion [18] with as little treatment burden and side effects as possible. We know from clinical experience that there are many possible adverse consequences and substantial reductions in HRQoL that differ between treatment options such as chemotherapy versus BCG, induction versus maintenance therapy, and impact of single instillation chemotherapy. However, these have not been well studied or reported, and the key data on PROs are lacking for NMIBC.

The most recent indexed comprehensive review of the literature investigating the impact of NMIBC on HRQoL is over 14 years old and is based on research published between 1966 and 2000 [19]. Our recent systematic review of PROMs in NMIBC (manuscript under review; Rutherford et al) found only 6 out of 19 papers that assessed PROs used a standardized measure. Other limitations of these studies include lack of comparison groups, poor adjustment for baseline physical and psychological functions, failure to distinguish between patients with varying degrees of risk and between treatments in the analysis, and small sample sizes. Consequently, key evidence on the impact of tumor resections, repeated cystoscopies, single chemotherapy instillations, multiple chemotherapy instillations, and BCG therapies on patients' HRQoL is lacking.

Our review did identify a NMIBC-specific PROM, the European Organisation for Research and Treatment of Cancer (EORTC)—EORTC QLQ-BLS24 questionnaire—developed in 1996. There is no publicly available information detailing its development, and it only recently underwent validation, 18 years after its development (now renamed the EORTC QLQ-NMIBC24) [20]. The validation study had some limitations: it was based on data from a single clinical trial, including only high- and intermediate-risk patients with little information about their treatments; the original content was not reviewed against contemporary treatments (which differ considerably from those in use before 1996 when the original content was developed); modifications to the scale structure were informed by clinical evidence only (ie, no patient perspective); and there is lack of assessment of test-retest reliability and clinical validity (eg, whether the module distinguishes between different risk groups for NMIBC) [20]. The question remains whether the EORTC QLQ-NMIBC24 adequately captures the impact of important symptoms and side effects associated with contemporary treatment for NMIBC.

Therefore, a patient-reported NMIBC-specific symptom index (NMIBC-SI), including possible symptoms and side effects of contemporary treatments for NMIBC, is needed to enable accurate, robust, and clinically relevant assessment of differences in PROs among contemporary treatments and to provide an evidence base for the ongoing improvement of future therapies for NMIBC. Such a measure has been developed based on existing literature and interviews with patients and clinicians [21] and pretested for face validity, comprehensiveness, comprehensibility, and clinical utility through interviews with key stakeholders (patients, urologists, and specialist nurses).

Aims and Objectives

The overarching aim of this study was to develop and evaluate the NMIBC-SI for reliability, validity, and responsiveness to ensure that it is fit for purpose in clinical research.

Psychometric Aims

- To evaluate the feasibility and acceptability of the NMIBC-SI; produce a shorter version, if appropriate, by selecting items that perform best against robust psychometric criteria; examine the legitimacy of summing items into scales; identify legitimate scales and subscales; and test scaling assumptions and scale performance in a large-scale Australian sample (field test 1).
- To psychometrically evaluate the measurement properties of the final version SI, testing for reliability, clinical validity (sensitivity to differences between patient groups and responsiveness to clinically important change), and interpretability of the final version NMIBC-SI in a new large-scale international sample (field test 2).
- To conduct a head-to-head comparison of the new NMIBC-SI with the EORTC bladder cancer module, QLQ-NMIBC24.

Clinical Aims (Field Test 2)

- To assess and compare key PROs across the full range of contemporary treatments for NMIBC and over-the-disease trajectory, including acute treatment and 1-year survivorship.
- To compare PROs between patients with low-, intermediate-, and high-risk NMIBC.

Methods

Overview of Project Research Design

This multicenter study was designed to evaluate the psychometric properties of an NMIBC-SI for patients treated for NMIBC. Guidance for developing and validating health outcome measures has been followed to ensure high quality and standardization for the development of the NMIBC-SI [11,22,23]. The guidance recommends that collaboration and expert discussion are sought and utilized through all stages of development, and it proposes distinct phases for the development and evaluation of PROMs. The research design includes 2 phases: (1) development of NMIBC-SI in 2 parts, conceptual framework to generate items and pretesting; and (2) evaluation of NMIBC-SI in 2 parts, a preliminary field test 1 for item reduction and a final field test 2 for psychometric properties (Figure 1). Phase 1 has been conducted, and results are summarized below.

In preliminary research and phase 1 development, a conceptual framework was developed by tapping into 3 sources: (1) a systemic review and narrative analysis of the HRQoL and PRO literature, identifying several local and systematic side effects associated with contemporary treatments for NMIBC (eg, urinary problems, discomfort, and malaise); (2) in-depth qualitative interviews with a sample of NMIBC patients that explored patients' experience of receiving treatment; and (3) in-depth qualitative interviews with treating clinicians (specialist nurses and urologists) that explored important issues from their perspective. This phase was important to ensure that high content validity was achieved and demonstrated [24]. An exhaustive list of clinically relevant issues (items) was generated from the conceptual framework and patient verbatims [21].

In phase 1 pretesting, further qualitative interviews explored the generated list of issues with patients and clinicians for clarity and overlap and the appropriateness of the NMIBC-SI's time frame, question stem, and response options. On the basis of information obtained from the interviews, the provisional NMIBC-SI was revised to produce a preliminary version ready for field testing.

The evaluation of the NMIBC-SI is phase 2 of this project. It will be undertaken in 2 parts: preliminary field test 1 (item reduction) and final field test 2 (psychometric properties). The preliminary field test will identify any items with poor psychometric performance for possible elimination. The final field test will be undertaken to evaluate the item-reduced version of the NMIBC-SI for reliability, validity, and responsiveness. Gold standard psychometric methods will be used [11,22,23].

Phase 2: Field Test 1

The psychometric properties of the NMIBC-SI will be evaluated in 2 field tests, including a preliminary field test (item reduction) to identify items with poor psychometric properties for possible elimination and to identify subscales, and a final field test

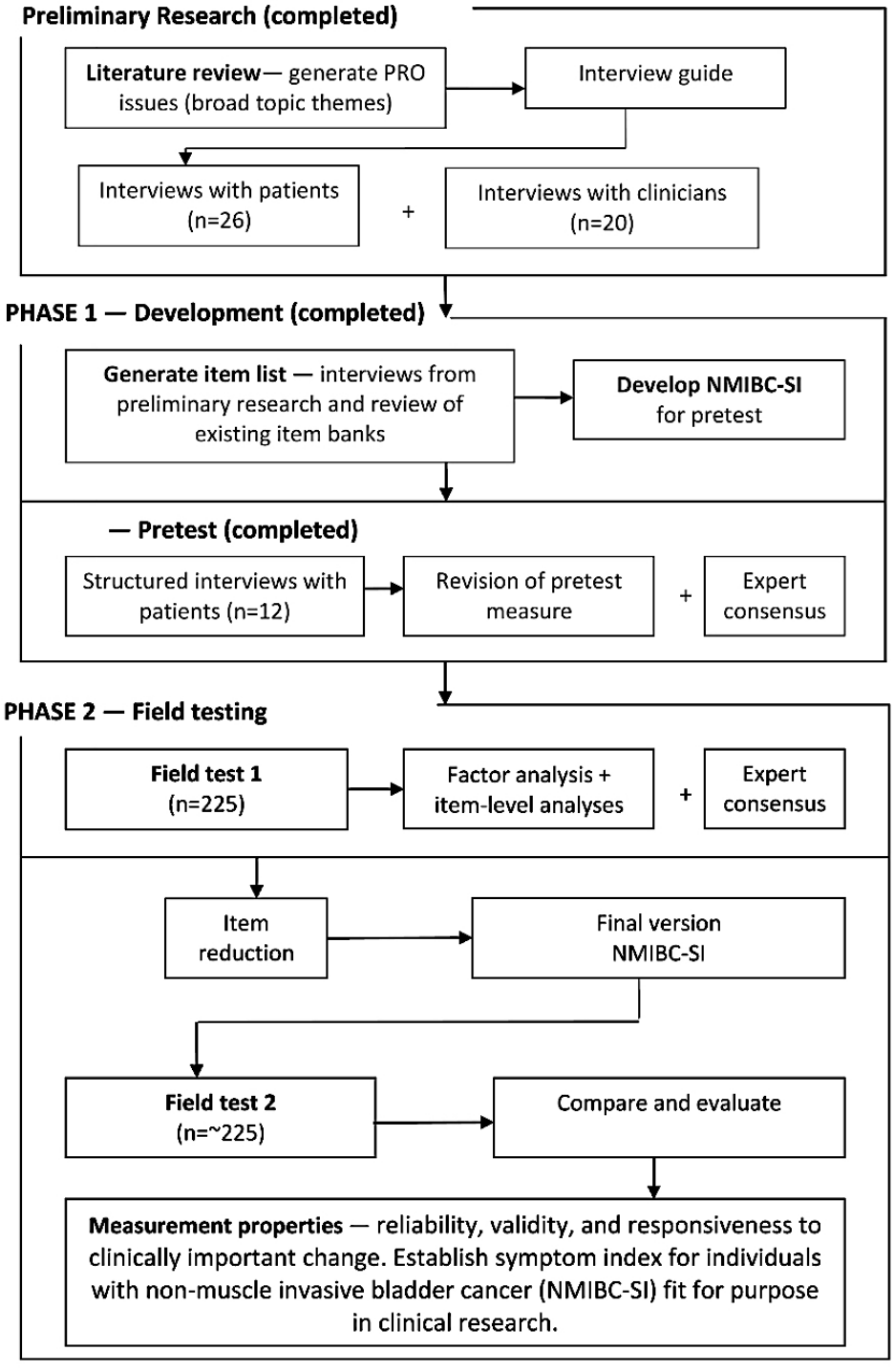
(psychometric evaluation) to evaluate the reliability and validity of the item-reduced version of the NMIBC-SI. The overall strategy and methods for the psychometric evaluation are based on the methods used to develop and validate PROMs in several other areas of medicine and surgery [24-26].

Design for Preliminary Field Test 1 (Item Reduction)

The purpose of the preliminary field test 1 is to produce a short (item-reduced) version of the NMIBC-SI and to undertake an initial psychometric evaluation of the item-reduced questionnaire. This will be done using a cross-sectional study design.

An item reduction strategy developed for evaluation of PROMs in other medical areas [25-27] will be used to: (1) identify items on the provisional version of the NMIBC-SI with poor psychometric properties for possible elimination; (2) conduct a preliminary evaluation of NMIBC-SI subscales; and (3) undertake a preliminary evaluation of the acceptability, reliability, and validity of the item-reduced NMIBC-SI.

Figure 1. Development and evaluation of the symptom index for individuals with nonmuscle invasive bladder cancer.



Results of the item reduction analyses will be used to develop a shorter version of NMIBC-SI for final psychometric field testing.

Eligibility

Inclusion Criteria

Adult patients (aged ≥18 years) from participating centers diagnosed with NMIBC, who are able to read and understand English and give their written informed consent will be included in the study. Patients will be recruited while undergoing active treatment (ie, 1 week after tumor resection or intravesical therapy) or when they have completed final treatment for NMIBC within the past week.

Exclusion Criteria

Patients will be excluded from the study if any of the following criteria apply:

- They are unconscious or confused.
- They have cognitive impairment.
- They are unable to speak, read, and/or write in English.
- They are diagnosed with muscle invasive disease.
- They are unable to provide informed consent.

Sample Size

Approximately 225 NMIBC patients will be required, purposively sampled to ensure representation of patients across the 3 NMIBC risk categories (Textbox 1) [6]. This sample size is based on recommendations for psychometric analyses of new summated scales; 5 to 10 subjects per item are needed to reduce the chance effect of sampling [28,29]. Following this recommendation, a 30-item NMIBC-SI would require a sample between 150 and 300 patients.

Recruitment and Consent Procedures

Patients from participating centers who meet the eligibility criteria will be informed about and invited to take part in the study either in person or via an invitation letter. Consecutive patients will be identified and approached to participate by either the named site investigator or the named site nurse. Accrual will be reviewed to ensure that there is balanced representation of patients in all NMIBC categories. A record of those identified as eligible, approached to participate, refusals, consenting patients, and questionnaire returns will be kept for progress monitoring and final reporting purposes (see Data Collection/Assessment section below).

A verbal explanation of the study and a patient information sheet will be provided for patients to consider. These will include detailed information about the rationale, design, and personal implications of the study. Following information provision, patients will have as much time as they need to consider participation. The right of the patient to refuse consent without giving reasons will be respected.

Assenting patients will then be invited to provide informed, written consent on the consent form at the end of the patient information sheet to collect baseline assessment data and to complete the questionnaire. The patient will remain free to withdraw from the study at any time without giving reasons and without prejudicing any further treatment. The original consent form will be filed within the investigator site file or at a designated secure location.

Registration

Following informed consent and confirmation of eligibility, participants will be provided with a study ID number and registered to the study.

Screening

The participating site staff will complete a log of all patients screened for eligibility. Screening logs will be returned to the University of Sydney.

Using the study ID number as an identifier, information will be collected for all eligible patients, including the age, gender, risk category, and treatment type.

For those who decline to participate in the study, reasons will be recorded.

Textbox 1. Nonmuscle invasive bladder cancer (NMIBC) patient risk groups.

High-risk tumors

Any of the following:

- T1 tumor
- G3 (high grade, which is a mixture of some G2 and G3) tumor
- Carcinoma in situ (CIS)
- Multiple and recurrent and large (>3 cm) Ta G1G2 tumors (all conditions must be presented at this point); low grade is a mixture of G1 and G2

Intermediate-risk tumors

- All tumors not defined in the adjacent categories (between the category of low- and high risk)

Low-risk tumors

- Primary, solitary, Ta, G1 (PUNLMP, low grade is a mixture of G1 and G2), <3 cm, no CIS

Data Collection/Assessment

Study data will be recorded by participating site staff on case report forms and by participants on questionnaire booklets either on paper or electronically. The study data are collected and managed using REDCap electronic data capture tools hosted at the University of Sydney [30].

Assessments will be undertaken as follows:

- Registration and baseline data
- Patient questionnaire booklet

Registration and clinical data will be completed by the clinician or specialist nurse at participating centers. Hard-copy questionnaires will be collected by the clinician or specialist nurse or posted by the patient back to the site. Study ID number coded data will be sent to the University of Sydney for central data management. Individually identifiable data and master lists linking study ID numbers to individual identity will be retained by the participating sites.

Registration and Clinical Data

Patients who meet the inclusion criteria and provide informed consent will be registered to this study. Registration and clinical information will be recorded by participating site staff including the following:

- Patient study ID number
- Age
- Gender
- Country of birth
- Marital status
- Living arrangements
- Education
- Risk category (clinical definitive category from medical records)
- Tumor grade
- Tumor stage
- Treatment type (information about which treatment interventions the patient is currently receiving)
- Comorbidity (Charlson Comorbidity Index [31] and history of prostate cancer)
- Name of site staff member completing clinical data
- Confirmation of eligibility

Questionnaire Booklet

Participants will self-complete the questionnaire booklet containing the NMIBC-SI, which will be provided to them by the clinician or specialist nurse at participating centers in hard copy or by link to the Web-based version. It is anticipated that completion of the questionnaire may take up to 20 min. Completed hardcopy questionnaires will be entered into REDCap by participating site staff directly or returned to the University of Sydney for data entry.

Mode of Questionnaire Administration

Participants will be given a hard copy of the questionnaire or provided with a link to the Web-based questionnaire, depending on their preference.

Analyses and Statistical Considerations

To determine whether the NMIBC-SI fulfills fundamental prerequisites for rigorous measurement as defined by established psychometric criteria [32] and the US FDA guidance [11], standard psychometric tests for acceptability, data quality, internal reliability, and factor analysis construct validity will be performed. Table 1, adapted from Gorecki, 2013 [33], presents full details of the tests and criteria used in the psychometric evaluation.

The purpose of the item reduction analysis is to produce a psychometrically robust version of the NMIBC-SI. Standard psychometric tests and criteria, as described in Table 1, will be performed to identify and retain items with strong psychometric properties and eliminate items with poor psychometric properties to produce a shorter, item-reduced version of the NMIBC-SI. These analyses will also evaluate the hypothesized subscales of the NMIBC-SI.

Missing data will not be imputed. The frequency of missing data will be determined, and items with a response rate of <80.0% (180/225) will be investigated.

Phase 2: Field Test 2—Evaluation of Reliability and Clinical Validity

Design for Field Test 2

The purpose of the final field test 2 is to assess the reliability and clinical validity (sensitivity to differences between patient groups and responsiveness to clinically important change) and interpretability of the final version NMIBC-SI in a new large-scale international sample. This phase will be conducted using a prospective longitudinal study design. The outcome will be a patient-reported NMIBC-SI that is reliable and clinically valid, with NMIBC-specific content that complements the more generic HRQoL content of the EORTC QLQ-C30.

Eligibility

Adult patients (aged ≥18 years) from participating centers diagnosed with NMIBC, after imaging or flexible cystoscopy but before endoscopic resection, who are able to read and understand English and give their written informed consent will be included in the study.

Sample Size

Approximately 225 patients newly diagnosed with NMIBC will be required to provide sufficient subjects for statistical assessment of test-retest reliability [34,35] and clinical validity in terms of both sensitivity to differences between patient groups [36] and responsiveness to clinically important change [37]. See section on Sample Size for Field Test 1 for sample size justification.

Table 1. Psychometric tests and criteria.

Property	Definition/test	Criteria for acceptability
1. Item analysis	Identify items for possible elimination due to weak psychometric performance; assessed on the basis of (1) exploratory factor analysis with principal axis factoring and (2) item- and scale-level analyses	Exploratory factor analysis: items with a factor-loading coefficient ≥0.4 will be retained in each subscale. Applied to all items: (1) missing data <5%; (2) maximum endorsement frequencies <80% (ie, the proportion of respondents who endorse each response category), including floor or ceiling effects <80% (ie, response categories with high endorsement rates at the bottom and top ends of the scale, respectively); (3) evidence of item responsiveness as assessed by significant improvement between baseline and test of cure assessments (field test 2 only)
2. Acceptability	The quality of data; assessed by completeness of data and score distributions	Missing data for summary scores <20%; normal distribution of endorsement frequencies across response categories (ie, absence of skew, endorsement rates between 0.20 and 0.80); and floor or ceiling effects for summary scores <10%
3. Reliability		
3.1 Internal consistency	The extent to which items comprising a scale measure the same construct (eg, homogeneity of the scale); assessed by Cronbach alpha and item-total correlations	Cronbach alpha for summary scores ≥.70 and item-total correlations ≥.30
3.2 Test-retest reliability (field test 2 only)	The stability of a measuring instrument; assessed by administering the instrument to respondents on two different occasions and examining the correlation between test and retest scores	Test-retest reliability and intraclass correlations for summary scores ≥.70
4. Validity		
4.1 Content validity	The extent to which the content of a scale is representative of the conceptual domain it is intended to cover; assessed qualitatively during the questionnaire development stage through pretesting with patients, expert opinion, and literature review	Qualitative evidence from patients, expert opinion, and literature review that items in the scale are representative of the construct being measured
4.2 Construct validity		
Within-scale analyses	Evidence that a single entity (construct) is being measured and that items can be combined to form a summary score	Confirmatory factor analysis: (1) items with a factor-loading coefficient ≥0.4 and (2) moderate to high correlations between scale scores
Analyses against external criteria		
Convergent validity	Evidence that the scale is correlated with other measures of the same or similar constructs; assessed on the basis of correlations between the measure and other similar measures	Correlations are expected to vary according to the degree of similarity between the constructs that are being measured by each instrument. Specific hypotheses are formulated and predictions tested on the basis of correlations
Discriminant validity	Evidence that the scale is not correlated with measures of different constructs; assessed on the basis of correlations with measures of different constructs	Low correlations between the instrument and measures of different constructs
Known groups differences	The ability of a scale to differentiate known groups; assessed by comparing scores for subgroups that are expected to differ on the construct being measured	Significant differences between known groups or difference of expected magnitude
5. Responsiveness	The ability of a scale to detect clinically significant change following treatment of known efficacy; assessed by examining within-person change scores before and after treatment and calculating an effect size statistic (mean change score divided by standard deviation of pretreatment scores)	Moderate to large effect sizes (small 0.2, moderate 0.5, and large 0.8 or higher)

Table 2. Patient-reported outcome assessment schedule.

Risk group	Assessed within 3 months before tumor resection	Assessed within 4 to 10 days after the tumor resection	Assessed within 1 month after the end of induction intravesical therapy[a]	Assessed within 1 month before the 1-year cystoscopy (or at early cessation due to adverse events[b])
High	T1	T2	T3	T4
Intermediate	T1	T2	T3	T4
Low	T1	T2	T3[c]	T4
~n	225	225	225	225

[a]A minimum of 25 participants from each risk group will be asked to complete an additional questionnaire pack 3 to 7 days after T3.

[b]Preferably before cystoscopy.

[c]For the low-risk group, T3 will be 8 weeks after resection.

Recruitment and Consent Procedures

Patients will be recruited at diagnosis, after imaging or flexible cystoscopy but before endoscopic resection. Eligible patients will be identified by the clinician investigators and their teams at participating centers, ensuring adequate representation of patients in the 3 risk groups (see Textbox 1) [6]. Patients who meet eligibility criteria will be approached in person and informed about and invited to take part in the study. Consent procedures are similar to field test 1, that is, using patient information sheet and consent form for field test 2.

Data Collection/Assessment

Registration and Baseline Data

Registration data will be collected as done for field test 1. Baseline questionnaires will be completed before endoscopic resection (Table 2).

Follow-Up Data Collection

Participants will complete follow-up questionnaire packs at scheduled follow-up time points (see Table 2). The clinician or specialist nurse at participating centers will be responsible for sending follow-up questionnaires, emails, and reminders to participants. Participants will either be posted a hard-copy questionnaire pack or emailed a link to their follow-up questionnaires, depending on their preference. Participants who complete the Web-based questionnaire pack will be given an option to provide their email address to receive automatic reminders from the REDCap system at follow-up time points. Participants will be advised that email addresses are stored within the REDCap system and used solely for the purpose of sending reminders. REDCap is a secure Web app that runs on the University of Sydney's servers, ensuring that data stay within the Sydney University data center. The provision of an email address for reminders is entirely voluntary, and participants will be free to change their mind at any point, after which any email address provided will be removed from the REDCap system.

PRO Assessment Time Points

Prospective assessment of newly diagnosed patients before and after treatment is required for the responsiveness analysis. It is expected that the NMIBC-SI will detect changes in symptoms due to specific treatments. As risk profile determines treatment schedule, the corresponding schedules of prospective assessments are indicated in Table 2. These time points will also provide PRO data to compare between treatment and risk groups and over time, addressing our clinical aims (see Aims and Objectives section).

In addition to the planned assessments (Table 2), a minimum of 25 participants sampled from each of the 3 risk groups will complete an additional NMIBC-SI 3 to 7 days after the T3 administration to evaluate test-retest reliability. The length of the test-retest interval must be short enough to ensure that clinical change in the NMIBC status is unlikely to occur but sufficiently long to ensure that respondents do not recall their responses from the first assessment. A short test-retest interval is necessary to ensure that stability per se is being evaluated, rather than clinical change during the test-retest interval, which will underestimate the NMIBC-SI's reliability.

Participants will be sent a hard copy or link to the questionnaires 2 weeks before their scheduled follow-up time point. Up to 2 email or telephone reminders to complete follow-up questionnaires will be made if questionnaires are not completed by the follow-up date. The clinician or specialist nurse at participating centers will be responsible for sending follow-up questionnaires, emails, and reminders to participants unless participants who complete the Web-based questionnaires have provided their email address to receive automatic reminders directly from REDCap. The assessment time windows are indicated in Table 2.

Mode of Questionnaire Administration

Participants will be given a hard copy of the questionnaire or provided with a link to the Web-based questionnaire depending on their preference.

Questionnaire Booklet

A questionnaire pack containing the NMIBC-SI, EORTC QLQ-C30, and the EORTC QLQ-NMIBC24 will be self-completed by all participants via hard copy or Web.

Participants will complete the item-reduced version of the NMIBC-SI, the QLQ-C30, and the QLQ-NMIBC24 measures to assess construct validity (convergent, discriminant, and known groups; see Table 2). The guiding principle in selecting the validating measures is to include measures that will allow a comparison of NMIBC-SI subscales with measures of similar

constructs (convergent validity) and with measures of different constructs (discriminant validity), and to compare NMIBC-SI scores in clinically defined known groups whose HRQoL would be expected to differ.

The QLQ-C30 [38] is a core questionnaire for evaluating the HRQoL of patients participating in cancer clinical trials. It is a 30-item questionnaire with 9 multi-item subscales and 6 single items. It incorporates 5 functional scales (physical, role, cognitive, emotional, and social functioning), 3 symptom scales (fatigue, pain, and nausea or vomiting), and a global health status or HRQoL scale. The single items assess dyspnea, appetite loss, sleep disturbance, constipation, diarrhea, and perceived financial impact of disease and treatment. Ratings for each item range from 1 (not at all) to 4 (very much). The QLQ-C30 is designed to be used across cancer populations and takes about 11 min to complete [38].

The QLQ-NMIBC24 [20] is a 24-item questionnaire for evaluating the HRQoL of patients with superficial (nonmuscle invasive) bladder cancer. The questionnaire is designed to supplement the QLQ-C30 and incorporates 6 multi-item scales and 5 single items. Ratings for each item range from 1 (not at all) to 4 (very much). The scales cover urinary symptoms, malaise, worries about the future, bloating and flatulence, sexual function, and male sexual problems. The single items assess intravesical treatment issues, sexual intimacy, sexual enjoyment, risk of contaminating partner, and female sexual problems.

All measures will be administered in the same order. It is anticipated that completion of questionnaire packs may take up to 20 min.

Analyses and Statistical Considerations

Analyses will evaluate the measurement properties of the final version of the NMIBC-SI, using psychometric tests described for field test 1 (Table 1). Additional tests for reliability (test-retest: correlations for summary scores ≥.70), clinical validity (in terms of sensitivity to groups known to differ clinically and responsiveness to clinically meaningful change over time [37]), and estimation of minimal important difference (interpretability) [39] will be undertaken. Evaluation of subscales will be determined by factor analysis and against external criteria (between-group validity: convergent, discriminant, and known group differences validity). To evaluate convergent and discriminant validity, we will compare NMIBC-SI scales with the scales within the EORTC QLQ-C30 and QLQ-NMIBC24 measures. NMIBC-SI scores for patients by risk and treatment groups will be compared to evaluate known group differences. Risk groups are defined as low, intermediate, and high (see Textbox 1) [6]. Treatment groups are defined as follows: (1) cystoscopy alone or TURBT, (2) course of intravesical chemotherapy, and (3) course of intravesical BCG. We hypothesize that low-risk patients will have lower levels of treatment-related problems at follow-up time points compared with high-risk patients, who have more intensive treatments. Factor analysis, together with the results of other item-level analyses described in Table 1, will be used to investigate hypothesized subscales.

Analyses of the clinical aims will include: (1) evaluation of PRO changes over time, from diagnosis to peak treatment and at 1 year; (2) comparison of PROs between the 3 risk groups at each time point; and (3) head-to-head comparison of the relative discriminatory ability of the NMIBC-SI and the EORTC QLQ-NMIBC24. The pretumor resection assessment (T1) will be at diagnosis and is considered our baseline assessment. Patients are not expected to have any treatment-related problems at this point. The subsequent 3 time points (Table 2) are intended to capture short-term, intermediate, and long-term levels of problems, and each will be compared with baseline (T1).

Results

Development of NMIBC-SI

A patient-reported NMIBC-SI, including all symptoms and side effects associated with contemporary treatments for NMIBC, has been developed based on a conceptual framework of PROs important to patients with NMIBC and their managing clinicians [21].

The conceptual framework was developed by utilizing 3 sources (see Figure 1): (1) a systematic review and narrative analysis of the PRO literature relevant to NMIBC identified several local and systemic side effects associated with contemporary treatments for NMIBC (eg, urinary problems, discomfort, and flu-like symptoms); (2) in-depth qualitative interviews with a sample of NMIBC patients explored patients' experience of receiving treatment; and (3) in-depth qualitative interviews with treating clinicians (specialist nurses and urologists) explored important issues from their perspective. These aspects were important to ensure that the new NMIBC-SI had high content validity [24]. An exhaustive list of clinically relevant issues (items) was generated from the conceptual framework and patient and clinician verbatims.

Pretesting of the NMIBC-SI

The draft version of the NMIBC-SI was pretested using structured interviews with key stakeholders (patients and clinicians), testing for face validity, relevance and comprehensiveness of content, comprehensibility, and clinical utility. Specifically, clarity and overlap of items and the appropriateness of the NMIBC-SI's time frame, question stem, and response options were explored. On the basis of information obtained from the interviews, the provisional NMIBC-SI was revised to produce a preliminary version ready for field testing.

The NMIBC-SI was designed to complement and be administered alongside the EORTC QLQ-C30 generic cancer questionnaire [38] (which includes core domains of functioning and HRQoL, fatigue and general pain but no NMIBC-specific symptoms).

Item Reduction of the NMIBC-SI: Field Test 1

The field testing phase is planned over 3 years. Recruitment for field test 1 commenced in February 2017 in 9 Australian centers. Recruitment for field test 2 is planned to commence in January 2018 in the same 9 Australian centers that participated in field test 1 plus an additional 10 international centers (2 in New Zealand, 4 in the United States, 2 in Canada, and 2 in Europe)

following the universal approach to using the same language in different countries [40]. These 19 centers include both public and private hospitals and treatment clinics. Final results are expected to be published in 2019. The NMIBC-SI will be freely available for use via registration.

Discussion

This study protocol contains detailed methods to be used across 19 international sites, including both public and private hospitals and treatment clinics that treat patients diagnosed with NMIBC. Field test 1 is a cross-sectional study and includes a sample of patients with NMIBC on active treatment. Field test 2 is a longitudinal study and includes a sample of newly diagnosed patients to enable assessment of possible treatment effects as well as responsiveness of the NMIBC-SI. No patients recruited for field test 1 will be included in field test 2. Phase 2 in the development of the NMIBC-SI will enable a comprehensive evaluation of its reliability, validity, and responsiveness to ensure that it is fit for purpose in clinical research and provides an evidence base for the ongoing improvement of future therapies for NMIBC.

Following evaluation, our NMIBC-SI will be suitable for use with English-speaking patients, diagnosed and treated for NMIBC in Australia, New Zealand, the United States, Canada, and the United Kingdom. Cross-cultural and language translations are planned following development and evaluation of the English version.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer Review Report.

[PDF File (Adobe PDF File), 482KB - resprot_v6i11e216_app1.pdf]

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Abbreviations

BCG: Bacillus Calmette–Guérin
EORTC: European Organisation for Research and Treatment of Cancer
HRQoL: health-related quality of life
NMIBC: nonmuscle invasive bladder cancer
NMIBC-SI: symptom index for individuals with NMIBC or NMIBC-specific symptom index
PRO: patient-reported outcome
PROM: patient-reported outcome measures
SI: symptom index

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Original Paper

An eHealth Intervention to Promote Physical Activity and Social Network of Single, Chronically Impaired Older Adults: Adaptation of an Existing Intervention Using Intervention Mapping

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Abstract

Background: Especially for single older adults with chronic diseases, physical inactivity and a poor social network are regarded as serious threats to their health and independence. The Active Plus intervention is an automated computer-tailored eHealth intervention that has been proven effective to promote physical activity (PA) in the general population of adults older than 50 years.

Objective: The aim of this study was to report on the methods and results of the systematic adaptation of Active Plus to the wishes and needs of the subgroup of single people older than 65 years who have one or more chronic diseases, as this specific target population may encounter specific challenges regarding PA and social network.

Methods: The Intervention Mapping (IM) protocol was used to systematically adapt the existing intervention to optimally suit this specific target population. A literature study was performed, and quantitative as well as qualitative data were derived from health care professionals (by questionnaires, n=10) and the target population (by focus group interviews, n=14), which were then systematically integrated into the adapted intervention.

Results: As the health problems and the targeted behavior are largely the same in the original and adapted intervention, the outcome of the needs assessment was that the performance objectives remained the same. As found in the literature study and in data derived from health professionals and focus groups, the relative importance and operationalization of the relevant psychosocial determinants related to these objectives are different from the original intervention, resulting in a refinement of the change objectives to optimally fit the specific target population. This refinement also resulted in changes in the practical applications, program components, intervention materials, and the evaluation and implementation strategy for the subgroup of single, chronically impaired older adults.

Conclusions: This study demonstrates that the adaptation of an existing intervention is an intensive process in which adopting the IM protocol is an invaluable tool. The study provides a broad insight in adapting interventions aimed at single older adults with a chronic disease. It is concluded that even when the new target population is a sizable segment of the original target population, the adapted intervention still needs considerable changes to optimally fit the needs and situational differences of the narrower target population.

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KEYWORDS

exercise; older adults; single; chronic disease; eHealth; social network; Intervention Mapping

Introduction

The international guideline for physical activity (PA) recommends that one should be physically active with moderate to vigorous intensity for at least 5 days a week with a minimum of 30 min a day [1]. Regular PA reduces the risks of multiple health problems, such as chronic diseases. For individuals with preexisting health problems, being sufficiently physically active may be accompanied with more barriers but can still result in an improved health and in a reduced risk of developing comorbidities [1,2]. Especially for older adults (people older than 65 years), the health benefits of sufficient PA are relevant as PA also prevents cognitive decline [3] and improves balance, thus decreasing the risk of fall-related injuries [4,5]. Moreover, PA is beneficial for mental health, as it reduces stress and depression and has positive outcomes on general well-being, such as an increased social connectedness [2,6].

Despite these benefits, PA decreases with age. In the Western world, 19% of the younger adults do not meet the recommended level of PA, compared with 55% of the older adults [7]. In certain subpopulations, a lack of sufficient PA is even more prevalent. In general, people with a chronic disease are less physically active than healthy people of their age group. In the Netherlands, 42% to 71% of the chronically ill people who are older than 55 years meet the recommended level of PA, whereas 84% of the healthy people in this age group meet the recommended level [8]. Western society in general shows a similar image [9]. Chronic diseases often come with impairments to PA [10,11]. The lack of PA causes the physical condition to increasingly deteriorate and daily activities to cost more energy, ultimately resulting in a downward spiral [12-14]. Another significant feature of older adults, who are less physically active, is not having a life partner [6,15]. In addition to their lower level of PA, older people who do not have a life partner are at risk for becoming socially isolated, which often results in feelings of loneliness. Loneliness is considered to be a significant risk factor for negatively affecting the physical and mental health of single older adults [16,17]. Promotion of PA, preferably done with others, in single older adults with a chronic disease is not only important from a physical and mental health perspective but also to stimulate participation in social life and society [18-20]. Several studies have shown reciprocal relations between PA and quality of life [21-23]. No international data are available on what part of the population is single, as well as older than 65 years and has a chronic disease. Available data in the Netherlands suggest that this group is a large proportion of the total population: in the age group of 65 to 84 years, the percentage of people with a chronic disease (with or without physical impairments) ranges between 78% and 93%; of the people older than 65 years, 39% are single [24]. It is assumed that the distribution of these characteristics is not very divergent from other Western countries. Stimulating PA is, therefore, of major relevance in this group, not only because of the benefits PA has for this group but also because of its proportion.

Previously, the computer-tailored Active Plus intervention (hereafter named Active Plus50) was developed to increase PA among people older than 50 years [25,26]. The intervention is available with a printed or a Web-based delivery mode. Active Plus50 provides tailored advice 3 times: after the first questionnaire at baseline, after 2 months, and after the second questionnaire (3 months after baseline). Although Active Plus50 was effective in stimulating PA in its target population (ie, people older than 50 years) [27,28], as well as in its subpopulation of single older adults (older than 65 years) with a chronic disease that impaired them in their PA behavior, this particular subpopulation often felt the intervention was not sufficiently adapted to their specific needs and expectations with regard to PA [25]. Furthermore, this subpopulation also indicated that even when they are stimulated to be more physically active, they often lack knowledge about their possibilities to be physically active in their own surroundings, given their impairment. Moreover, results of the qualitative evaluation showed that this subpopulation would like more opportunities for personal and social contacts in the program. With these findings, it became apparent that the intervention could remain as it was for the general target population of people older than 50 years, but that it needed adaptation for the specific subpopulation of single older adults with a chronic impairment in PA. This study describes how the proven effective, evidence-based Active Plus50 intervention, aimed at raising and maintaining the amount of PA for people older than 50 years, was systematically adapted to better fit the needs and characteristics of older adults who are single and have one or multiple chronic physical impairments. To increase the chance that the adapted intervention (hereafter named Active Plus65) will remain effective, the Intervention Mapping (IM) protocol was used [29]. This study adds to the current knowledge on adaptation processes for existing interventions—a broad insight in adapting existing interventions was established by combining theory, previous research, and input from the target population and health care professionals.

Methods

Intervention Mapping Steps for Modifying an Intervention

When an evidence-based intervention is modified, it may lose its effectiveness. Therefore, it is essential to carefully consider which components of the intervention are crucial to its effectiveness and, therefore, cannot be modified, and which elements can be modified without changing the effectiveness substantially. To develop new interventions and modify existing ones, several models and protocols have been developed. A well-studied and often used protocol is the IM protocol [29]. Compared with other models and protocols, IM enables the developer of the intervention to take all the necessary steps to develop or modify an intervention. The IM protocol for modifying an existing intervention differs from the IM protocol for developing new interventions. There are also 6 consecutive steps, but the content of the steps is different from that of the development model. The basic content of these steps, and how they are executed specifically in this study, are stated below.

Step 1: Needs Assessment and Determination of Fit With the Problem

In this step, a logic model for the problem is constructed, that is, the problems for the target group regarding health, quality

of life, related behavior, and environment are assessed. Step 1 should result in a description of discrepancies between the problems as they are seen in the existing intervention and in the adapted intervention for the new (or in this study, a specific part of the original) high-risk target population. A literature study was conducted to achieve this goal in adapting Active Plus50. Furthermore, inputs from process evaluations from previous studies on Active Plus50 were used.

Step 2: Defining a Logic Model of Change and Matrices

This step aims to determine whether performance objectives, behavioral determinants, and change objectives of the original intervention need to be modified to better fit the new target population. The original performance objectives resulting from the development of Active Plus50 [26] are shown in Table 1.

Performance objectives consist of behavior that the target population has to perform to reach the program objective. The performance objectives can be regarded as specifications of the program objective, that is, the ultimate goal of the intervention; in Active Plus50, this is enhancing and maintaining the amount of PA.

Active Plus50 focusses on influencing behavioral determinants as well as the perception of environmental determinants [26]. These are shown in Textbox 1.

Crossing the performance objectives with determinants results in change objectives. Change objectives are the intervention objectives that are specific for this intervention. The result of step 2 according to IM should be a description of the change objectives that have to be added to, altered, or removed from the original program. To optimize the change objectives to the target population, focus group interviews with the target population as well as a survey among health care professionals were conducted.

One of the theoretical frameworks that was applied in the original intervention [26] is the Theory of Planned Behavior (TPB) [30]. TPB stipulates that behavior is the result of a person's intention, which is influenced by the following three psychological factors: attitude, subjective norm, and perceived behavioral control. Many proven effective interventions to stimulate PA were based on TPB [31]. The I-Change Model [32] is an adaptation of the TPB model. Compared with TPB, the I-Change model considers more social influences than just subjective norm, such as social support. As Active Plus65 also has a focus on the social network of participants, the I-Change model with its broader definition of social influence has been applied in this adaptation of Active Plus instead of TPB. Perceived behavioral control is called self-efficacy in I-Change but to a large degree remains the same construct. To test the opinions of the target group, the focus group questions were based on the I-Change model. Two focus group interviews with participants were conducted in January 2016. Each focus group session lasted 2 hours, and 3 researchers acted as mediators (2 PhDs in Health Psychology and 1 MSc student). The participants were recruited via local organizations for older adults, patient support groups for people with a chronic disease, a gymnastics club for older adults, and by distributing flyers in local supermarkets. A semistructured focus group interview guide was made, which contained a list of topics and open-ended questions to be discussed, based on previous evaluations of the Active Plus intervention [25], literature on behavior change strategies [32,33], and literature on the diffusion of innovations theory [34]. The focus group started with a broad opening question per topic (eg, perceived barriers) and a priori defined follow-up questions. Examples of questions that were presented to the focus group participants are as follows: "what barriers does a person as yourself with a chronic disease face, that a healthy person does not face, when being physically active?" or "what is your opinion on exercising together with other people?" Discussions were stimulated with the posing of new open questions until no new input was attained. Of both focus group interviews, audio recordings were made and transcribed verbatim. The transcripts were thematically analyzed by the first and second author, according to guidelines for content analysis of focus groups [35]. These guidelines entail (1) getting familiarized with the data, (2) generating initial codes, (3) searching for themes, (4) reviewing themes, and (5) defining and naming themes. Examples of themes were as follows: *barriers for PA when being single* and *motivation to participate in the intervention*. The findings of the first and second researcher were independently reviewed by the third researcher. After reaching agreement on the analyses, conclusions were drawn.

Table 1. Performance objectives (PO) of Active Plus50.

Number	Description
PO[a] 1	Target population monitors their PA[b] level.
PO 2	Target population indicates reasons to be physically active.
PO 3	Target population identifies solutions to remove barriers to being physically active.
PO 4	Target population decides to become more physically active.
PO 5	Target population makes specific plans to become more physically active.
PO 6	Target population increases their PA.
PO 7	Target population makes specific plans to cope with difficult situations occurring while being physically active.
PO 8	Target population maintains their PA by enhancing their routine and preventing relapses.

[a]PO: performance objectives.

[b]PA: physical activity.

Textbox 1. Determinants of physical activity (PA), operationalized by the performance objectives, among people older than 50 years.

- Awareness
- Knowledge
- Commitment
- Attitude
- Self-efficacy
- Intrinsic motivation
- Intention
- Action planning
- Coping planning
- Relapse prevention skills
- Habit
- Social influence
- Perceived social environment or having an exercise partner
- Perceived physical environment

Furthermore, to optimize the match of the change objectives to the new high-risk target population, a survey among physiotherapists was conducted. It was conducted in the same municipality where the evaluation of use, appreciation, and effectiveness of the altered intervention was to be studied. By incorporating the opinion of physiotherapists, the knowledge and experience of health care experts concerning PA for older people with a chronic disease was added. Health care professionals have practical experience with the target population and may provide additional, more qualitative information than a literature study alone. This provided insights into which chronic disease needs special attention regarding PA, what type of PA is not recommendable, and how to communicate the content of advice messages. The survey was performed using a questionnaire that was sent by email. The questionnaire was sent to all 35 physiotherapists who were registered in the municipality of Heerlen, the Netherlands. The first question was to rate the necessity of a tailored PA advice for each of the most prevalent chronic diseases in the Netherlands, such as arthritis, cardiovascular pathology, lung disease, rheumatism, diabetes, cerebrovascular incidents, severe backaches, osteoporosis, and overweight [36]. The importance was rated on a scale of 1 (*not important*) to 10 (*very important*). Per the chronic disease, the physiotherapists were asked to state the three most recommendable types of PA, and the three types of PA that are not advisable.

Step 3: Selection of Theoretical Methods and Practical Applications

In this step, it is necessary to make sure that there are appropriate and sufficient methods for all the change objectives. For all the essential methods, it needs to be ascertained that they are properly addressed with appropriate practical applications. One of those essentials upon which Active Plus50 is based is computer tailoring. Computer tailoring is a method that assesses features, beliefs, behavior, etc, of the individual participant by using questionnaires upon which a computer program independently produces feedback. The computer program is based on if-then algorithms and deducts the appropriate advice messages from a message library. These messages are subsequently combined in a tailored advice letter. In computer tailoring, the feedback is optimally tailored to the personal characteristics of the participant. The advice messages that single older adults with a chronic disease receive, therefore, need adaptation. The effectiveness of computer tailoring in Active Plus50 has been demonstrated [27]. Apart from computer tailoring, various other theoretical methods and practical applications are used in Active Plus50. As they form the constructional base of the intervention, these have been maintained [37]. Examples of the applied theoretical methods and applications are shown in Table 2.

When the core of the change objectives remain the same, no new theoretical methods and practical applications need to be added in this step. The result of this step should be a description of the theoretical methods and practical applications that need to be added, that need to be deleted, or that must be retained.

Step 4: Producing Programs

In the fourth step, all the information gathered from step 1 to step 3 is combined. At this moment of the invention modification, it has been established that the program objectives and methods are appropriate. In step 4, the materials, time frame, and preferred delivery channels are analyzed. This should result in the modified intervention program.

Table 2. Examples of theoretical methods and practical strategies in Active Plus50.

Determinant	Theoretical method	Practical strategy	Intervention components	
			Print-delivered	Web-based
Motivation	Social modeling	Provide role model stories about intrinsic motives to be physically active.	Picture of similar individuals (same age group and gender) with quotes about their (intrinsic) motivation to be physically active	Short video of similar individuals (same age group and gender) who tell about their (intrinsic) motivation to be physically active
Awareness	Self-monitoring	Encourage monitoring of own behavior	Logbook scheme to write down their own behavior. An example was included in the advice. An empty form was attached to the advice.	Logbook scheme to write down their own behavior. An example was included in the advice. An empty form (PDF format) could be downloaded from the website.
Perceived social environment or having a sports partner	Linking members to networks of people	Provide opportunity to contact others	Post cards to invite someone to be physically active together, attached to the advice	E-cards on the website to invite someone to be physically active together
Action planning	Active learning	Invite to formulate action plans	Weekly scheme to write down plans to be physically active (when, what, where, and with whom). An example was included in the advice. An empty form was attached to the advice	Weekly scheme to write down plans to be physically active (when, what, where, and with whom). An example was included in the advice. An empty form (PDF format) could be downloaded from the website.

To achieve this goal, the existing program materials were discussed in the focus groups with the target population. Their opinions and suggestions regarding the intervention materials of Active Plus50 were identified. The first focus group was presented with the original program materials from Active Plus50; their remarks were used to adapt the program materials. The adapted materials were then presented to the second focus group, after which final adaptations were made. The materials that were presented in both focus groups were as follows: (1) the part of the questionnaire that focuses on physical impairments. As the intervention targets people with chronic diseases, it is important to get a good insight into which chronic diseases are present, and into the related impairments; (2) a bar graph showing the PA of the participant and the daily recommended PA of the Dutch population in the relevant age category. The target population, however, only consists of single people with a chronic disease, who have a lower level of PA than the general population. It was studied whether comparing the PA behavior of the new target population with the PA behavior of the general population within a bar graph was possibly perceived as unfair because chronic disease impairs PA; and (3) a modeling text. A method that is frequently used in Active Plus50 is modeling, for example, a video of a role model performing the targeted behavior. A parameter for the effectiveness of modeling is that the participant is able to identify himself with the role model. Therefore, we examined whether this identification still matched with the specific target population.

Step 5: Development of an Adaption and Implementation Plan

The main focus of step 5 is to plan the adoption and actual implementation of the intervention. One of the actions in this step was to ask the participants of the focus groups about their opinion on the recruitment materials of the Active Plus program. Discussed materials included a personalized letter in which people are invited to join the program and a flyer containing information about the program. The questions for the focus groups were based on the diffusion of innovations theory by Rogers [34].

According to this theory, there are several features of innovations that indicate decisively whether the innovation will actually be used. These features are relative advantage, trialability, observability, compatibility, and complexity. The relative advantage of the intervention, for example, was addressed by asking participants whether the invitation letter and flyer explained the benefits of Active Plus65 compared with existing PA programs clearly. One way in which trialability was addressed was by assessing whether the participants understood that they could participate in the program for free and could stop at any time. Whether observability was addressed properly was, among other questions, checked by asking whether the member of the focus groups expected that the results of the program would be visible among participants who had already joined the program. By asking whether there are elements in the letter or flyer that made the program sound too difficult, and that might deter them from joining the program, the perceived complexity was checked. One way in which compatibility was investigated was by asking whether the participants thought, based on the information they read in the implementation materials, that they could easily fit the program into their existing routines, and whether they disliked elements in the program.

Step 6: Development of Evaluation Design

In this final step, a plan was developed by which the evaluation for effectiveness and use of the altered intervention can be determined. Evaluation will progress into 2018 and contains, among other elements, conducting a longitudinal study on the level of implementation. The main outcome that will be assessed is the difference in the amount of PA between the baseline

measurement and at 3 and 6 months. The relationship between social network, feelings of loneliness, and PA over time will also be assessed. Furthermore, an evaluation study will be conducted on the differences in the characteristics of the participants in relation to entry channel (Web-based or paper-based), on dropout, and on effects.

Ethics Approval and Consent to Participate

This study was reviewed and approved by the Committee for Ethics and Consent in Research of the Open University of the Netherlands (reference number: U2016/02373/HVM). Trial registration was not applicable as this study does not report on the results of an intervention. Participants provided written informed consent to participate in the study.

Results

In the Methods section, the theoretical processes of the IM protocol, and the way these were addressed in this research, were stated. The results and practical implications of these steps are presented in the Results section as per the individual step of the protocol.

Step 1: Needs Assessment and Determination of Fit With the Problem

Literature shows that at older age, the majority of the people have a chronic disease. In Europe, 43% of the people in the age group of 55 to 64 years has one or more chronic diseases; this increases from 53% (64-74 years) to 64% (75-84 years) to 69% (>85 years) [38]. The most prevalent are cardiac disease, chronic pulmonary disease, and diabetes mellitus. People with a chronic disease have an enhanced risk of developing another chronic disease, that is, multimorbidity [39,40], which worsens the health situation. The prevalence of multimorbidity is increasing significantly since last decade, not only because of the aging of society but also because of changes in lifestyle risk factors, such as a lack of PA [41]. Enhancing or maintaining health is, therefore, at least equally important for the specific high-risk target population of Active Plus65 as for the original population of Active Plus50.

In the age group of 50 to 59 years, 16% of the general population report having a mobility limitation that impairs them in PA. This percentage increases from 25% (60-69 years) to 37% (70-79 years) to 61% (>80 years) [42]. In general, people with a chronic disease are less physically active than healthy people [43,44]. Chronic diseases commonly cause mobility limitations that form impairments regarding PA. People with a chronic disease may be between 1.2 and 2.7 times more likely to have a mobility disability compared with those who do not have a chronic disease [45]. Not only the mobility limitation in itself but also the fear of pain or fear of injury are related to a low level of PA for older people with a chronic disease [46,47]. The World Health Organization [1] recommends that all adults, regardless of age or the presence of a chronic disease, should perform a minimum of 150 min per week of at least moderate to intensive PA. The main behavioral target and primary aim for Active Plus65 is stimulating participants to reach a level of PA that meets this recommendation. This is the same as in the original intervention, although the point of departure with respect to PA differs substantially in the adapted target group, where all participants have one or more chronic diseases.

Apart from the limitations that are specific for older adults with a chronic disease, age in itself comes with limitations, such as impaired eyesight or hearing, which can interfere with PA [6,48-50]. In addition, here the aim with regard to PA is the same in Active Plus50 and Active Plus65; however, the target population in Active Plus65 possesses some characteristics that require a refinement of the intervention.

Another significant feature of older adults, who are less physically active, is the absence of a life partner [6,15]. Single older adults are at risk for becoming socially isolated, especially bereaved older people [51-53]. Living alone and social isolation often results in feelings of loneliness [54]. Loneliness is considered to have a significant negative influence on the physical and mental health of older adults [16,17,55]. Feelings of loneliness increase with age—the highest percentages of people who are lonely are older than 65 years [56-58]. Participating in PA, when done with others, is a way to decrease loneliness as it stimulates social contacts [59,60]. From this, the secondary goal of Active Plus65 is derived, which is stimulating PA together with other people.

The literature study, thus, reveals that the health problems and the related health behavior targeted by the original intervention (Active Plus50) are at least equally relevant for the target group in Active Plus65, which is a specific segment of the target population in the original intervention. The main aim of the original intervention, that is, to raise and maintain the level of PA, remains the same; however, an additional emphasis will be put on being physically active with others to increase the social network.

Step 2: Logic Model of Change and Matrices

The needs assessment (step 1) has revealed that Active Plus65 aims to increase and maintain the PA of single people older than 65 years with a chronic disease. As this primary behavioral outcome of Active Plus65 is the same as for Active Plus50, the performance objectives (as previously shown in Table 1) in both interventions are identical. The secondary behavioral outcome (ie, to stimulate PA with others) is enclosed in the existing performance objectives. For example, in the second performance objective (ie, the target population can indicate reasons to be physically active), one of the reasons to be physically active could be that it enables one to engage with other people when being active with others. Another example can be found in the third performance objective (ie, the target population identifies solutions to remove barriers to being physically active); finding a stimulating partner to be physically active with can be a solution to remove a barrier.

In the Active Plus50 intervention [26], important psychological determinants have been established that need to be addressed to stimulate PA. Three major characteristics can be identified in which the target population of Active Plus65 differs from the original Active Plus50 population; these characteristics can change the impact of the established determinants. The first of these is that the entire target population of Active Plus65 has one or more chronic diseases, whereas in Active Plus50, only

45% of the participants reported having a chronic disease [27]. The number of chronic diseases, the physical limitations, and fatigue caused by the chronic disease can influence the amount of PA as well as the determinants [10,11,44,46]. The second characteristic is that the target population of Active Plus65 consists entirely of single people; in Active Plus50, only 21% of the participants were single. The social support of a partner, family, or friends as well as the available practical support they provide, such as having a sports companion, is known to influence PA [52,60,61]. The third characteristic in which the new target population differs from the original population is age; in Active Plus50, 37% of the participants were older than 65 years, whereas in Active Plus65, this will be 100%. With regard to age, experience with PA in the past, as well as perceived level of fitness and general fitness (eg, impaired eyesight, ie, not chronic diseases) may have an effect on PA [43,62,63]. The potential influence of these characteristics on PA has been endorsed by the research of Peels et al [37] on Active Plus50, which showed that especially single older people with a chronic disease expressed the need to receive more information about PA with their specific chronic disease, and the need for more personal interaction when being physically active.

Considering these characteristics, it is concluded that the determinants in Active Plus50 and Active Plus65 are identical but that the relative importance of the determinants is different. People with a chronic disease, for example, can develop a fear of PA as a result of pain avoidance beliefs [10,11,43,46]. The personal determinant attitude, under which pain avoidance beliefs can be categorized, therefore, has a relative higher importance than it has in Active Plus50.

As the performance objectives and determinants are comparable in the Active Plus50 and Active Plus65 intervention, the intervention did not require major adaptations in overall structure. The change objectives did require further refinement as the relative importance of the determinants is different. These refinements were established by the interviews with the focus groups and by the input from the physiotherapists as described below.

Focus Groups

The features of the 14 participants who took part in the focus groups are shown in Table 3.

By conducting focus group interviews, the opinions, wishes, and preferences of the target group were taken into consideration in the adaptation of the intervention, that is, in specifying the change objectives. Focus groups interviews were also used in the development of the original intervention [26]. According to literature, two focus groups are needed to discover the large majority of relevant themes [64]. By also including people who did not comply with the characteristics of the target group, such as married people and people without a chronic disease, potential differences of opinion between the target group and nontarget group could be identified and discussion could be stimulated. The questions for the interviews were based on the I-Change-model [32,33], and special attention was given to the characteristics that are stated above.

Attitude

The majority of the participants expressed that everyone can be physically active to some degree:

> *I exercise more now that I have a chronic impairment…I live more conscious now.*

They also expressed the opinion that some people stop exercising because they experience pain because of performing their exercises in the wrong way. The reasons why the participants started exercising were diverse, such as for the exercise in itself or for the social contacts with other people during exercising:

> *Someone who listens to you…I really need that.*

On the other hand, the participants indicated that they know people who are hesitant to join an exercise group because they do not feel comfortable to socially engage with people they do not know:

> *Getting out and making contact with new people…I really had to learn that again after my husband died.*

Self-Efficacy

The participants thought that most people do not exercise because they just do not know that there are simple exercises that one can do and, therefore, do not exercise at all:

> *Some simple exercises that I could do in my own house would be really helpful.*

Table 3. Features of the focus group participants.

Characteristics	Focus group 1	Focus group 2
Gender		
Male, n	1	3
Female, n	7	3
Marital status		
Married, n	4	3
Widowed, n	4	3
Mean age in years (range)	72 (62-83)	78 (70-94)
Participants with chronic disease, n	6	3

Table 4. Example of opinion of focus groups and resulting change in intervention.

Determinants of PA[a]	Opinion focus groups	Recommended change in intervention
Attitude	Walking and cycling are unpleasant because of busy streets	Stressing that not only outdoor activities are relevant but that performing PA at home can also be beneficial
	Future benefits are an important reason for PA	Stressing that PA is beneficial for long-term health
	Possible contacts with others are an important reason for PA	Stressing that PA can be a way to interact with others
	Lack of knowledge about PA possibilities is why people do not exercise	Adding a list of local venues and providing specific information on PA that can be done together with others
	Fear of pain deters people from PA	Encouraging people to seek advice from their physiotherapist or general practitioner so they can be reassured that the pain does not have to be harmful
Self-efficacy	Pain when exercising makes PA difficult	Adding information that pain is not necessarily bad and information on PA exercises that are less painful so people feel confident.
	Facilities not accessible for those without a car	Stressing that there are exercises to do at home, or nearby with a list of local venues
	Fear of reaction by others when joining an exercise club	Stressing that everybody feels awkward the first time but that it becomes easier soon
Social influence	Fear of going outside when it is dark	Stressing possibility to ask a friend to join them or to exercise in day time
	Lack of desire to engage in social contacts	Stressing that PA with someone else can be a pleasant way to combine sports and socializing and that after the first time, exercising in a group becomes less awkward
	Fear of initial contacts if joining an existing PA group	Using modeling to let a role model tell that they were hesitant to join a PA group but that they were pleasantly surprised by the welcome

[a]PA: physical activity.

Finding initial contacts with others is awkward when joining an exercise group for the first time; it may deter people from PA with others. About half of the participants said that a lot of venues where you can exercise are difficult to reach for older people, because you need a car to get there (and they often do not drive anymore). Some do not feel physically fit to walk alone to the exercise facility or consider their surroundings not safe enough, especially after dark:

> *I really do not want to get into trouble, so I stay indoors in the evenings.*

Social Influence

The participants who had lost their partners referred to the challenges of joining social activities again after bereavement and that personal support from friends and family is essential to get on with life. They expressed that they joined an exercise group for social contacts rather than for the exercise itself. The participants also referred to people who seem to be lonely but not able to take action and socialize again:

> *They just don't seem to be able to take action, no matter how much effort you put into them.*

According to the participants, it is very difficult to reach those people or to stimulate them to join exercise clubs. Not having a partner also has some practical barriers, such as having no one to bring you to an exercise venue:

> *Going places is difficult now that I am dependent on public transport.*

Table 4 provides the most relevant results of the focus group interviews.

Survey of Physiotherapists

Of the 35 physiotherapists who were invited to participate, 10 physiotherapists completed the questionnaire; known reasons for nonresponse were lack of time or no longer being active as physiotherapists. The physiotherapists indicated that cardiovascular problems, lung diseases, and rheumatism resulted in the largest barriers for being physically active. Cerebrovascular incidents, diabetes, severe backaches, and osteoporosis represented the second most important diseases, and overweight and arthritis the third. This information was used to determine the sequence in which advice on being physically active with a chronic disease was presented, that is, if a participant had multiple diseases, the participant only received tailored information on a maximum of three chronic diseases, and the disease for which a tailored advice is most important (ie, resulted in the largest barriers for being physically active, as defined by the physiotherapists) is presented first.

The physiotherapists were asked to give top three types of PA that were to be recommended, and PA that were to be discouraged, per chronic disease. There was a large diversity in the kind of PA that was recommended per chronic disease;

this was also the case for nonrecommendable forms of PA. As reason for this diversity, all physiotherapists indicated that a standard PA advice cannot suffice because of variability of complaints within a chronic disease and degrees of severity. Moreover, the physiotherapists explained that a lot of people have more than one chronic disease, and types of PA that are beneficial to one chronic disease may be harmful to the other chronic disease. In addition, older people generally have other issues, such as poor eyesight or balance, which might impair being physically active more than the chronic disease in itself. Apart from these physical matters, the physiotherapists express the opinion that other matters can interfere with PA, such as the level of insight that people have in the seriousness of the disease, the fear of pain, and the amount of PA earlier in life. However, these matters need not to deter people from being physically active by focusing on the possibilities instead on the barriers. This feedback from the physiotherapists resulted in an increased prudence in advising participants to become more physically active; participants were, therefore, additionally advised to contact a physiotherapist or general practitioner when in doubt about their PA potential.

On the basis of the input from the focus groups with the target population and results from the survey among physiotherapists, the existing change objectives of Active Plus50 [26] were refined for the more specific high-risk target population of Active Plus65. Table 5 shows examples of existing and new change objectives.

Step 3: Theoretical Methods and Practical Applications

No new theoretical methods and practical applications have been added, as the methods and applications used in the existing intervention already had been proven effective [27], and only needed more specific targeting to the population. Computer tailoring remained the core of the intervention; single older adults with a chronic impairment in PA received adapted advice texts, whereas participants from other subgroups received the original advice texts. The practical content, therefore, has been refined to better meet the demands of the specific target population. This is discussed in step 4.

Step 4: Producing Programs

The questionnaire that the participants in Active Plus50 have to fill in is the core of the intervention, as it forms the input for providing tailored advice; this questionnaire was, therefore, also used in Active Plus65. All questions have been carefully reviewed to determine whether they matched the adapted change objectives.

Table 5. Examples of change objectives (COs) in the original and adapted intervention.

Performance objectives	Determinants			
	Attitude	Action planning	Self-efficacy	Knowledge
2. Participant indicates reasons to be physically active	Original CO[a]: participant feels positive about being sufficiently physically active			Original CO: participant knows about the health benefits of sufficient PA[b]
	Adapted CO: participant feels positive about being sufficiently physically active even if they sometimes experience pain			Adapted CO: participant knows about the health benefits of sufficient PA specifically for people with a chronic disease
3. Participant identifies solutions to remove the barriers to being physically active		Original CO: participant makes specific plans to remove barriers to being physically active	Original CO: participant feels confident about being able to take away the barriers to being physically active	Original CO: participant knows how to identify difficult situations and know manners to take away these barriers
		Adapted CO: participant makes specific plans to remove barriers to being physically active and to incorporate others into their plans	Adapted CO: participant feels confident about being able to take away the specific barriers for chronically impaired	Adapted CO: participant knows how to identify situations that are specifically difficult for single people and knows manners to take these barriers away
5. Participant makes specific plans to become more physically active	Original CO: participant feels positive about making plans to increase their PA	Original CO: participant makes specific plans to increase their PA		
	Adapted CO: participant feels positive about making plans to increase their PA and to incorporate others into their plans	Adapted CO: participant makes specific plans to increase their PA activities on their own as well as with others		

[a]CO: change objectives.

[b]PA: physical activity.

Table 6. Examples of changes in practical content.

Determinant	Theoretical method	Practical strategy	Practical content	
			Active Plus50	Active Plus65
Attitude	Feedback	Provide information on pros and cons	General information on benefits of PA[a]	Adding more information on being physically active with specific impairments by adding fact sheets about the recommended kind of PA per chronic condition
	Improve knowledge			Confirming that fear of pain can influence commencing PA but that there are special activities that can be done with a minimum level of pain: a specific suggestion is added: for example, a person with arthritis is advised to join a local swimming club for people with their impairment
Social influence	Facilitating	Stimulate participants to seek partners for PA	General statements in tailored advice that PA is more entertaining when done with a partner	Adding more information on local sports clubs and local patient support groups
				Adding advice that PA is a possible way to engage with other people
				Adding possibilities on the Active Plus65 website to look for a PA buddy
				Adding a brochure of social activities for older people that are organized in the municipality
				Video and pictures of people exercising alone were replaced by comparable people exercising in a group
Self-efficacy	Social modeling	Provide role model stories about difficult situations and how to cope	Picture or film of similar others (same age group and gender) with quotes about how they coped with a similar perceived difficult situation	The peers in the pictures and film were replaced by older people
				Less pictures and films with people cycling, as cycling is often too challenging for older adults, but more with people walking
				Content was added in the advice, which acknowledges that it may be awkward to join an exercise club for the first time but that these feelings diminish soon

[a]PA: physical activity.

In the questions where participants score positive and negative attributes of PA, additional items were added, based on the new change objectives. An example of a positive attribute is “PA brings me in contact with others” and an example of a negative attribute is “I avoid PA because of the pain I anticipate.” In the message library, corresponding advice messages were added. For example, those participants who avoid PA because of anticipated pain receive an advice message on coping with unavoidable pain. In addition, questions were added to determine the loneliness experienced. In the message library, corresponding advice messages were added to emphasize the positive effects of being physically active with others. Furthermore, questions were added to check whether participants used devices such as walking sticks; considering the older age of the participants in Active Plus65, tailoring to being physically active with those devices is appropriate. For these people an advice message was added to the message-library explaining that PA with these devices is possible.

For all the advice messages of Active Plus50, it was checked whether they matched the target population adequately. First, text about being physically active with a spouse, for example, was removed. Furthermore, modeling videos, pictures, and voice-overs were replaced by content with age-matched persons, that is, people older than 65 years. When making these new videos and pictures, the emphasis was put on people who were exercising with others instead of alone. In the new modeling content, mainly walking was illustrated instead of cycling as walking can generally be done better and is safer at older age than cycling.

The adequateness of the intervention materials was further studied by presenting the participants of the focus groups with the following: (1) the part of the questionnaire that addresses physical impairments; (2) a bar graph showing the PA of the participant, the average PA in their age category, and the daily recommended PA; and (3) a modeling text. Focus group participants were asked to fill in the questionnaire to detect problems in the intervention or tailoring questionnaire. Half of the participants in the focus groups experienced difficulties while filling in the questionnaire, resulting in the redesign of this part of the questionnaire.

Table 7. Examples of feedback from focus groups and modifications to original Active Plus program.

Results focus group	Objective or strategy	Modifications
Introduction letter is not clear about Web-based and printed possibilities	Raising participation levels by giving people a choice in the delivery method of the intervention	Rewriting the introduction letter so that the choice between Web-based and printed is clearer
Identity of sender of introduction letter is not clear	Emphasizing importance of the intervention by making clear that the sender is the municipality	Having the letter signed by the principal council member of the local municipality
Kick-off meeting is considered to be interesting	Giving information about the program and giving opportunity to meet others	Organizing a kick-off meeting for potential participants

The bar graph was shown and the focus groups were questioned to check whether they could interpret the bar graph correctly. The majority of the participants were not able to do so; therefore, a written explanation was added to the bar graph. The modeling text was also presented to the focus groups. Four participants found the text inspiring. One participant interpreted the text that PA could cure a chronic disease; therefore, the text was refined. In Table 6, examples are given of how the comments from the focus groups were used to adapt the practical content of Active Plus65.

Step 5: Implementation

During the focus groups, participants were presented with the following recruitment materials for the program: (1) a personalized letter in which people are invited to join the program, (2) a flyer containing information about the program, and (3) information on a kick-off meeting. The flyer was considered to be clear and motivating, but all participants found the letter confusing and not arousing interest in the program. After the first focus group, the letter was altered and presented to the second focus group. In this group, the letter was considered to be clear and motivating. The participants were also asked whether they would participate in a kick-off meeting of the program where they could receive more information on the program and meet other participants; this produced positive reactions. In Table 7, examples of the alterations in implementation materials after conducting the focus groups are given.

Step 6: Planning Evaluation

To complete the systematic adaptation, a plan for the evaluation of the intervention was developed. For this, a longitudinal study will be conducted in one Dutch municipality. All citizens who are registered as single and are 65 years or older will be invited to participate in Active Plus65 (N=6751). The invitation letter will make it clear that the program is especially targeted at single older people with a chronic disease.

The primary outcome is the difference in PA between baseline and 3 and 6 months. The amount of social contacts and perceived feelings of loneliness will also be measured. Furthermore, possible moderators or mediators of the results on the primary outcome will be assessed, such as age. To compare the effects on PA of the altered intervention with the proven effective intervention, data on participants in Active Plus50 will serve as a reference group. The evaluation of the intervention will also focus on the relationship between the demographics of the participants of Active Plus65 and characteristics such as participation in the Web-based and paper version as well as attrition ratios.

Discussion

Principal Findings

The aim of this study was to describe the systematic development of a computer-tailored eHealth intervention aimed at increasing PA for single people older than 65 years who have a chronic disease. This intervention, Active Plus65, was developed by adapting the proven effective PA intervention, Active Plus50 (for the general population older than 50 years), to better fit the abovementioned narrower target population.

It is concluded that even when the new target population is a sizable segment of the original target population, the original proven effective intervention may not optimally fit the different subpopulations. Therefore, the original intervention needed enhancement to achieve this. The necessary adaptations were performed in a systematic way by using the IM protocol [29] to ensure that both theory and empirical evidence are encased in the intervention. The intervention will be evaluated in a longitudinal study by comparing the adapted intervention with the original intervention.

Methodological Issues

As adapting interventions in a systematically planned way increases the likelihood of effectiveness, the use of the IM protocol increases the chance that the adapted intervention will still demonstrate effectiveness. It enables the developer to retain the components that are crucial to the effectiveness by carefully considering the elements that can be modified without lowering the effectiveness substantially. Another strength of this study is that it combines data gathered from existing research, from focus groups, as well as from health care professionals. Different angles and interests could, therefore, be incorporated; limitations when using each of these research methods separately are thus overcome.

However, there are some limitations for the approach we used within this research that need to be considered. First of all, selection bias in the focus groups might have occurred as those who participated may not have been the most optimal representatives for the target population. The majority (57%) of participants in the focus groups consisted of the members of a gym club who are possibly more physically active than others of their age and more willing to participate in joined activities. However, 64% of them had one or more chronic diseases by which representativeness issues were balanced. By adding information from a literature study and from health care professionals, potential representativeness issues were also overcome. The latter have an expert opinion on PA for

chronically ill older adults and, moreover, have practical experience with their PA behavior. Furthermore, as the main goal of the intervention is to raise the level of PA, preferably together with others, the opinion of people who already are physically active is of major interest.

Another matter to consider is that recommendations for the advised amount of PA for people with a chronic disease are not totally clear yet because of a lack of scientific evidence. For this reason, the focus in Active Plus65 is put mainly on increasing PA, and not on achieving an advised amount. The planned effect evaluation will, therefore, not be able to compare the effects with a generally accepted norm.

Furthermore, there are some practical matters to consider when applying the IM protocol to adapt an existing intervention. First of all, even when not designing a new intervention, but merely adapting an existing intervention, IM is a process that is time-consuming, which should be taken into account in planning human resources and applying for funds. Although we have been able to systematically follow the IM procedure completely, a lack of time or resources could potentially result in researchers skipping elements of IM. Second, another challenge was to adequately limit the information that was added to the intervention for the specific target population to prevent an overload of advice. By adding information on being physically active with others or on being physically active with a chronic impairment, a constant balance had to be made between what to add and what could possibly be deleted. The IM protocol for adapting interventions does not specifically seem to address the issue of potential information overload. Third, although IM describes the general tasks for each step of adapting an intervention, a practical elaboration on how these matters can be addressed is lacking. Adding this information to the protocol might form a practical and valuable guideline for researchers.

Conclusions and Further Research

Notwithstanding the abovementioned limitations, it is concluded that this paper provides valuable information for the process of adapting lifestyle interventions. The next phase in the adaptation process is a pilot testing of the adapted intervention, which may result in further refinement. After this, a longitudinal study of the implementation results will be conducted. If the effects are similar to the original Active Plus50 program, which has been proven to be effective, Active Plus65 will be implemented on a broader scale.

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Authors' Contributions

LL and CB designed and wrote the original proposal for obtaining the funding. DP and BB were also involved in the original proposal. JB, BB, and DP were responsible for conducting the interviews, writing, and programming of the intervention content. LL and CB critically reviewed and approved the intervention content. JB, BB, and DP were responsible for the recruitment procedure. JB was responsible for drafting the manuscript. This manuscript is original and not under consideration or published by any other journal. There are no potentially overlapping publications.

Conflicts of Interest

None declared.

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Abbreviations

PA: physical activity
IM: Intervention Mapping
PO: performance objective
CO: change objective
TPB: theory of planned behavior

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Original Paper

A Group of 500 Women Whose Health May Depart Notably From the Norm: Protocol for a Cross-Sectional Survey

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Abstract

Background: Longitudinal studies of women's health often seek to identify predictors of good health. Research has shown that following simple guidelines can halve women's mortality. The ongoing Australian Longitudinal Study of Women's Health (ALSWH) shows that Australian women are getting better at reducing their smoking and alcohol use, and are generally diligent about attending recommended health screenings, but are becoming less successful at dealing with obesity. There are communities of women who live unusually healthy lives (Rosetans, Seventh-Day Adventists, traditional Japanese women), but their lifestyles are unlikely to be adopted widely. Universal Medicine (UM) is a complementary-to-medicine approach that emphasizes personal empowerment and the importance of menstrual health symptoms.

Objective: This survey investigates whether the approximately 500 women associated with UM exhibit health status significantly above the norm. As part of this investigation, questions for a newly developed menstrual attitudes questionnaire will also be evaluated.

Methods: A quantitative cross-sectional survey of women in a UM cohort was designed with the help of three focus groups of women at three life stages: in menses, peri-menopausal, and menopausal. The menstrual attitudes portion of the survey incorporates the insights of these women regarding female health issues. The survey also includes 41 questions taken from the ALSWH. Focus groups generated additional questions about symptoms experienced and attitudes toward female health issues. ALSWH questions, including a range of health scales like the Short Form 36 (SF-36), Center for Epidemiologic Studies Depression Scale, Perceived Control Scale, Kessler Psychological Distress Scale, and the Multi-Item Summed Score for Perceived Stress, along with questions about experienced major health events, were investigated and incorporated if considered suitable. At the time of publication of this protocol, data collection has been completed.

Results: The validity of the menstrual attitudes questionnaire will be evaluated with Cohen's kappa. ALSWH respondents and UM participants will be compared, using unweighted regression or regression weighted or normalized by age, education, and interest in alternative treatments (to increase comparability), as appropriate. Analyses will determine whether UM-related variables

(being a UM participant, length of UM participation, number of UM events attended) are associated with: differences in the number of major health events and health symptoms experienced; SF-36 physical and mental health scores; body mass index; and consumption of alcohol, tobacco, sugar, salt, caffeine, and dairy.

Conclusions: If women in the UM cohort are truly in substantially better health than the norm, further investigations may be worthwhile to see whether UM plays a causal role, and whether the women's practices are generalizable.

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KEYWORDS

women's health; survey; public health; menstruation questionnaire; SF-36; ALSWH; Universal Medicine; preventive medicine; health care costs

Introduction

Various behavioral dimensions are strong predictors of health for both women and men. One study identified seven behaviors as being of health significance in a cohort of 6928 46-to-70-year-old people from Alameda county (near San Francisco, California) who were followed from 1965 to 1984: (1) not smoking; (2) using alcohol moderately (if at all); (3) exercising at least moderately; (4) sleeping 7 to 8 hours each 24-hours; (5) maintaining moderate weight; (6) eating regular meals; and (7) eating breakfast [1,2]. Respondents who reported performing six or seven of these behaviors had less than half the mortality, and those who performed four or five of the behaviors had approximately two-thirds the mortality, compared with those who performed fewer than three [1,2].

Exemplary Populations

There are groups of people who have been documented as having unusually healthy profiles, including the inhabitants of the small American town of Roseto, Pennsylvania [3], Seventh-Day Adventists [4], Japanese living a traditional Japanese lifestyle [5], and senior Whitehall (United Kingdom) civil servants [6].

In Roseto, people were living according to traditional Italian roles, where residents tended to have very strong community ties. The diet of this population was nutritionally poor, and many did hard and dangerous work in a slate quarry, but their heart disease morbidity and mortality were much lower than those of inhabitants of surrounding towns [3]. Seventh-Day Adventists have lower coronary heart disease rates and lower rates of many cancers, among other health indicators, but they are a traditionalist Christian offshoot with strict rules [4]. Strict hierarchies were, and are, an important feature of Japanese life [7]. The better health of high-level British public servants may simply be evidence that those with better general habits are better able rise to higher positions [6]. Therefore, none of these four groups is without its limitations in terms of producing lifestyles that the general population would be likely to embrace.

Women-Specific Research

A 1999 report that investigated the inclusion of women in various types of medical research found that in nongender-specific research, women were vastly underrepresented as research subjects [8]. Rodin and colleagues [9] have contributed significantly to the understanding of women's health concerns, which differ from those of men. These researchers described women-specific health concerns such as hysterectomy, dysmenorrhea, caesarean section, almost all incidences of breast cancer, and some concerns not exclusively (but primarily) relevant to women, such as rheumatoid arthritis, lupus, osteoporosis, and eating disorders [9]. It has also been documented that 70% of psychoactive medications (eg, antidepressants, tranquilizers) are prescribed to women [10], and two-thirds of all surgeries are performed on women [11].

Measuring and improving female health is an important task for many governments, particularly those that have aging populations, and in which the incidence and prevalence of illness and disease are rising sharply. Unfortunately, this is a widespread problem: the rates of large-scale health issues like obesity and diabetes are rising [12,13]. The associated rise in health care costs adds to the urgency of this problem [14].

In Australia, the Australian Longitudinal Study on Women's Health (ALSWH), with 58,000 women, was inaugurated in 1986 and added a further 17,000 women aged 18-23 years in 2012/2013. The purpose of the ALSWH is to, "clarify cause-and-effect relationships between women's health and a range of biological, psychological, social, and lifestyle factors" [15]; hence, this study's data holds promise for elucidating predictors of good health in women.

Weight and Obesity

An important predictor of health is being overweight or obese. A 2014 review [16] cited the ALSWH papers on weight. Among the findings, it was found that the proportion of obese individuals rises until the approximate age of 65 years and then falls [16]. Overweight women are significantly more likely to develop hypertension, heart disease, asthma, diabetes, depressive symptoms, and polycystic ovary syndrome, and to report hysterectomy [16]. Women who gained at least 5 kg over three years reported more menopausal symptoms [16]. The review further reports that individuals well over 60 years of age who are overweight have an increased chance of developing foot problems, arthritis, incontinence, declining physical functioning, acute health events, and stroke [16]. The exception to this pattern of disease susceptibility is osteoporosis, "because the increased load on the skeleton of high body mass index (BMI) individuals promotes higher bone mineral density" [17].

A potentially worrying point from the perspective of future population health was that in the 1973-1978 cohort, the

18-year-olds gained approximately 200 grams/year more weight than did the 23-year-olds [16]. In that 1973-1978 cohort, having a partner added 1.8 kg, and delivering a first baby added 4.0 kg over 10 years [16]. Lower levels of education, working full time, and having a mother with lower education were also associated with gaining weight [16].

The 1973-78 cohort will be approximately 8 kg heavier in middle age than the 1946-1951 cohort was. Consistent with the pattern documented by Gomersall et al [16], the Australian Bureau of Statistics reports that obesity in the population at large peaks at a 35% prevalence at age 65 and then drops to 25% at age 80 [18]. The absence of being overweight or obese is a predictor of good health, but currently the prevalence of being overweight or obese is increasing on a worldwide basis [13].

Health and Behavior Change

There is a plethora of associations between adhering to health guidelines and better health outcomes, as described in a major ALSWH report [19]. The report shows that women appear to be able to reduce their intake of clearly harmful substances (eg, smoking, alcohol; whether the latter is beneficial in moderate doses or not) and their adherence to screenings is consistently high and stable, or rising [19]. However, in practice it seems currently impossible to improve people's daily behaviors of eating less or exercising more on a population-wide level. In fact, the opposite seems to be the case with Australians: the percentage of overweight and obese adults is continuously increasing [18], which is a process that seems to be happening in other countries as well [13]. Interventions that empower women to address factors of diet, weight management, stress, and mood will likely be most effective in improving their health.

Good health practices are well known to medical science; the issue is less one of knowing *what* to do than knowing *how* to increase interest and action in adopting a healthy lifestyle overall among the wider population. For example, even diagnosis of a chronic disease (eg, heart disease, diabetes, asthma, breast cancer, arthritis, or depression) does not lead to improved levels of physical activity [20]. Such a diagnosis in itself is not generally adequate to induce women to improve their health behavior; although some women do make improvements, this gain is offset by those whose behavior actually worsens [20]. Counselling from doctors has been shown to work for high-risk patients [21], but is not being implemented on a level that would improve population health. In addition, adherence to doctors' guidelines for chronic ailments is typically 50% or less [22]. A substantial group of women who are managing to adopt good health practices would therefore be of great interest to medical science and those responsible for public health, especially if the women's lifestyle skills and habits are teachable and transferable. Our goal is to study participants in a program called Universal Medicine (UM), to determine whether they have health advantages over women at large.

Universal Medicine

UM was founded in 1999 by Serge Benhayon, with the stated goal of, "providing Complementary Health & Healing Services that are Universal in their approach towards medicine and healing" [23]. Although Benhayon has no background in medicine or healing, as of 2015, approximately 200 men and 500 women were coming regularly to workshops and seeking treatments from UM-accredited practitioners. Benhayon describes UM's mission as follows:

> *Through practical philosophies that inspire more self-caring and self-loving choices in daily life, Universal Medicine supports people to explore their overall well-being, the development of energetic awareness, and the depth they can bring to their quality of life and relationships [23]*

UM teachings are delivered in the form of lectures, audio recordings, and treatments from UM clinics. Regular courses, workshops, and retreats are conducted throughout Australia and internationally. Individual participation levels range widely from consuming one or more webcasts per year to regular physical attendance at events in North Eastern New South Wales, Australia or in Frome, Somerset, United Kingdom, which receives approximately 700 regular visitors, including a number of health care professionals.

Over time the authors of this paper became aware of the fact that the large majority of participants in UM appear to lose weight with little or no effort and yet also report gains in vitality, as evidenced by observations that participants seem to be able to work or study for longer periods of time. These changes occur despite the fact that neither weight loss nor increased vitality is ever explicitly considered or targeted during UM events. Informal surveys have also indicated that very few members of the group eat gluten or dairy, drink alcohol or smoke, or consume caffeine. These individuals appear to have less added sugar and salt in their diets than the normal population does, and also seem to have little or no difficulty maintaining such a diet.

If these observations are accurate, and if the skills and behaviors associated with UM participants' dietary choices and weight loss are transferable to the population at large, then UM holds a key to very substantial decreases in population health expenditure via reductions in obesity levels and decreased consumption of alcohol and tobacco. UM also differs from the norm in its attitude toward women's health. The numerous and varied menstrual health issues that women encounter are not treated as nuisances to be managed or as illnesses to be cured, but as messages from the body that a change in attitude or lifestyle, or both, is needed. Such changes may be substantial at times, and do not supplant (but rather augment) visits to registered medical practitioners and adherence to prescribed treatments.

If this group of women is particularly skilled at managing menstrual health issues, and if these skills are transferable, then because menstrual symptoms like dysmenorrhea have prevalence rates as high as 90% [24] and menstrual symptoms are widespread [25,26], there would be further substantial population health benefits.

Serge Benhayon describes the lifestyle associated with UM as *The Way of the Livingness*, and *Livingness* is described as follows:

> *In a nutshell The Livingness is simply about living as our true selves... It is our ability to live and express who we truly are inside, and taking this into our day to day life. Everything we do say or think and every action we take or do not take contributes to our Livingness. Our choices, actions and inactions have a direct effect on our health, physical body, planet and each other. They can be the cause of our greatest healing or harm [27]*

What is Taught by Universal Medicine?

The core teaching of UM is that our bodies are a source of truth. An introductory course (Livingness 1) teaches how to *connect* to one's body and to experience the consequences of that connection. The next course (Livingness 2) addresses emotions we have absorbed in the past. For example, a commonly used term is *feeling sick to our stomach* from emotions, and the extension of that everyday wisdom in UM is that some of the effects of emotions may linger much longer than the physical symptoms. The third course (Livingness 3) shows how to deal "with the sabotaging hindrances that prevent the real you from being in the fore" [28], showing that the quality in which everyday actions are performed can make a substantial difference to one's well-being. Each of these courses can be completed in one day. In addition, UM presents training in its healing modalities [29], which consists of approximately 10 philosophical lectures in Australia annually, and three 5-day retreats annually.

Possible Universal Medicine Effects

A medical doctor who treats a number of UM participants reported to one of the researchers (CS) that the participants are particularly able to take on a treatment plan and adhere to it. In addition, UM-affiliated women also appear more prone to adhere to health guidelines that are very similar to government-recommended ones. A visual gallery of the typical changes UM participants experience is available [30].

Hence, there is a possibility that the group is above average or even well above average in a substantial number of physical and mental health indicators. UM has developed a number of modalities that are complementary to medicine (ie, not developed within a mainstream medical environment). Evaluating these intervention techniques is beyond the scope of this survey; however, a randomized controlled cross-over trial of one of the UM modalities, chakra-puncture, is underway. A randomized controlled trial of another UM modality (esoteric connective tissue therapy) has received ethical approval from the University of Queensland, with a published protocol paper [31].

Female Menstrual Symptoms

A further substantial, but under-investigated, area of women's health is common menstrual symptoms. Approximately 80% of women in an ALSWH study [32] reported experiencing premenstrual syndrome, and 60% reported dysmenorrhea over the 12-year period in which members of the cohort were aged 22-27 years at the start and 34-39 years at the end. However, some women experienced increasing prevalence, others had decreasing prevalence, and some had constant high or low prevalence [32]. These findings suggest that there may be external or internal factors influencing these symptoms, and invites the possibility of changing these factors. For example, smoking increases menstrual symptoms and miscarriages, with odds ratios increasing with numbers of cigarettes smoked and younger age of smoking onset [33].

Women who have fewer menstrual symptoms or conditions have a reduced rate of hysterectomies [34]; hence, reducing these symptoms and conditions may have positive implications for the cost of health care. There is evidence that some female health issues are associated with choices women make in their lives. Herber-Gast et al [35] showed that both night sweats and hot flushes are positively associated with education, weight, smoking, drinking, premenstrual tension, diabetes status, and early age at first pregnancy. These associations were present whether or not the women were peri-menopausal or menopausal.

Women who are 45-50 years old experience physical declines, with those who are peri-menopausal or on hormone replacement therapy reporting substantially stronger declines (expressed in reduced SF-36 scores [36]) compared with those who remained premenopausal [37]. Therefore, a group of women whose physical health does not decline when their menstrual status changes, even after accounting for age, may be of interest, as might a group with a consistent drop in these symptoms.

Objectives

The proposed survey will investigate whether women who participate in UM have a superior health profile compared with the respondents to the ALSWH. These data would allow a conclusion as to whether UM is worth investigating further to assess the presence of any causal links between specific aspects of the program and improved health.

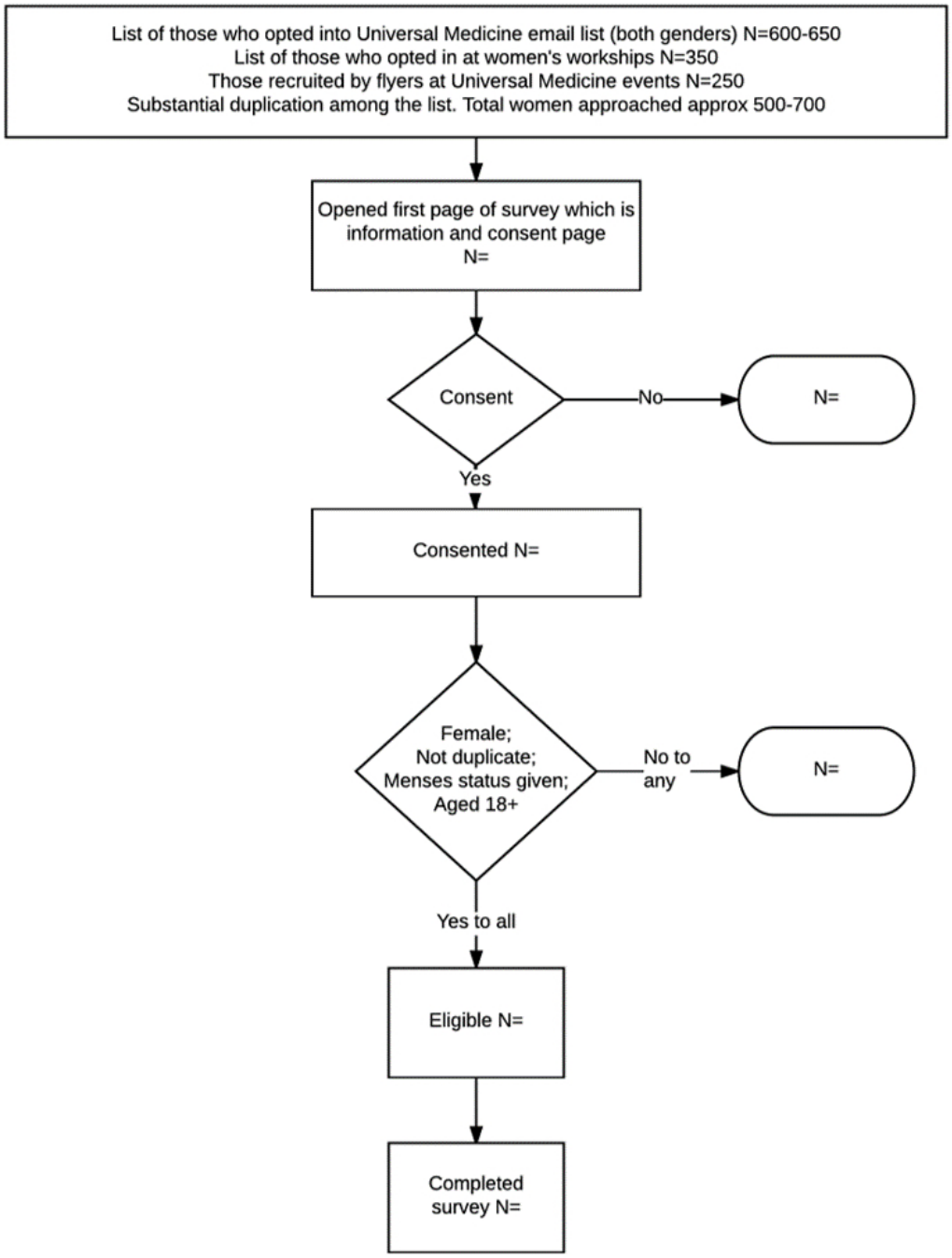
Methods

Design

A quantitative cross-sectional survey design will be used to collect data via an online survey. No directly identifying data (name, address, or birthdate) will be collected; however, indirectly identifying data such as partial medical history and age in years will be collected. Hence, parts of the data will not be available for inclusion in the public repository. Age will be presented as a range, and medical history data will be excluded.

A recruitment flow diagram is presented in Figure 1. Recruitment will be undertaken by sending emails to a general information mailing list of approximately 650 members, of whom approximately 72% are female, who are targeted as regular UM events visitors. A second list of women who participated in UM-run women's workshops (approximately 350 members with substantial overlap to the first email list) will also be used. In addition, visitors to several UM events will be given flyers with the same introductions given in the email circulars. These three methods are expected to reach over 90% of the target population. The same recruitment strategies used in previous surveys led to 482 and 393 respondents, representing 89% and 94% completion rates. The availability of the survey is to be approximately 7 weeks.

Figure 1. Recruitment flow diagram.



Preliminary Focus Groups

As a starting point in developing the survey for the proposed study, two of the researchers (CS and VM) created three focus groups: (1) women in menses, (2) peri-menopausal women, and (3) menopausal women. Each group met four or five times via audio conferencing. The 15 participants were aged 18-72 years and were from Australia, the United Kingdom, Germany, and New Zealand. The education level of these women ranged from school-leaver to PhD and included a registered nurse, midwife and physiotherapist, an unregistered health practitioner, an exercise physiologist, and a university lecturer. Two members had a PhD. All 15 participants tested later versions of the survey.

Two menstrual attitude questionnaires [38,39] were investigated for possible use, but the tone of these questionnaires implies that menstrual health issues are problems to be minimized or avoided. This perspective did not agree with the experience of the women in the focus groups, who considered menstrual health issues useful, and thought that supportive signals from the body should be heeded; therefore, at the women's suggestion, we decided to create a new questionnaire.

Focus group members read through the two existing menstrual attitude questionnaires and worked with the researchers to develop further questions based on recommendations from the researchers. Questions that achieved consensus were taken into the first draft and offered to the other focus groups as suggested questions for their part of the survey. This process was then

repeated through 4 or 5 meetings, until the questions became stable. There was substantial overlap in questions among the three groups because, according to the focus groups, even women in their earlier menopausal years still have reproductive health issues. The developed questionnaire included objective items regarding physical and mental health symptoms and actions taken, and the participants' attitudes toward their female health issues.

All three focus groups worked cooperatively to offer their opinions on which of the ALSWH questions to adopt to keep the survey to an acceptable length, while including as many ALSWH questions as possible. The focus was on questions that the researchers felt would yield the most relevant information about the respondents. One difficult issue was food, because the ALSWH questions are lengthy and were deemed not very relevant to the UM-affiliated respondents (eg, few UM respondents eat potatoes). Therefore, a short question about food items and their frequency of use and a question about current alcohol consumption were added. The focus group participants stated that they were in various stages of reducing their caffeine, added sugar, salty food, dairy, and alcohol consumption. The food question is designed to elicit which stage of reduction each participant is undertaking, if any. The question was adopted from a smaller biostatistics student project survey that had been developed with respondent feedback, so the food question was clearly understood by focus group members.

Survey Development and Administration

This study emphasizes women's health, and the survey will only be distributed to female UM respondents, who constitute over 70% of the UM population. The survey is comprised of two parts: (1) the newly developed menstrual attitudes questionnaire; and (2) the selection of questions commonly used in the ALSWH [40], to enable comparisons of the UM respondents to the ALSWH population.

The survey will be completed online using the *survs.com* survey platform [41]. Issues of a personal or sensitive nature are regularly and openly discussed at UM events, although anyone who opts out of any discussion is fully supported. To maintain this spirit of support, the survey was designed so that a respondent can skip any question that she does not wish to answer. The consent form at the beginning of the survey also makes it clear that the survey can be terminated at any time.

The ALSWH was chosen for comparison purposes with Australian women, as the estimated mean age of UM participants is the late 40s, and one of the ALSWH cohorts had their first particularly voluminous survey done in 1996, when the cohort's ages ranged from 45-50 years. The second survey (in the 1998 ALSWH cohort) then filled in a number of gaps so that it was possible to extract the bulk of the comparative questions from those two surveys.

The Respondent Population

The respondent population is approximately 500-600 women who, as users of complementary medical services, may have had a similar profile to women who use alternative practitioners (ie, more likely to be middle-aged, have poorer health, and a higher usage of conventional medicine) [42]. On the basis of some researchers' observations and informal surveys, the population's average age is now in the high 40s, they have lost substantial weight since joining UM activities, and may have higher than average levels of vitality.

Final Composition of the Study Survey

After consultation with the focus groups, it was decided that all participants would answer the same selection of questions from the ALSWH, plus the newly developed question about food. Early versions of the survey were completed by individual members of the focus groups, and their feedback was incorporated into the survey. When the survey was nearing its final version, 10 of the focus group members completed it, and their feedback was also taken into account.

The first section of the survey asks for consent and confirms that the respondent is at least 18 years of age. Respondents are also asked about the date of their first UM event and their overall level of participation in UM. This section comprises 4 items. A major part of the survey for the proposed study is the SF-36 [36] questionnaire, which is also part of the ALSWH. The SF-36 is used to assess parameters of physical and mental health. In the proposed study, all items of the SF-36 will be used. Further ALSWH-employed scales used in the survey are questions from the Center for Epidemiologic Studies Depression Scale [43,44], Perceived Control Scale [45], Kessler Psychological Distress Scale [46], and the Multi-Item Summed Score for Perceived Stress [47].

On the menstrual attitudes section of the survey, menopausal women answer 42 questions, peri-menopausal women answer 54 questions, and women in menses answer 48 questions. Those who have never had any periods are invited to answer the menopausal women's questions. Women self-select into the group that they think best fits their situation; however, if after choosing a group, they find that the questions do not appear to apply to them, they can back out of the survey and choose a different group.

The first set of questions consists of a list of symptoms with a response scale including *Yes*, *definitely/Yes*, *sometimes/No*, *not much/No*, and *not at all*, which is the same as that in the widely used Women's Health Questionnaire [48]. This response scale was adopted after several more complicated response schemes were tried and discarded to reduce satisficing [49]. The survey contains 24, 26, and 26 menopausal, peri-menopausal, and menses symptom questions, respectively (of which 13 are common to all three groups). The survey also contains 24, 29, and 16 menstrual attitude questions, respectively (of which one is common to all three groups and seven are common to menopausal and peri-menopausal groups). The attitude questions use a 5-point Likert-type response scale ranging from "strongly disagree" to "strongly agree". Multimedia Appendix 1 presents the derivations of the questionnaire items. A copy of the survey is provided in Multimedia Appendix 2.

The members of the focus group who tested the survey took approximately 75 minutes to complete it, but did not feel that this was excessive. The survey is similar in length to the ALSWH full surveys that are held once every 3 years. To make

this study's survey questions more comparable with those on the ALSWH, wherever possible the former have retained precisely the same wording as the latter, so the responses can be evaluated using the tools adopted by ALSWH-associated researchers [50].

At the time of publication of this protocol, data collection has been completed.

Results

Menstrual Attitudes Questionnaire

The validity and reliability of the developed questionnaire will be assessed using Cohen's kappa [51-53]. Factor analyses for the questions common to all respondents will be used to ascertain the underlying factors for symptom questions. If the number of respondents is sufficient, the same will be attempted for the attitude questions and symptoms questions that are not common to all three menstrual statuses [54,55]. These preliminary validation steps may support the development of a draft menstrual attitudes questionnaire that can then undergo a full process of validation.

Summary Analysis

Key indicators of health and comparisons of those indicators to ALSWH statistics (where available) that this survey aims to measure are: (1) SF-36 physical and mental health scores; (2) BMI; (3) symptoms experienced over the previous 12 months; (4) consumption of alcohol, tobacco, sugar, salt, caffeine, and dairy; and (5) prevalence and levels of depression, stress, distress, and perceived control, as measured by standard scales.

Comparative and Detailed Analyses

Comparisons between UM participants and ALSWH respondents are planned, using both simple comparisons and comparisons weighted or normalized by age, education, and interest in alternative treatments (to increase comparability).

Regression analyses will be performed to determine whether SF-36 scores or BMI are associated with: (1) UM-related variables (length of UM participation, number of UM events); (2) demographic variables (age, age of menopause, age of menarche, education history); (3) menstruation-related attitudes and symptoms; (4) frequency of health-related symptoms; (5) major health events experienced; (6) alcohol and tobacco consumption; (7) sugar, salt, dairy, and caffeine consumption; (8) frequency of medical and other health practitioner visits; or (9) scores on other standardized scales (depression, perceived control, psychological distress, perceived stress), all of which are derived from the questions taken from the ALSWH questionnaires.

The expected sample sizes are relatively small (200-400 respondents per item, given that all items are optional), so any odds ratios and regression coefficients will be considered significant if their 95% confidence intervals exclude 1.0 (for odds ratios) or 0.0 (for regression coefficients).

Discussion

An important issue is that this is the first attempt to collect scientific evidence about UM participants, and it is not even known whether the UM participants are more or less healthy (or both in different areas of health) than the general population. This survey will attempt to collect data to establish whether this group of people warrants further investigation. If the group is worth investigating scientifically, the survey could generate data that will allow the first steps of comparative effectiveness research [56,57] by testing for associations between health outcomes and other variables. A longitudinal study could then establish the sequence of events that lead to any associations. If these women do not spend substantially higher sums on health care than the general population but are markedly healthier, then this may be a pointer to insights that improve health care economics [58].

We have chosen to construct a survey that attempts to determine whether this group of women actually does experience exceptionally good health and, as a second step, to ascertain whether there are any connections between the attitudes of these women regarding women's menstrual health issues and any aspects of their health status. The World Health Organization states that the focus on biological health for women in medical research led to a neglect of mental health research, with numerous negative consequences for the state of scientific knowledge [59]. This survey, with its coverage of physical and mental health and attitudes towards health, may allow research to see how these three areas relate to each other in this group of women.

Issues with the SF-36 Instrument

The scoring instructions used by the ALSWH for the SF-36 will be employed [60]. The SF-36 physical and mental health summary scores are normalized to a mean of 50 and a standard deviation of 10. However, giving perfect answers to every question leads to a physical score on this questionnaire of only 56.5, and a mental score of only 62.5 (for this mental score one would, for example, need to tick *none of the time* in response to, "How often during the past four weeks did you feel tired?").

A further SF-36 scoring feature is that to some extent, mental and physical health scores are mutually inhibiting. Physical health items are added as a negative score to the mental health score and mental health items are added as a negative score to the physical health score. This means that achievement of mental scores above 62.5 is only possible for people with less than perfect physical health and vice versa. The best theoretically possible mental health score can only be achieved by a person with very bad physical health and vice versa. This may affect the usefulness of the SF-36 if many respondents actually have a high level of both physical and mental health. One question is whether there will be a ceiling effect, with many scores near the surprisingly low upper limits of the SF-36.

The dose-response approach proposed here uses length of association and number of events or visits as the estimator of the UM *dose*. If results of the proposed study suggest that this group is worth investigating further, then in a longitudinal study,

UM participants could be surveyed–perhaps in combination with objective health measures–at or near the beginning of their association with UM, and at designated follow-up intervals.

Conclusions

If the surveyed women's health is substantially better that the ALSWH cohort, if they are easily able to maintain that improved health, and if any of their practices can be translated in part or in whole to the general population, then investigating these women may be very valuable for obtaining insights into improving health and quality of life, and reducing the cost of health care in the general population.

Ethics, Consent, and Permissions

Ethical approval CS23062015 was given by the School of Public Health Research Ethics Committee on June 23, 2015. The first question on the survey will obtain informed consent from all participants: "Do you give your consent to participate in this research survey?", with response options, "Yes, I consent to participate in this survey" and, "No, I do not give consent." Unless the respondent explicitly chooses *Yes*, the survey concludes at that moment.

Availability of Data and Materials

Deidentified data will be made available. Such data will not include potential identifiers, as outlined in, "Preparing raw clinical data for publication: guidance for journal editors, authors, and peer reviewers" [61]. Specifically, this means that age (which will be categorized into intervals), lists of medical procedures undergone, and lists of major illnesses will be excluded. The data will most likely be stored with the Open Science Framework [62].

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Authors' Contributions

CS and VM convened and ran the focus groups. CS wrote the majority of the paper. EJM and JK helped write the paper. JK was a member of the focus groups. All authors read and approved the final manuscript.

Conflicts of Interest

All four authors have varying degrees of association with Universal Medicine and are currently members of the Esoteric Practitioners' Association (EPA) which is the body regulating practitioners who are qualified to practice Universal Medicine modalities.

Universal Medicine has a focus on complementary-to-medicine practices, that aim to support and augment medical treatments.

Jane Keep has attended Universal Medicine workshops since October 2003. Jane Keep was a director of Universal Medicine UK until 2013. She is a member of the EPA, and a committee member of the EPA, and has been accredited by the EPA to offer Esoteric Healing Modalities since 2010. From 2009-2012 Jane ran a small clinic in England which offered Universal Medicine healing modalities. Since 2012 Jane has been working in corporates/universities/hospitals and occasionally offered paid private Esoteric Healing sessions, though since 2014 she has offered no paid private Esoteric Healing sessions. She was a contributor to Unimed Living 2013 – 2016. Jane has a PhD which referenced the work of over 300 people including Serge Benhayon.

Eunice Minford is a Consultant General Surgeon, and has trained as an Interfaith Minister and Spiritual Counsellor. She also attended the National University of Ireland and obtained a degree of "Master of Applied Christian Spirituality" studying Sacred Esoteric Healing in her thesis. Eunice is also editor of the website "Medicine and Serge Benhayon" and a contributor to that website and to the "Unimed Living" website. She has her own blog "The Soulful Doctor" where she discusses, et al, Universal Medicine. She is also on the EPA professional committee as well as a medical advisor to, and the International Patron of, the EPA. She is a trained esoteric healing practitioner and provides occasional private sessions.

Christoph Schnelle is a financial adviser and has some Universal Medicine associated persons among his client base. Christoph is currently working towards his PhD with The University of Queensland, the subject of which is two randomised controlled trials of Esoteric Connective Tissue Therapy (a Universal Medicine modality) on chronic low back pain and has accumulated case studies as part of this project. Christoph Schnelle's wife, Nicola Lessing, is involved in voluntary activities around producing content for "Unimed Living" and other websites. Nicola is company secretary of Unimed Living and does this in an honorary capacity. She is not a director or shareholder of Unimed Living. She is not employed by Universal Medicine or Unimed Living and does not receive any financial incentives from Universal Medicine or Unimed Living.

Vanessa McHardy is involved in voluntary activities around producing content for "Unimed Living", presenting at a conference on Psychological Well Being in 2013 on the Gold Coast of Australia. She has no other involvement other than what is set out below.

All four authors have experienced substantial health benefits since they started visiting Universal Medicine events. They all have published blogs on Universal Medicine associated websites and all four have commented on other blogs published on those websites.

All four have no financial ties and have received no money from Universal Medicine or its related entities including no reimbursements of expenses. Each one attends more than 10 Universal Medicine events a year and regularly receive treatments from Universal Medicine accredited practitioners.

Multimedia Appendix 1

ALSWH scales to which UM participants respond, and the instruments from which the questions were derived.

[PDF File (Adobe PDF File), 55KB - resprot_v6i11e234_app1.pdf]

Multimedia Appendix 2

Women in Livingness Survey.

[PDF File (Adobe PDF File), 2MB - resprot_v6i11e234_app2.pdf]

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Abbreviations

ALSWH: Australian Longitudinal Study of Women's Health
BMI: body mass index
SF-36: Short Form 36
UM: Universal Medicine

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Protocol

The Effect of Aging on Physical Performance Among Elderly Manual Workers: Protocol of a Cross-Sectional Study

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Abstract

Background: In 2012, the Danish Parliament decided to increase retirement age. Unfortunately, elderly people working in a physically demanding environment may be rendered unable to retain the ability to adequately perform the physical requirements of their jobs, due to age-related decreases in physical performance. Therefore, increasing the retirement age may not necessarily lead to the goal of keeping everybody in the labor market for a longer time. To date, our knowledge about the variations in physical performance of the elderly workforce is limited.

Objective: In this cross-sectional study we seek to investigate the effects of aging on physical performance among elderly manual workers.

Methods: Approximately 100 Danish manual workers between 50 and 70 years of age will be recruited. The main measurement outcomes include: (1) inflammatory status from blood samples; (2) body composition; (3) lung function; (4) static and dynamic balance; (5) reaction time, precision, and movement variability during a hammering task; (6) handgrip strength, rate of force development, and force tracking; (7) estimated maximal rate of oxygen consumption; and (8) back mobility. Additionally, information regarding working conditions, physical activity levels, and health status will be assessed with a questionnaire.

Results: Data collection is expected to take place between autumn 2017 and spring 2018.

Conclusions: This study will increase the knowledge regarding variations in physical performance in the elderly workforce and may identify potential workplace hazards. Moreover, this study might shed light on the potentially problematic decision to increase retirement age for all Danish citizens.

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KEYWORDS

older workers; functional capacity; spirometry; inflammation; body composition; balance; force tracking

Introduction

It is expected that the world's proportion of elderly people above the age of 60 years will almost double within the next 35 years [1]. At this time, approximately one fourth of the Danish population is above the age of 65 years [2]. Due to a longer life expectancy than seen in the past, in 2012 the Danish Parliament decided to increase retirement age [3], thereby increasing the number of elderly workers. In practice, this means that individuals born after 1966 can expect to be at least 69 years old at the time of retirement. The increased life expectancy was one of the central arguments; however, this may be problematic as increased lifespan is caused by other factors than delayed onset of the aging processes, such as healthier nutrition, better living standards and education, and public-health efforts [4]. Hence, elderly people working in a physically demanding

environment (eg, building and constructions sites) may be rendered unable to retain the ability to adequately perform the physical requirements of their jobs, due to age-related decreases in physical performance. In healthy elderly people, increased longevity may lead to a postponed retirement age, but that is far from certain for people with chronic conditions such as osteoarthritis and osteoporosis. Therefore, increasing the retirement age may not necessarily lead to the goal of keeping everybody in the labor market for a longer time [5]. Knowledge about the variations in physical performance of the elderly workforce when physically challenged is limited [6-8]. Accordingly, the effects of an increased retirement age among elderly manual workers are difficult to predict.

Aging is associated with a gradual loss of muscle mass, strength, and power [9-11], in addition to reductions in maximal rate of oxygen consumption (VO_{2max}) [12], lung capacity [13,14], and impairment of postural control [15]. Reductions in VO_{2max} have been observed to be approximately 10% per decade after the age of 30 (a process which seems to accelerate further after the age of 70 [16-18]), whereas forced expiratory volume in 1 second (FEV_1) declines approximately 20 mL annually from the age of 25 years [19]. This annual decline increases to 38 mL after the age of 65 years [14], which means that on average a person at the age of 70 has lost 1 L in FEV_1 over the preceding 45 years. Concomitant to these changes, forced vital capacity (FVC) is reduced at a slightly slower speed [19]. Furthermore, the age-related reductions in muscle strength affects both inspiratory and expiratory muscles [20], possibly inhibiting ventilation during physical activity.

Contrary to the age-related loss of respiratory capacity, skeletal muscle strength is relatively well preserved until the age of 50 years. From this age, the annual decline in strength is approximately 1-2%, whereas muscle power is lost at an even faster rate [11,21]. Regarding rate of force development (RFD), a previous study demonstrated that a significant loss of rapid force capacity would be evident after the fifth decade, while loss of maximal strength would be more pronounced after the sixth decade of life [22]. Some authors argue that RFD is of more functional significance in elderly people compared to maximal strength because rapid force production is more related to tasks such as postural control and grabbing a rail to regain balance and prevent falls [23]. Conversely, daily activities that involve the manipulation of objects rarely require maximal force or explosive force, but rely mostly on submaximal force production. Hence, measurements of submaximal force production in both static and dynamic conditions (eg, force tracking) may provide additional information about force steadiness and coordination [24], which is needed during activities of daily living at work and during leisure.

Sarcopenia, also known as the age-related loss of muscle mass, typically starts from the end of the fifth decade of life [9,25], and may sometimes be accompanied by an increase in fat mass [26]. Thus, body mass may remain somewhat stable in the elderly [27]; however, a negative change in body composition may have detrimental consequences [28]. Given that people with physically demanding occupations are required to be physically active throughout a workday, a decrease in muscle mass together with an increase in fat mass would be especially problematic in this population. Another challenge for elderly individuals is that comorbidity (ie, having more than one chronic condition) increases with age [29]. Additionally, some conditions may interact, thereby exacerbating the negative impact of a disease on quality of life and work ability. For instance, chronic obstructive pulmonary disease is usually accompanied by skeletal muscle weakness, musculoskeletal disorders, osteoporosis, and chronic inflammation [30,31]. Moreover, the prevalence of hip and knee osteoarthritis increases with age, while physically demanding work may accelerate the development of this pathology [32]. Several risk factors have been proposed to explain this interaction, including age and physical inactivity. The exact pathogenesis contributing to these comorbidities, together with the treatment strategies, are not clearly established. Interestingly, systemic inflammation, which is typically elevated in patients with chronic obstructive pulmonary disease, is not only associated with an age-related decline in lung function [33], but is also negatively associated with muscle mass in elderly people [34]. These findings call for research initiatives assessing both the respiratory and the musculoskeletal system in relation to occupational exposures, and other risk factors such as body composition and inflammatory status.

Balance is typically compromised in elderly people. Although postural control is largely related to muscle strength and the ability to produce rapid force, it also requires an integration of the information from the visual, vestibular, and somatosensory systems to generate the appropriate motor response to maintain static and dynamic balance [15,35]. Thus, a combination of the alterations in the musculoskeletal system and the afferent information from sensory systems are responsible for the reduced ability to maintain motor coordination (including balance) among the elderly [35]. Paradoxically, although visual acuity is progressively compromised with increasing age, the reliance on the visual system to maintain postural control increases with age, especially when balance is challenged [35]. These changes may therefore result in impairments in physical performance and, as a result, the ability to sustain the required level of efficiency in a physically demanding job. Hence, the physiological changes in relation to aging may challenge the ability of elderly manual workers to maintain an adequate level of performance in their workplace. Moreover, these changes may result in elderly manual workers working closer to their maximal capacity on a daily basis, which may result in an increased risk of developing musculoskeletal disorders [36,37].

To date, we know too little about how physically demanding work affects physical performance and how declining physical performance affects the ability to perform physically demanding work in elderly populations. Specifically, more information is needed about how different work exposures, health statuses, and physical activity levels relate to different measures of physical performance. Although some of the reductions in physical performance might begin as early as the third decade of life, the most pronounced impairments occur starting from the fifth decade. Thus, information regarding the variations in physical performance among elderly manual workers in the last two decades of working life is of importance, so that

recommendations related to their work environment can be made. Lastly, chronological age (ie, time since birth) may well be an important risk factor for several adverse outcomes; however, all people age differently. The term *biological age* has been used to describe a person's health status, thereby giving a better prediction of physical capacity later in life than chronological age [38]. Although a single marker of biological age has not been discovered, a combination of several putative biomarkers (including handgrip strength, standing balance, muscle mass, inflammatory status, and lung function) have been suggested to create a model for determining biological age [39,40]. Hence, the present study will enable us to not only investigate the effect of chronological age on physical performance, but may also give insight into the biological age of elderly manual workers.

The present paper describes the study protocol for a study that aims to investigate variations in physical performance among elderly Danish manual workers aged 50 to 70 years. Our primary outcomes include handgrip strength, FEV_1, and FVC. Secondary outcomes include force steadiness, reaction time, aerobic capacity, motor coordination, balance, body composition, back mobility, and inflammatory status. Tertiary outcomes are self-reported levels of physical activity, health status, and different work exposures. This is the first study to combine measurements of respiratory and musculoskeletal systems in elderly manual workers, and the collected data will therefore increase our knowledge regarding the elderly workforce. The main research questions in the study are:

1. To what extent does physical performance change in elderly manual workers with physically demanding occupations during the last two decades of working life?
2. To what extents do work environment and physical activity levels predict respiratory and musculoskeletal function in elderly manual workers?

Based on the available literature, we hypothesize that physical performance is negatively associated with age, and that physical work magnifies this negative relationship when compared to the general population. Thus, we expect work environment and physical activity to be predictive of respiratory and musculoskeletal function in this cohort.

Methods

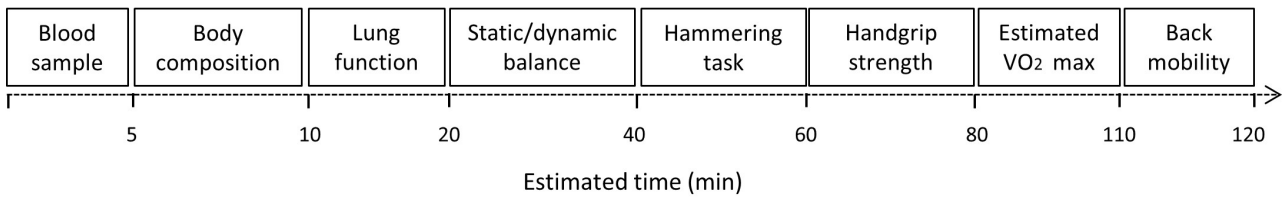
Study Design

The present study is a cross-sectional investigation which explores the variations in physical performance in elderly (aged 50-70 years) Danish manual workers working in a physically demanding trade. Data collection is expected to take place between autumn 2017 and spring 2018. All tests will be conducted in a research laboratory at Aalborg University, Denmark. Each experimental session is expected to last for approximately 2 hours. The order in which the tests will be conducted is the following: (1) inflammatory status will be measured from venous blood samples; (2) anthropometrics (ie, height, weight) and blood pressure will be measured, followed by an estimation of body composition based on bioelectrical impedance analysis (BIA); (3) lung function will be measured using spirometry; (4) static and dynamic balance will be measured on a force platform during quiet standing and a sit-to-stand motion; (5) reaction time, precision, and movement variability will be measured during a hammering task; (6) handgrip strength, RFD, and force tracking will be measured with a hand dynamometer; (7) estimated VO_{2max} will be measured on a bicycle ergometer; and (8) back mobility (Figure 1).

Recruitment of Participants

We aim to include approximately 100 manual workers aged 50-70 years. The study subjects will be recruited from a questionnaire sent out to more than 5000 Danish manual workers as a part of the ALdring og Fysisk Arbejde cohort (ALFA; Aging and Physical Work), which was created from a register-based cohort of all manual workers in Denmark aged 39 years and older in 1999 (n=155,358). Briefly, the questionnaire included 86 items, mostly regarding work and working conditions, but also 23 items regarding health. Lastly, the questionnaire included a question asking if the subject would like to participate in a clinical study of physical performance. Those who respond in the affirmative to this question will be contacted via email. The selection will aim to ensure representability over the age range by recruiting in bins of 5 years from 50 to 70 years. Subjects with musculoskeletal disorders, osteoarthritis, cardiovascular disease, or any other health condition that contradicts physical testing will be excluded from tests they cannot safely perform. Hence, hypertensive subjects will not complete the cycling test, whereas subjects with severe shoulder pain will not complete the hammering test. All participants will be informed about the purpose of the study and will give written informed consent to participate in the clinical examination. The study will be carried out in accordance to the Helsinki declaration and is approved by the ethics committee of region North Jutland (N-20160023).

Figure 1. Test order and estimated time.



Measurements

Biochemistry

Blood will be drawn from the antecubital vein into 6 mL ethylenediamine tetraacetic acid tubes followed by centrifugation and extraction of plasma. Plasma will be used for high sensitivity analysis of C-reactive protein with a latex particle-enhanced immunoturbidimetric assay, and interleukin-6 will be analyzed by an enzyme linked immunosorbent assay.

Bioelectrical Impedance Analysis

Body composition will be estimated using a direct segmental multi-frequency bioelectrical impedance machine (InBody 370, Biospace). The apparatus uses three frequencies (5, 50, and 250 kHz) at five body segments (right arm, left arm, trunk, right leg, and left leg), with a test duration of approximately 45 seconds. The main measurement outcomes include fat-free mass, fat mass, and percent body fat. Although not recognized as the *gold standard* for estimation of body composition, BIA is widely used in large cohort-based and cross-sectional studies [41] due to its low cost and noninvasive technique. Several studies have found direct segmental multi-frequency BIA to be a valid tool for assessment of body composition in both young and older men and women [42,43].

Spirometry

Basal lung function will be measured using a Spirobank II SMART (Medical International Research [MIR], Rome, Italy) spirometer, disposable MIR turbine flowmeters, and MIR winspiroPRO software (version 6.5.0). The main outcomes include FEV_1, FVC, and peak expiratory flow, which will be conducted as recommended by The European Respiratory Society [44] and The American Thoracic Society [45] standards. Briefly, from a standing position the subjects will be asked to inhale fully, place the spirometer in their mouth, immediately (<1 second) followed by a forced maximal expiration, which is ended when they are unable to expire more air, or after at least 6 seconds. A nose clip will be worn during the testing. The subjects will be asked to avoid pursing their lips, closing their teeth around the spirometer, or letting any air leak between their lips and the mouthpiece during the expiration. Each subject will perform a minimum of three trials and a maximum of eight trials until at least three satisfactory trials have been performed, and the difference between the highest and the second highest FVC or FEV_1 is no more than 150 mL [44]. The spirometer will be calibrated daily using a 3 L calibrated airtight syringe.

Static and Dynamic Balance

Static and dynamic balance will be measured during quiet standing and during a sit-to-stand motion on a force platform (AMTI AccuSway, Watertown, MA, USA). Static balance will be assessed during three conditions: first during quiet standing with eyes open; second during quiet standing with eyes closed; and third during quiet standing with eyes open, while counting backwards from 30 in multiples of three (ie, 30, 27, 24, and so on) to increase cognitive load. In each of the above-mentioned conditions the subjects will be asked to stand for 1 minute, which will be repeated three times for each condition, and they will be instructed to stand as quietly as possible [46]. Dynamic balance will be assessed with the subjects completing a sit-to-stand motion from a chair with five rises as fast as possible. This sit-to-stand test is a part of the short physical performance battery and is used to assess lower extremity function [47]. Spatial-temporal changes in displacement of the center of pressure (CoP) will be computed in the anterior-posterior and medial-lateral directions. Additionally, the standard deviation and sample entropy of the CoP will be computed, as described previously [48].

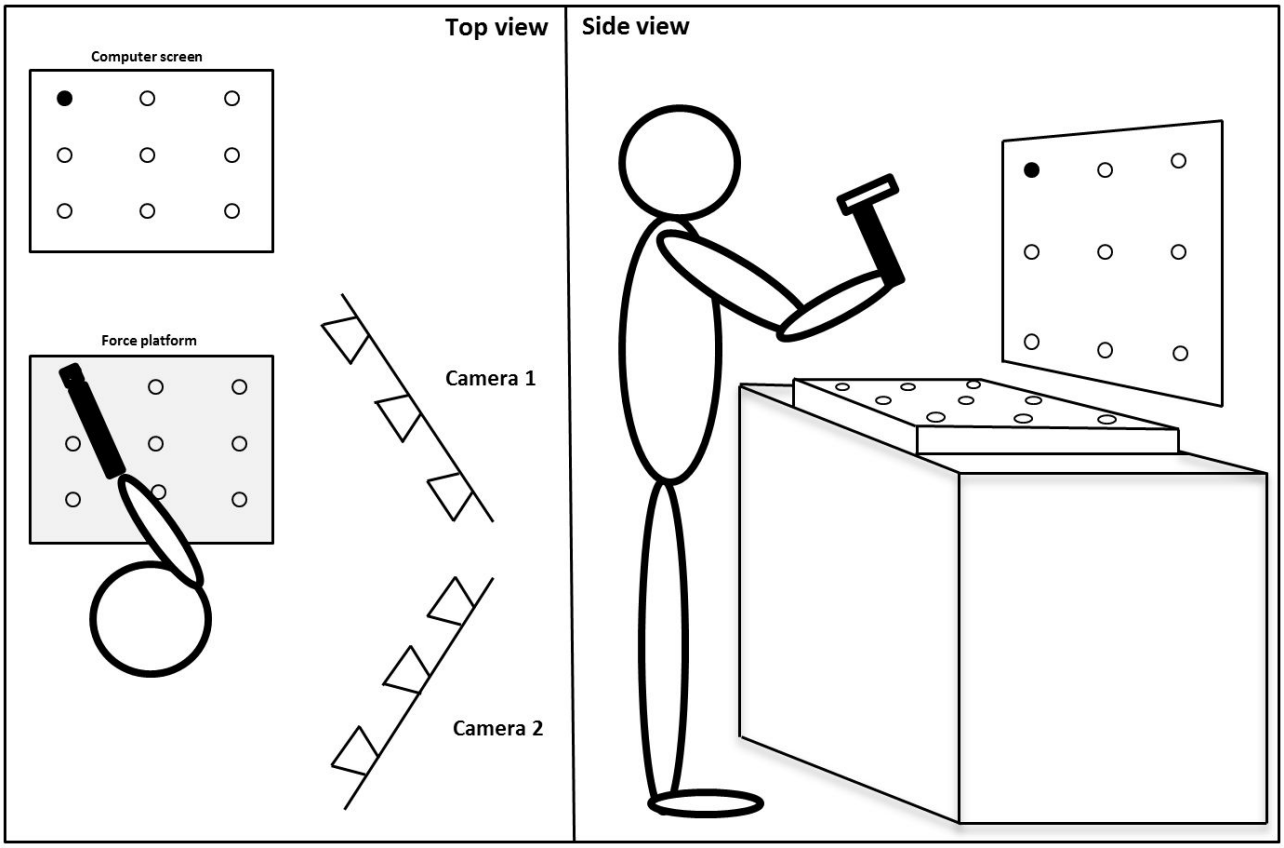
Hammering Task

Reaction time, precision, and movement variability will be measured using a force platform (AMTI AccuSway, Watertown, MA, USA), a computer screen for visualization, and a rubber hammer (Figure 2). From a standing position, subjects will be instructed to hammer as fast and precisely as possible on the correct mark on the force platform, as visualized on the computer screen. The program will be set to randomly (and with equal probability) indicate one out of nine marks at 1-second intervals. Active markers will be attached to the hammer and the dominant arm. The hammering motion will tracked by the Visualeyez II system set up with two VZ4000 trackers (Phoenix Technologies Inc., BC, Canada) and sampled at 100 Hz. The movement will then be decomposed in three dimensions using Euler angles. All recordings will be synchronized by the end of frame pulse generated by the motion capture system indicating the first frame of the recordings. Movement amplitude and variability will be computed, as described previously [49].

Handgrip Strength

Maximal handgrip strength, RFD, and force tracking will be measured using a digital hand dynamometer (Model G100, Biometrics Ltd, Gwent, UK). The subjects will be seated in a chair with their lower arms resting on an armchair (90-degree angle in the elbow) while holding the dynamometer. The test begins with the subjects generating their maximal force onto the dynamometer and ends when the force starts to decline. Three trials will be performed using the dominant hand. Thereafter, the subjects will perform an endurance trial using their dominant hand, in which they are asked to exert 20% of their maximal force until task failure, which is defined as an inability to maintain the output force within 2% of maximal force around the set value. Maximal grip strength (measured as peak force in Newtons) and RFD (measured as the rate of force rise [change in peak force/change in time] in Newtons per second) will be calculated during the maximal contractions, whereas the standard deviation (absolute variability), coefficient of variation (relative variability), and the sample entropy (structural variability) of the force signal will be computed during the submaximal trial, as described previously [50]. Measurement of handgrip strength has previously been shown to be a reliable measure of strength in the upper extremities [51] and low levels of handgrip strength are reported to be a strong predictor of disability and mortality, and a marker of sarcopenia [52,53].

Figure 2. Illustration of experimental set-up during the hammering task.



Estimated Maximal Rate of Oxygen Consumption

The estimated VO_{2max} test will be conducted using a bicycle ergometer (Monark AB, Varberg, Sweden) and a Polar A300 heart rate monitor (Polar Electro Oy). Instructions will be given, as recommended by the Danish Health Authority [54]. Briefly, the cycle ergometer will be adjusted to the individual subject, followed by an 8-minute warm-up on a low resistance (measured in Watts) that increases the subject's heart rate approximately 20 beats/minute from resting levels. The resistance will then be increased to a level that raises the heart rate of the subject to somewhere between 130-160 beats/minute. Heart rate will be registered every 30 seconds and the test will be terminated when the heart rate has been stable for at least 2 minutes. The criterion for a stable heart rate is less than 4 beats/minute change, as measured every 30 seconds for 2 minutes, and the test will continue until this criterion is met. The average heart rate across the four last measures, together with the selected ergometer resistance, will be used to estimate VO_{2max} using the Åstrand nomogram and linear extrapolation, with correction for gender [55]. This method has shown a high degree of precision [56].

Back Mobility

Back mobility will be measured using the fingertip-to-floor (FTF) test. The FTF test is a reliable measure used to assess forward mobility of the spine and pelvis [57], and it is able to predict changes in disability in patients with lower back pain [58]. The subjects will be standing barefoot on an elevated platform. Keeping their knees fully extended, subjects will bend forward and reach as low as possible with their arms. The vertical distance between the platform and the tip of their middle finger will be noted. This value can be both positive and negative (ie, if their fingers reach below the platform the value will be noted as negative in centimeters) [57].

General Health and Work Ability

The answers to the ALFA questionnaire, which includes questions about general health, work ability, and environment, as well as social and psychological wellbeing, will be used as covariates in this study. To get a current assessment of some of these covariates, a shorter version of the questionnaire will be answered at the time of the clinical examinations. This short questionnaire will include questions about general health, leisure-time physical activity, pain, and work ability (see Multimedia Appendix 1).

Statistics

All continuous data will be tested for normality using the Shapiro-Wilk test. Appropriate data transformation will be applied if normality is not met. Subject characteristics and descriptive results will be presented as means and standard deviations or standard errors, and percent distribution. Associations between age (dependent variable) and the measured outcomes (independent variables) will be analyzed with univariate linear regression models, whereas multivariate linear regression models will be constructed using backwards elimination (with adjustment for gender in both cases). When available, the measured outcomes will also be compared with normative data assessing the general population in this age group. Pearson's Chi-square tests will be used to assess the probability of independency between different self-reported work exposures (eg, work experience, seniority, heavy lifts in

the workplace) and the measured outcomes (made categorical by dividing outcomes into *high* or *low*, based on either available reference values [59] or cluster analysis). In models with categorical variables, odds ratios will be calculated and statistical significance levels will be set *a priori* to $P<.05$.

Sample Size

Our primary outcomes are handgrip strength, FEV_1, and FVC. Based on previous studies, we expect age to be a stronger predictor of handgrip strength compared to FEV_1 or FVC; hence, the latter was used to calculate sample size. Considering three predicators (age, height, smoking) describing the primary outcome (FEV_1 or FVC) variations with a medium average correlation between each of the predictors and the outcome (rho=0.3), and a low average correlation between the predictors (rho=0.1), the sample size was calculated to be 102 subjects in a multiple regression analysis to obtain 5% type I and 20% type II errors [60].

Results

Subjects are currently being contracted via telephone and email. It is expected that data collection will be completed by March 2018.

Discussion

In several jobs, the physical demands for elderly workers are at the same level as for younger workers [37,61,62]. Due to a potential decrease in working capacity, the resulting workload may change from an acceptable load into daily physical *overload*, which might result in negative long-term health effects, such as chronic musculoskeletal symptoms [63,64], work absenteeism, and early pension retirement. Physical overload is often related to the positive adaptive responses of endurance and resistance training. Most studies, however, find no training effect of prolonged exposure to heavy manual labor [65-68]. Therefore, a more detailed understanding of the effects of age on physical performance in elderly manual workers will provide additional knowledge regarding issues related to changes in physical performance, confounding factors (eg, smoking, work environment, health status), and the balance between physical workloads and physical work capacity. Some studies have investigated the effect of age on physical performance among elderly workers; however, these studies have either been restricted by testing relatively young (<60 years) workers [65,67,69,70] or by assessing only a limited number of parameters [68,71]. Therefore, an extensive test-battery with direct measures of respiratory capacity and musculoskeletal function in the oldest of workers, along with health profiles and work exposures, will enable us to identify associations between age and physical performance in this specific population. Moreover, this study might shed light on the potentially problematic decision to increase retirement age.

Strengths and Limitations

The present study is strengthened by the objective and extensive clinical examination of physical performance employed in a relatively understudied group. One of the limitations of this study includes the use of a cross-sectional design. Specifically, cross-sectional studies investigating alterations in physical performance with increasing age tend to find different changes compared to findings in longitudinal studies. Such discrepancies may stem from several issues, including differences in working conditions, environmental factors, and research methodologies [37]. However, the financial and time-saving advantages of cross-sectional studies may be compensatory and should still give insight into areas for future longitudinal investigations. Moreover, establishing this cohort will enable us to conduct follow-up studies in the future. Another limitation may be that the oldest workers recruited for this study represent a highly selected cohort. The “average” elderly manual worker may have already (prematurely) withdrawn from the workforce, thereby leaving only the older workers with the highest physical performance in the labor market. This issue is known as the *healthy worker effect* [72,73], and should be kept in mind when interpreting our findings.

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Authors' Contributions

ØO and PM had the original idea for the study. PM, ØO, AS, JHB, and KLN conceived the study design. ØO, PM, and JHB obtained the funding. KLN, PM, and AS will be responsible for developing the technical measurements and analyzing the results. KLN wrote the draft of the manuscript before all authors read, critically reviewed, and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Questionnaire.

[PDF File (Adobe PDF File), 47KB - resprot_v6i11e226_app1.pdf]

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Abbreviations

ALFA: ALdring og Fysisk Arbejde
BIA: bioelectrical impedance analysis
CoP: center of pressure
FEV1: forced expiratory volume in 1 second
FTF: fingertip-to-floor

FVC: forced vital capacity
MIR: Medical International Research
RFD: rate of force development
VO_{2max}: maximal rate of oxygen consumption

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