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Protocol

The Fetal Growth Restriction at Term Managed by Angiogenic Factors Versus Feto-Maternal Doppler (GRAFD) Trial to Avoid Adverse Perinatal Outcomes: Protocol for a Multicenter, Open-Label, Randomized Controlled Trial

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Abstract

Background: Fetal smallness affects 10% of pregnancies. Small fetuses are at a higher risk of adverse outcomes. Their management using estimated fetal weight and feto-maternal Doppler has a high sensitivity for adverse outcomes; however, more than 60% of fetuses are electively delivered at 37 to 38 weeks. On the other hand, classification using angiogenic factors seems to have a lower false-positive rate. Here, we present a protocol for the Fetal Growth Restriction at Term Managed by Angiogenic Factors Versus Feto-Maternal Doppler (GRAFD) trial, which compares the use of angiogenic factors and Doppler to manage small fetuses at term.

Objective: The primary objective is to demonstrate that classification based on angiogenic factors is not inferior to estimated fetal weight and Doppler at detecting fetuses at risk of adverse perinatal outcomes.

Methods: This is a multicenter, open-label, randomized controlled trial conducted in 20 hospitals across Spain. A total of 1030 singleton pregnancies with an estimated fetal weight ≤10th percentile at 36+0 to 37+6 weeks+days will be recruited and randomly allocated to either the control or the intervention group. In the control group, standard Doppler-based management will be used. In the intervention group, cases with a soluble fms-like tyrosine kinase to placental growth factor ratio ≥38 will be classified as having fetal growth restriction; otherwise, they will be classified as being small for gestational age. In both arms, the fetal growth restriction group will be delivered at ≥37 weeks and the small for gestational age group at ≥40 weeks. We will assess differences between the groups by calculating the relative risk, the absolute difference between incidences, and their 95% CIs.

Results: Recruitment for this study started on September 28, 2020. The study results are expected to be published in peer-reviewed journals and disseminated at international conferences in early 2023.

Conclusions: The angiogenic factor–based protocol may reduce the number of pregnancies classified as having fetal growth restriction without worsening perinatal outcomes. Moreover, reducing the number of unnecessary labor inductions would reduce costs and the risks derived from possible iatrogenic complications. Additionally, fewer inductions would lower the rate of early-term neonates, thus improving neonatal outcomes and potentially reducing long-term infant morbidities.

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KEYWORDS

fetal growth restriction; small for gestational age; PlGF; sFlt-1; Doppler; angiogenic factors

Introduction

Background

Fetal smallness affects around 10% of pregnancies [1]. Small fetuses are at a higher risk of intrauterine death and adverse perinatal outcomes [2]. In order to prevent these adverse outcomes, identification and appropriate management of small fetuses are crucial [3,4]. Based on gestational age (<32 weeks of gestation versus ≥32 weeks of gestation) at the time of disease onset, 2 distinct patterns of severity are observed in small fetuses, with the more severe cases being those with onset early in pregnancy (<32 weeks of gestation) [5]. In these cases, management is mainly based on fetal Doppler and indications for delivery are quite consistent [2], generally resulting in preterm neonates. However, most cases are diagnosed at a later gestational age (≥32 weeks) and, in this particular context, there is no clear consensus on the appropriate interventions to prevent adverse perinatal outcomes [6-8].

Moreover, the severity of fetal smallness is usually classified into 2 categories: fetal growth restriction (FGR), which is defined as a fetus failing to reach its genetically predetermined growth potential, and small for gestational age (SGA), which is defined as a fetus being small but without an increased risk of adverse perinatal outcomes. SGA fetuses are commonly referred to as constitutionally small fetuses [1,8]. Several criteria based on Doppler studies, growth velocity, and biometric percentiles are available to discriminate between SGA and FGR fetuses [2,8,9]. One of the most widely used classifications, as well as the one used in most maternity wards in Spain, is the one proposed by Figueras and Gratacós [8]. This classification, based on estimated fetal weight (EFW) and feto-maternal Doppler, allows the identification of the subset of small fetuses at a greater risk of perinatal complications (ie, true FGR fetuses) and the subset of small fetuses with a risk of perinatal complications similar to that of a normally growing fetus (ie, constitutionally small or SGA fetuses). According to several guidelines, FGR fetuses may benefit from early-term elective delivery (at 37-38 weeks), while SGA fetuses require closer

monitoring, but not elective delivery until full term (39-40 weeks). FGR/SGA classification based on Doppler and EFW percentiles has a high sensitivity for adverse perinatal outcomes; nevertheless, more than 60% of fetuses with an EFW below the 10th percentile are classified as FGR and, therefore, will be delivered at 37 to 38 weeks [8]. Neonates delivered at 37+0 to 38+6 weeks+days of gestation are considered early-term and have poorer neonatal outcomes than full-term neonates (≥39 weeks of gestation) [10-12]. For this reason, early-term elective delivery should be restricted to FGR fetuses at an actual risk for adverse outcomes.

Placental Insufficiency and SGA/FGR

The precise pathophysiology of SGA/FGR is unknown, but placental insufficiency is a common finding [13,14]. Several studies have reported histopathological findings related to placental malperfusion in SGA and FGR pregnancies [15,16]. The severity of the underlying placental insufficiency can be assessed by Doppler of the feto-maternal circulation [15,17]. Some studies have also shown an association between placental findings consistent with maternal vascular malperfusion and angiogenic imbalance involving a decrease of placental growth factor (PlGF), a proangiogenic factor, and an increase in soluble fms-like tyrosine kinase-1 (sFlt-1), an antiangiogenic factor, resulting in an increased sFlt-1/PlGF ratio [18-20].

Management of SGA/FGR Pregnancies: EFW

As is widely known, there is an inversely proportional relationship between EFW and the risk of adverse perinatal outcomes [21-23]. For this reason, in DIGITAT (Disproportionate Intrauterine Growth Intervention Trial At Term), the only clinical trial ever conducted to evaluate the role of early-term elective delivery in improving perinatal outcomes of small fetuses, the only inclusion criterion was an EFW below the 10th percentile [24]. In that study, fetuses with an EFW below the 10th percentile were randomized into two groups: (1) early-term induction of labor and (2) expectant management until the onset of spontaneous labor. Perinatal outcomes were compared between the groups, showing that systematic early-term labor induction in pregnancies with small fetuses did not improve perinatal outcomes. By contrast, there was a significant increase in the number of admissions to the neonatal intensive care unit (NICU) and intermediate care unit for early-term neonates (51.1%) as compared to full-term neonates (39.8%). Since no differences were found in the baseline characteristics of the groups at enrollment, it is fair to assume that this 11.3% difference in neonatal admissions was mainly due to differences in gestational age at delivery between the groups. For this reason, a Cochrane review in 2015 [7] concluded that there is no evidence suggesting that early-term elective delivery of small fetuses (based only on EFW) should be recommended to avoid adverse perinatal outcomes. It must be noted that in DIGITAT, other factors predictive of poor prognosis in small fetuses, such as the amount of amniotic fluid, feto-maternal Doppler, or biophysical profile score, were not taken into account. Therefore, it might be possible that with more accurate identification of small fetuses who are actually at a higher risk of perinatal complications (ie, those with FGR), early-term elective delivery would have been found to improve perinatal outcomes as compared to the expectant management group.

Management of SGA: Feto-Maternal Doppler

In recent years, and after the publication of DIGITAT, several studies have evaluated the role of feto-maternal circulation assessment by Doppler ultrasound in small fetuses [25-28]. These studies have shown that Doppler assessment allows identifying the subset of small fetuses at a higher risk of adverse perinatal outcomes (ie, those with FGR). Historically, umbilical artery (UA) pulsatility index (PI) assessed with Doppler has been considered the standard parameter to identify FGR. However, a large proportion of small fetuses with normal UA PI (ie, <95th percentile) have poorer perinatal outcomes than normally growing fetuses [21,29,30]. Thus, UA PI alone cannot be used to discriminate SGA from FGR fetuses [1,29]. Further studies showed that other Doppler parameters might have a greater predictive ability for adverse outcomes in late-onset SGA and FGR: cerebroplacental ratio (CPR), middle cerebral artery (MCA) PI, and uterine artery (UtA) PI [1,26,31,32]. According to these studies, abnormal CPR (ie, <5th percentile), MCA PI (ie, <5th percentile), or UtA PI (ie, >95th percentile) may be able to identify small fetuses at a higher risk of adverse outcomes (ie, FGR). A study including these criteria showed that small fetuses with abnormal Doppler parameters accounted for 60% of all small fetuses, indicating that more than half of fetuses with an EFW below the 10th percentile would be classified as FGR and that according to our current protocol, early-term induction of labor would therefore be recommended [25]. In the earlier study, induction of labor was recommended at 37 weeks of gestation in FGR fetuses (small fetuses with an EFW below the 3rd percentile or with an EFW below the 10th percentile accompanied by the presence of any abnormal Doppler parameter), while for other pregnancies with an EFW below the 10th percentile (ie, SGA fetuses) induction of labor was recommended at 40 weeks. Following that protocol, 134 cases (26.3%) had an adverse outcome, including, nonexclusively, 46 cases of neonatal acidosis and 106 cases of emergency cesarean delivery due to nonreassuring cardiotocography (CTG). Neonatal acidosis in that study was defined as a UA pH below 7.15 and a base excess greater than –12 mEq/L.

Management of SGA: Angiogenic Factors

To date, few studies have evaluated the usefulness of angiogenic factors (AFs) in the management of late-onset or term SGA/FGR pregnancies. These studies show that the higher the sFlt-1/PlGF ratio, the worse the prognosis for small fetuses and the greater the risk of developing preeclampsia (PE), which in turn worsens maternal prognosis [19,33-35]. Recently, a large observational study compared the identification of term (36+0 to 37+6 weeks+days) small fetuses (EFW below the 10th percentile) at a higher risk of adverse outcomes using the standard Doppler assessment versus a new approach based on AFs [36]. In that study, 521 fetuses were identified as small, of which 102 had abnormal AF values (sFlt-1/PlGF ratio ≥38), whereas 412 had abnormal Doppler parameters. Therefore, according to the Doppler-based protocol, 79.1% (412/521) of small fetuses would have been classified as FGR, whereas according to the new

AF-based approach, only 19.6% (102/521) of small fetuses would have been classified as FGR. By contrast, both approaches had a similar negative predictive value for adverse perinatal outcomes (99.3% and 99%, respectively), indicating a good, similar prognosis for those pregnancies not classified as FGR regardless of the classification used. Therefore, classification based on AFs seems more accurate and may have a lower rate of false positives than the Doppler-based protocol for the identification of small fetuses at a higher risk of adverse outcomes.

Early-term Delivery: Short-term and Long-term Consequences

It might seem that whether a delivery is early term (<39 weeks) or full term (≥39 weeks) is not very relevant in terms of postnatal prognosis. However, several studies have found increased immediate postnatal morbidity (such as admission to the NICU due to a need for respiratory support) [10] and poorer long-term outcomes, such as the development of diabetes, obesity, and respiratory morbidity, in infants born early term as compared to full term [11,12]. Thus, a reduction in the number of elective early-term deliveries due to FGR overdiagnosis would certainly lead to improved short-term and long-term postnatal outcomes, ultimately resulting in healthier infants and adults.

Rationale for the Study

The most common protocols used worldwide for the management of late-onset SGA/FGR are based on Doppler assessment, which recommends elective delivery at 37 weeks (or even earlier) in FGR pregnancies [25,37,38]. According to a classification based on Doppler parameters and EFW percentiles, up to 79.1% of small fetuses would be classified as FGR. By contrast, when using the AF-based approach (sFlt-1/PlGF ≥38), only 19.6% of small fetuses would be classified as FGR [36]. Additionally, both approaches seem to have a similar ability to identify small fetuses at risk (ie, those with FGR), which may benefit from an earlier elective delivery. Therefore, the AF-based protocol may potentially reduce by up to 75.2% (from 79.1% to 19.6%) the number of pregnancies classified as FGR (in which labor would be induced at 37 weeks) without worsening perinatal outcomes. Moreover, reducing the number of unnecessary labor inductions would not only improve patients' perception of medical attention, but also would reduce the costs and risks derived from possible iatrogenic complications, which in turn would reduce the rate of cesarean deliveries. Additionally, fewer inductions would lower the rate of early-term neonates, thus improving neonatal outcomes and potentially reducing long-term infant metabolic, endocrine, and respiratory morbidities.

The sFlt-1/PlGF ratio has been shown to accurately predict PE and associated complications several weeks before onset [39-42]. Therefore, a management protocol based on AFs may potentially reduce the rate of PE and other maternal complications associated with PE, such as placental abruption or eclampsia.

Objectives

Primary Objective

To determine whether the classification of small fetuses as FGR or SGA based on AFs is not inferior to the standard clinical approach (based on EFW and Doppler percentiles) for the identification of fetuses at a higher risk of adverse perinatal outcomes (neonatal acidosis and cesarean section due to nonreassuring CTG).

Secondary Objectives

To determine whether (1) the lower false-positive rate using AFs instead of Doppler to identify small fetuses as FGR results in a reduced number of elective deliveries before 38, 39, and 40 weeks, (2) a lower rate of early-term elective deliveries results in a reduced number of deliveries (elective and spontaneous) before 38, 39, and 40 weeks, (3) a lower rate of early-term elective deliveries results in a reduced number of cesarean deliveries, (4) a lower rate of early-term elective deliveries results in a reduced number of neonatal admissions to the NICU and a lower rate of adverse perinatal outcomes, (5) the AF-based approach reduces PE incidence in pregnancies with small fetuses, and (6) the AF-based classification reduces the incidence of placental-related complications.

Methods

Study Setting

The study will be conducted in 20 hospitals across Spain with experience in managing term SGA/FGR pregnancies: Vall d'Hebron Barcelona Hospital Campus (Barcelona), Hospital Universitario de Torrejón (Torrejón de Ardoz), Hospital Universitari de Tarragona Joan XXIII (Tarragona), Hospital General Universitario de Alicante (Alicante), Hospital Clínico Universitario Virgen de la Arrixaca (Murcia), Parc Taulí Hospital Universitari (Sabadell), Hospital Universitari Germans Trias i Pujol (Badalona), Hospital Universitario de Cabueñes (Gijón), Hospital Universitari Son Llàtzer (Palma de Mallorca), Hospital Clínico Universitario Lozano Blesa (Zaragoza), Fundació Althaia (Manresa), Hospital Universitario de A Coruña (A Coruña), Hospital General Universitario de Elche (Elche), Hospital Universitario Virgen de Valme (Sevilla), Consorci Sanitari de Terrassa (Terrassa), Hospital Universitari Mútua Terrassa (Terrassa), Hospital Universitario de Getafe (Getafe), Hospital Universitario Puerta del Mar (Cádiz), Hospital Universitari de Girona Doctor Josep Trueta (Girona), and Hospital Universitario Nuestra Señora de Candelaria (Santa Cruz de Tenerife).

Trial Design

This is a multicenter, open-label, randomized clinical trial. The study design adheres to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) quality standard criteria for randomized trials [43]. A pragmatic approach will be adopted in order to evaluate the effectiveness of the intervention in real-life, routine practice conditions. Therefore, each participating site will use the fetal growth charts, Doppler reference values, and methods for cervical ripening and labor induction usually applied in their clinical practice.

The clinical trial was entered in the ClinicalTrials.org registry on August 6, 2020 (NCT04502823).

Inclusion Criteria

Inclusion criteria at the time of enrollment are as follows: (1) age at least 16 years, (2) singleton pregnancy, (3) ultrasonographic EFW ≤10th percentile between 36+0 and 37+6 weeks+days of gestation, (4) sFlt-1/PlGF ratio measured between 36+0 and 37+6 weeks+days of gestation, (5) randomization between 36+0 and 37+6 weeks+days of gestation, and (6) gestational age confirmed by fetal crown-rump length measurement during the first trimester scan (from 11+0 to 13+6 weeks+days of gestation) or by in vitro fertilization dates.

Exclusion Criteria

Exclusion criteria at the time of enrollment are as follows: (1) major fetal malformations or genetic disorders, (2) fetal death, (3) absent or reversed end-diastolic flow in UA Doppler, (4) nonreassuring CTG, (5) preeclampsia, (6) diminished fetal movements, (7) biophysical profile score ≤6, (8) oligohydramnios, and (9) refusal to give informed consent.

Intervention

First, gestational age (by fetal crown-rump length measurement at 11+0 to 13+6 weeks+days) [44] and EFW ≤10th percentile will be confirmed [45-49]. After giving their written informed consent, trial participants will be randomized into 2 groups: intervention and control.

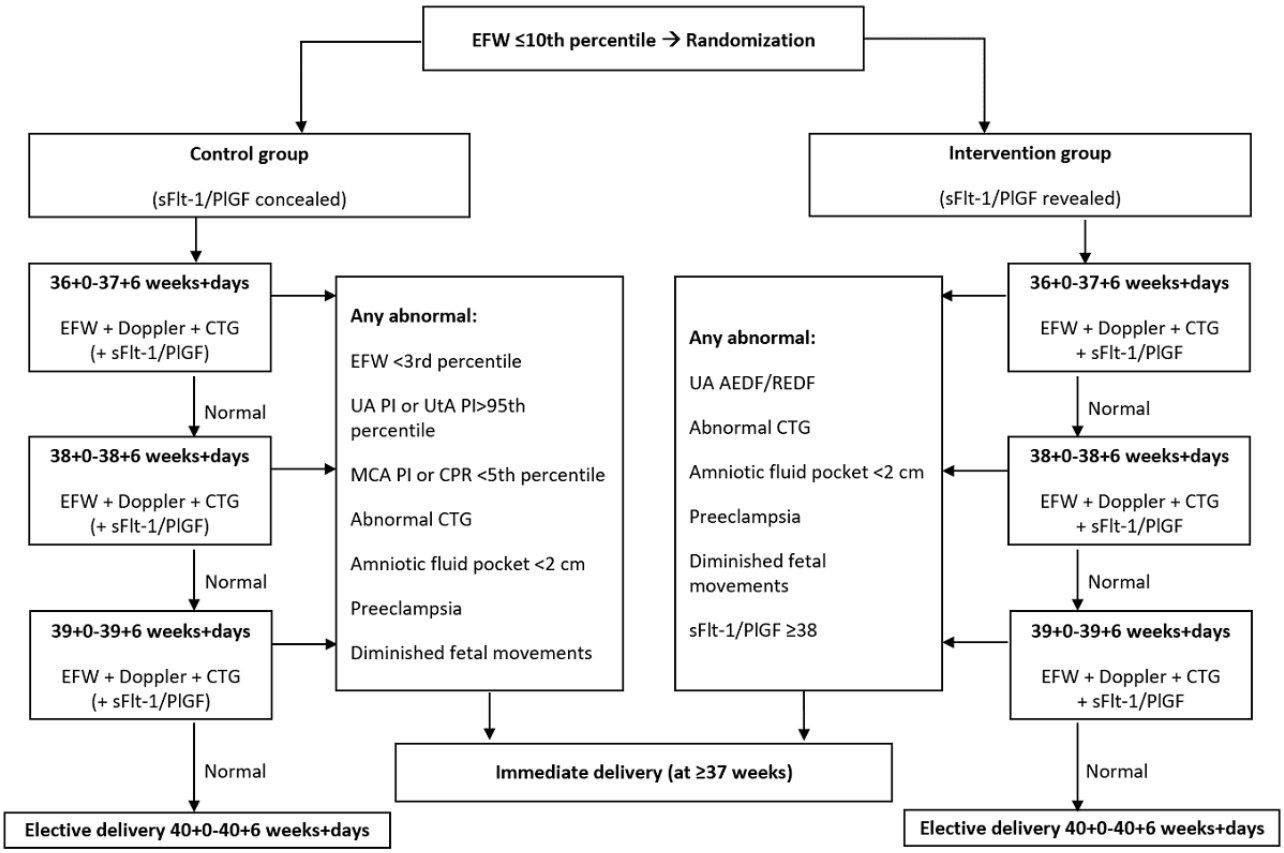
In the intervention group, the sFlt-1/PlGF ratio will be revealed to investigators so they can act according to the results. When the sFlt-1/PlGF ratio is ≥38, the fetus will be classified as FGR. The remaining cases will be classified as SGA. In the intervention group, the UA PI, MCA PI, CPR, and UtA PI percentiles will be concealed to obstetricians in order to avoid any influence that this information might have on their interpretation of fetal movements or CTG.

In the control group, the sFlt-1/PlGF ratio will be concealed to investigators and the standard Doppler-based approach will be used for fetal monitoring [1]. Thus, fetuses with an EFW <3rd percentile or ≤10th percentile accompanied by an abnormal feto-maternal Doppler (UA PI >95th percentile, MCA PI <5th percentile, CPR <5th percentile, UtA PI >95th percentile, or a combination of these markers) [50-53] will be classified as FGR. The remaining cases will be classified as SGA.

In both groups, when a fetus is classified as FGR, immediate (within 24 hours) elective delivery at ≥37 weeks of gestation will be recommended; when a fetus is classified as SGA, elective delivery will be delayed until 40 weeks of gestation. From randomization to delivery, all SGA pregnancies in both groups will receive weekly follow-ups consisting of fetal ultrasound (including fetal growth, amniotic fluid deepest vertical pocket, fetal movements, and feto-maternal Doppler), conventional CTG, and measurement of the sFlt-1/PlGF ratio (which will be concealed or revealed depending on the allocated group).

In both groups, if at any time after enrollment any of the following is present, immediate (within 24 hours) delivery will be recommended: UA with absent or reversed end-diastolic flow, nonreassuring CTG, PE, diminished fetal movements, biophysical profile score ≤6, or oligohydramnios (largest vertical pocket <2 cm). The flow chart in Figure 1 illustrates the management of participants from consent through follow-up.

Figure 1. Flow chart of study intervention and management. AEDF: absent end-diastolic flow; CPR: cerebroplacental ratio; CTG: cardiotocography; EFW: estimated fetal weight; MCA: middle cerebral artery; PI: pulsatility index; PlGF: placental growth factor; REDF: reversed end-diastolic flow; sFlt-1: soluble fms-like tyrosine kinase-1; UA: umbilical artery.



According to recommendations of the National Institute for Health and Care Excellence (NICE) [54], labor will be induced in pregnancies with a Bishop score [55] ≤6 by promoting cervical ripening with vaginal administration of dinoprostone or misoprostol or with a cervical balloon, as per each site's usual protocols (Table 1).

In pregnancies with a Bishop score >6, labor will be induced by amniotomy, intravenous oxytocin infusion, or both in all participating sites. Indications for elective cesarean delivery will be as follows: at least 2 previous cesarean deliveries, UA with absent or reversed end-diastolic flow, nonreassuring CTG, abnormal fetal presentation (breech or transverse lie position), placental abruption, PE with severe features requiring immediate delivery (pulmonary edema, serum creatinine >1.1 mg/dL, oliguria [≤500 ml in 24 h or <20 ml/h], persistent hypertension despite appropriate antihypertensive therapy, persistent cerebral or visual disturbances, or eclampsia), and participants refusing induction of labor. Other less frequent indications may occur and will be classified as "other." Indications for intrapartum cesarean delivery will be as follows: prolonged labor, failed induction of labor, nonreassuring CTG, placental abruption, and PE with severe features requiring immediate delivery. Other less frequent indications may occur and will be classified as "other."

Prolonged labor will be defined according to the NICE guidelines for intrapartum care of healthy women and babies [56]. According to these guidelines, a delay in the first stage of labor is suspected if cervical dilatation is <2 cm after 4 hours. After 2 hours, delay will be confirmed if progress is <1 cm, and oxytocin will be offered. Prolonged labor will be confirmed if dilatation has increased <2 cm after 4 hours of oxytocin infusion. The maximum duration of cervical ripening treatment will vary depending on the method, with 12 hours for the cervical balloon, 16 hours for misoprostol, and 24 hours for dinoprostone. Failed induction of labor will be defined as not entering the active phase of labor after cervical ripening along with 6 to 8 hours of oxytocin infusion.

Table 1. Cervical ripening mechanisms used at each participating site. For labor induction, classification of fetuses as being small for gestational age or having fetal growth restriction will be based on the Doppler criteria, as in the control group [1]. Dinoprostone (Propess; Ferring Pharmaceuticals Ltd) was administered at a 10-mg dose with a vaginal delivery system. Misoprostol (Misofar; Exeltis Healthcare SL) was administered at a 25-µg dose with a vaginal tablet. Cervical balloons used a double-balloon catheter plus stylet (Cook Medical).

Hospital	Fetal growth restriction	Small for gestational age
Vall d'Hebron	Dinoprostone	Dinoprostone
Torrejón	Cervical balloon	Dinoprostone
Joan XXIII	Misoprostol	Misoprostol
Alicante	Dinoprostone	Dinoprostone
Arrixaca	Dinoprostone	Dinoprostone
Parc Taulí	Dinoprostone	Dinoprostone
Cabueñes	Dinoprostone	Dinoprostone
Germans Trias	Dinoprostone	Dinoprostone
Son Llàtzer	Dinoprostone	Dinoprostone
Lozano Blesa	Cervical balloon	Dinoprostone
Althaia	Dinoprostone	Dinoprostone
A Coruña	Dinoprostone	Dinoprostone
Elche	Cervical balloon	Dinoprostone
Valme	Cervical balloon	Cervical balloon
Hospital Terrassa	Dinoprostone	Misoprostol
Mutua Terrassa	Dinoprostone	Misoprostol
Getafe	Cervical balloon	Cervical balloon
Puerta del Mar	Cervical balloon	Misoprostol
Josep Trueta	Misoprostol	Misoprostol
Candelaria	Dinoprostone	Dinoprostone

Predictive Variables

Predictive variables include maternal sFlt1 and PlGF plasma levels (pg/ml), fetal EFW, results of a Doppler assessment (UA PI, MCA PI, CPR, and UtA PI percentiles), amniotic fluid vertical pocket, fetal movement and biophysical profile score, and conventional CTG interpretation. PlGF and sFlt-1 levels will be measured using the automated Elecsys electrochemiluminescence immunoassay platform (Cobas Analyzers; Roche Diagnostics).

Nonreassuring CTG before and during labor will be defined as sinusoidal fetal heart rate tracing or absent fetal heart rate variability accompanied by recurrent late decelerations, recurrent variable decelerations, or bradycardia [57].

In all settings, EFW will be calculated using the Hadlock formula [49]. EFW percentiles will be calculated using the reference charts of each site's protocol. Fetuses with an EFW ≤10th percentile will be classified as small [45-48]. Doppler assessments will be performed following the International Society of Ultrasound in Obstetrics and Gynecology Practice Guidelines [58]. All participating sites will use the same reference values for calculating UtA PI percentiles [51]. Doppler percentiles for UA PI, MCA PI, and CPR will be calculated according to gestational age using the charts of each site's protocol (Table 2). Gestational age will be determined by fetal crown-rump length measurement at 11+0 to 13+6 weeks+days of gestation [44] or in vitro fertilization date.

Table 2. Reference charts at each participating site.

Hospital	Estimated fetal weight percentile	Umbilical artery pulsatility index percentile	Middle cerebral artery pulsatility index percentile	Cerebroplacental ratio percentile
Vall d'Hebron	Mikolajczyk RT et al [47]	Ciobanu A et al [50]	Ciobanu A et al [50]	Ciobanu A et al [50]
Torrejón	Marsál K et al [48]	Arduini D and Rizzo G [52]	Baschat AA and Gembruch U [53]	Baschat AA and Gembruch U [53]
Joan XXIII	Hadlock FP et al [49]	Arduini D and Rizzo G [52]	Baschat AA and Gembruch U [53]	Baschat AA and Gembruch U [53]
Alicante	Mikolajczyk et al [47]	Ciobanu A et al [50]	Ciobanu A et al [50]	Ciobanu A et al [50]
Arrixaca	Figueras F et al [45]	Arduini D and Rizzo G [52]	Baschat AA and Gembruch U [53]	Baschat AA and Gembruch U [53]
Parc Taulí	Hadlock FP et al [49]	Arduini D and Rizzo G [52]	Baschat AA and Gembruch U [53]	Baschat AA and Gembruch U [53]
Cabueñes	Hadlock FP et al [49]	Arduini D and Rizzo G [52]	Baschat AA and Gembruch U [53]	Baschat AA and Gembruch U [53]
Germans Trias	Hadlock FP et al [49]	Arduini D and Rizzo G [52]	Baschat AA and Gembruch U [53]	Baschat AA and Gembruch U [53]
Son Llàtzer	Figueras F et al [45]	Arduini D and Rizzo G [52]	Baschat AA and Gembruch U [53]	Baschat AA and Gembruch U [53]
Lozano Blesa	Figueras F et al [45]	Arduini D and Rizzo G [52]	Baschat AA and Gembruch U [53]	Baschat AA and Gembruch U [53]
Althaia	Figueras F et al [45]	Arduini D and Rizzo G [52]	Baschat AA and Gembruch U [53]	Baschat AA and Gembruch U [53]
A Coruña	Figueras F et al [45]	Arduini D and Rizzo G [52]	Baschat AA and Gembruch U [53]	Baschat AA and Gembruch U [53]
Elche	Papageorghiou AT et al [46]	Ciobanu A et al [50]	Ciobanu A et al [50]	Ciobanu A et al [50]
Valme	Figueras F et al [45]	Arduini D and Rizzo G [52]	Baschat AA and Gembruch U [53]	Baschat AA and Gembruch U [53]
Hospital Terrassa	Figueras F et al [45]	Arduini D and Rizzo G [52]	Baschat AA and Gembruch U [53]	Baschat AA and Gembruch U [53]
Mutua Terrassa	Hadlock FP et al [49]	Arduini D and Rizzo G [52]	Baschat AA and Gembruch U [53]	Baschat AA and Gembruch U [53]
Getafe	Figueras F et al [45]	Arduini D and Rizzo G [52]	Baschat AA and Gembruch U [53]	Baschat AA and Gembruch U [53]
Puerta del Mar	Mikolajczyk et al [47]	Ciobanu A et al [50]	Ciobanu A et al [50]	Ciobanu A et al [50]
Josep Trueta	Mikolajczyk et al [47]	Ciobanu A et al [50]	Ciobanu A et al [50]	Ciobanu A et al [50]
Candelaria	Figueras F et al [45]	Arduini D and Rizzo G [52]	Baschat AA and Gembruch U [53]	Baschat AA and Gembruch U [53]

Amniotic fluid volume will be determined measuring the deepest vertical pocket and oligohydramnios will be considered when depth is <2 cm [59]. Depending on each site's protocol, fetal movement will be assessed subjectively or based on biophysical profile score, as described by Manning [60]. PE will be defined as new-onset high blood pressure (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg), worsening of previous high blood pressure in addition to new-onset proteinuria (≥300 mg protein in a 24-hour urine collection, protein/creatinine ≥0.3, or a dipstick reading of 1+), worsening of previous proteinuria, or according to at least one of the following signs and symptoms: cerebral or visual symptoms, raised liver enzymes, low platelet count, renal insufficiency, and pulmonary edema. PE with severe features will be defined as either systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥110 mm Hg, or PE with any of the following signs and symptoms: cerebral or visual symptoms, raised liver enzymes, low platelet count, renal insufficiency, and pulmonary edema [61].

Outcomes

Primary Outcome

The primary outcome is the prevalence of cesarean delivery due to nonreassuring fetal status or the prevalence of neonatal acidosis. Neonatal acidosis will be defined as a UA pH <7.15 and a base excess greater than –12 mEq/L.

Secondary Outcomes

Composite adverse perinatal outcome will be defined as the presence of at least one of the following: fetal death, Apgar

score <7 at 5 minutes, UA pH <7.05, admission to the NICU or a transitional care unit within 48 hours, birthweight <2000 grams, maternal admission to the obstetric intensive care unit within 48 hours (before or after delivery), and PE.

Composite adverse neonatal outcomes will be defined as the presence of at least one of the following: respiratory distress syndrome (respiratory rate >60 or <30 breaths/min, grunting on expiration, chest indrawing, central cyanosis, apnea, or the need for surfactant therapy in the neonatal period) [62], transient tachypnea, required ventilatory support, grade III or IV intraventricular hemorrhage, neonatal sepsis, hypoglycemia, necrotizing enterocolitis, neonatal jaundice (treated with phototherapy), neonatal seizures, pneumonia, meningitis, and neonatal death.

Other secondary outcomes will include the following: rates of elective delivery before 38, 39, and 40 weeks of gestation; rates of deliveries (elective and spontaneous) before 38, 39, and 40 weeks of gestation; rate of birthweight <2500 grams; rate of UA pH <7.10; rate of elective cesarean delivery; rate of cesarean delivery due to failed labor induction; rate of emergency operative vaginal delivery; and rate of placental-related complications, such as placental abruption, pregnancy hypertension, severe PE, eclampsia, stroke, maternal death, and postpartum hemorrhage.

Statistical Analysis

Statistical analysis will be performed based on the intention-to-treat approach, considering all randomized women. A sensitivity analysis will be carried out to take into account the effect of withdrawal of consent and loss to follow-up. Outcomes and covariates will be imputed by multiple imputation chain equations. Patients deemed ineligible after randomization (eg, due to identification of congenital defects or EFW >10th percentile) will be excluded in the per-protocol analysis.

Univariate descriptive analysis will be used for the study variables. We will assess differences between the groups for the primary and secondary outcomes, calculating differences in the incidence and relative risks with their respective 95% CIs. Type I errors will be set at $P<.05$. The statistical software packages R and R Studio (R Foundation) will be used for statistical analyses. An interim analysis will be performed by an independent statistician once 50% of the sample size has been recruited. This analysis will ascertain the safety of the new approach with the O'Brien-Fleming boundary [63]. As FGR pregnancies have a higher risk of stillbirth and other adverse outcomes compared to SGA pregnancies, women with SGA fetuses will probably be more willing to participate. Enrollment of a greater proportion of SGA pregnancies might hinder identification of differences between groups. For this reason, a subgroup analysis will be performed for FGR and SGA pregnancies according to the Doppler classification at enrollment. Categorical variables will be reported as frequencies, normally distributed continuous variables will be reported as means and standard deviations, and continuous variables that do not follow a normal distribution will be reported as medians and interquartile ranges. The Fisher exact test or chi-square test, as appropriate, will be used to assess differences in categorical variables between groups. The Student *t* test (2-tailed) or Mann-Whitney *U* test, as appropriate, will be used for continuous variables.

During the design stage of the trial, no financial support was available. Nevertheless, if this trial receives a specific grant from a funding agency, monitoring by the Academic Research Organization of the Vall d'Hebron Research Institute will be contracted.

Sample Size

A management protocol based on EFW and Doppler assessment has shown a prevalence of adverse perinatal outcomes of 26%, meaning that there is a prevalence of 74% of pregnancies with no complications [25]. The estimated rate of pregnancies with no complications in the intervention group has been set at 74%, with a lower limit of 65.5% (a maximum achievable difference of 8.5%). Based on these considerations and an estimated dropout rate of 3%, the sample size needed for a noninferiority design with a power of 80% and a significance level of 5% is 1030 participants, that is, 515 in each group. Noninferiority will be demonstrated if the lower limit of the 95% CI of the difference between incidences of pregnancies without neonatal acidosis is less than –8.5%. If the dropout rate is greater than 3%, the number of participants will be increased so as to achieve 1000 participants with complete data for the primary outcome.

Randomization, Masking, and Data Collection

Participants will be randomly assigned to the intervention or control group in a 1:1 ratio using variable-size block randomization. The randomization sequence will be centralized and generated by the web-based system Sealed Envelope (Sealed Envelope Ltd) and will be concealed to investigators. Owing to the nature of the intervention, it will not be possible to conceal the study group to the participants, investigators, or outcome assessors.

A RedCap (Research Electronic Data Capture; Vanderbilt University) electronic database has been specifically designed for this study [64]. The electronic database has a randomization module that will allow allocation of participants to the study groups. Data will be entered prospectively during the study. Access to this database will be restricted to the investigators involved in each participating site.

Ethics Approval

The current version (version 3.0) of the study protocol was approved by the Vall d'Hebron Ethics Committee (PR[AMI]527/2019) on February 18, 2020. Subsequent approval by individual ethical committees has been granted. Written informed consent will be obtained from all participants before randomization.

Results

The first patient was recruited on September 28, 2020, and at the time of submitting this manuscript, the study was in the recruitment and data collection phase. The study results are expected to be published in peer-reviewed journals and disseminated at international conferences in early 2023. No funding has been obtained for this trial.

Discussion

Newborns under 39 weeks have poorer perinatal outcomes than full-term newborns [10]. After classification with EFW and Doppler, more than 60% of small fetuses are delivered at 37 to 38 weeks of gestation [8]. However, classification with AF seems to have a lower false-positive rate [36]. In this trial, we aim to assess whether the classification of small fetuses as FGR or SGA based on AF is not inferior to the standard clinical approach (EFW and Doppler percentiles) for the identification of fetuses at a higher risk of adverse perinatal outcomes (neonatal acidosis and cesarean section due to nonreassuring CTG). This is the first trial that includes term pregnancies with an EFW below the 10th percentile and is designed to compare perinatal outcomes with a management protocol based on the sFlt-1/PlGF ratio and the standard management protocol, based on feto-maternal Doppler assessment. The main strength of this study is the comparison of 2 randomized groups and the large size of the study population. A pragmatic and multicenter design will evaluate the effectiveness of both interventions in the conditions of real-life routine practice, which will allow extrapolating the results to other settings. On the other hand, the sample size will not allow assessment of the effect of the management protocol on the incidence of rare adverse outcomes, such as stillbirth, placental abruption, or eclampsia. All pregnant women with fetuses having an EFW ≤10th percentile at 36+0 to 37+6 weeks+days of gestation will be invited to participate; however, since FGR pregnancies are at a higher risk of stillbirth and other adverse outcomes, women with FGR pregnancies might be more reluctant to participate than women with SGA, which could introduce a selection bias.

The AF-based protocol may reduce the number of pregnancies classified as FGR without worsening perinatal outcomes, improve patients' medical attention perception, reduce the rate of cesarean deliveries, and reduce the rate of placental complications, such as PE, placental abruption, or eclampsia. Moreover, the rate of early-term neonates may be reduced, improving neonatal outcomes and long-term morbidity.

Acknowledgments

Roche Diagnostics provided the reagents used for the placental growth factor and soluble fms-like tyrosine kinase-1 measurements. Roche Diagnostics had no influence on the study design, data collection, or analysis or interpretation of the results.

Data Availability

The data that support the findings of this study are available from the corresponding author, MM, upon reasonable request.

Authors' Contributions

MM and EC were involved in the conception and design of the study. PGM and MM drafted the manuscript. All authors have read and given approval of the final manuscript.

Conflicts of Interest

MM, LM, and AP received lecture fees from Roche Diagnostics. MMG has received reagents in kind contribution from Roche. The other authors have no conflicts of interest to declare.

References

1. Figueras F, Gratacós E. Update on the diagnosis and classification of fetal growth restriction and proposal of a stage-based management protocol. Fetal Diagn Ther 2014;36(2):86-98 [FREE Full text] [doi: 10.1159/000357592] [Medline: 24457811]
2. McCowan LM, Figueras F, Anderson NH. Evidence-based national guidelines for the management of suspected fetal growth restriction: comparison, consensus, and controversy. Am J Obstet Gynecol 2018 Feb;218(2S):S855-S868. [doi: 10.1016/j.ajog.2017.12.004] [Medline: 29422214]
3. Lees CC, Marlow N, van Wassenaer-Leemhuis A, Arabin B, Bilardo CM, Brezinka C, TRUFFLE study group. 2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial. Lancet 2015 May 30;385(9983):2162-2172. [doi: 10.1016/S0140-6736(14)62049-3] [Medline: 25747582]
4. Meler E, Mazarico E, Eixarch E, Gonzalez A, Peguero A, Martinez J, et al. Ten-year experience of protocol-based management of small-for-gestational-age fetuses: perinatal outcome in late-pregnancy cases diagnosed after 32 weeks. Ultrasound Obstet Gynecol 2021 Jan;57(1):62-69 [FREE Full text] [doi: 10.1002/uog.23537] [Medline: 33159370]
5. Savchev S, Figueras F, Sanz-Cortes M, Cruz-Lemini M, Triunfo S, Botet F, et al. Evaluation of an optimal gestational age cut-off for the definition of early- and late-onset fetal growth restriction. Fetal Diagn Ther 2014;36(2):99-105. [doi: 10.1159/000355525] [Medline: 24217372]
6. Baschat AA. Planning management and delivery of the growth-restricted fetus. Best Pract Res Clin Obstet Gynaecol 2018 May;49:53-65. [doi: 10.1016/j.bpobgyn.2018.02.009] [Medline: 29606482]
7. Bond DM, Gordon A, Hyett J, de Vries B, Carberry AE, Morris J. Planned early delivery versus expectant management of the term suspected compromised baby for improving outcomes. Cochrane Database Syst Rev 2015 Nov 24(11):CD009433 [FREE Full text] [doi: 10.1002/14651858.CD009433.pub2] [Medline: 26599471]

8. Figueras F, Gratacós E. An integrated approach to fetal growth restriction. Best Pract Res Clin Obstet Gynaecol 2017 Jan;38:48-58. [doi: 10.1016/j.bpobgyn.2016.10.006] [Medline: 27940123]
9. Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, et al. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol 2016 Sep;48(3):333-339 [FREE Full text] [doi: 10.1002/uog.15884] [Medline: 26909664]
10. Sengupta S, Carrion V, Shelton J, Wynn RJ, Ryan RM, Singhal K, et al. Adverse neonatal outcomes associated with early-term birth. JAMA Pediatr 2013 Nov;167(11):1053-1059. [doi: 10.1001/jamapediatrics.2013.2581] [Medline: 24080985]
11. Paz Levy D, Sheiner E, Wainstock T, Sergienko R, Landau D, Walfisch A. Evidence that children born at early term (37-38 6/7 weeks) are at increased risk for diabetes and obesity-related disorders. Am J Obstet Gynecol 2017 Nov;217(5):588.e1-588.e11. [doi: 10.1016/j.ajog.2017.07.015] [Medline: 28729012]
12. Walfisch A, Beharier O, Wainstock T, Sergienko R, Landau D, Sheiner E. Early-term deliveries as an independent risk factor for long-term respiratory morbidity of the offspring. Pediatr Pulmonol 2017 Feb;52(2):198-204. [doi: 10.1002/ppul.23529] [Medline: 27458900]
13. Altshuler G, Russell P, Ermocilla R. The placental pathology of small-for-gestational age infants. Am J Obstet Gynecol 1975 Feb 01;121(3):351-359. [doi: 10.1016/0002-9378(75)90011-3] [Medline: 1115149]
14. Zur RL, Kingdom JC, Parks WT, Hobson SR. The placental basis of fetal growth restriction. Obstet Gynecol Clin North Am 2020 Mar;47(1):81-98. [doi: 10.1016/j.ogc.2019.10.008] [Medline: 32008673]
15. Paules C, Youssef L, Rovira C, Crovetto F, Nadal A, Peguero A, et al. Distinctive patterns of placental lesions in pre-eclampsia vs small-for-gestational age and their association with fetoplacental Doppler. Ultrasound Obstet Gynecol 2019 Nov 14;54(5):609-616 [FREE Full text] [doi: 10.1002/uog.20350] [Medline: 31115105]
16. Roberts DJ, Post MD. The placenta in pre-eclampsia and intrauterine growth restriction. J Clin Pathol 2008 Dec;61(12):1254-1260. [doi: 10.1136/jcp.2008.055236] [Medline: 18641412]
17. Ganer Herman H, Barber E, Gasnier R, Gindes L, Bar J, Schreiber L, et al. Placental pathology and neonatal outcome in small for gestational age pregnancies with and without abnormal umbilical artery Doppler flow. Eur J Obstet Gynecol Reprod Biol 2018 Mar;222:52-56. [doi: 10.1016/j.ejogrb.2018.01.009] [Medline: 29408751]
18. Shinar S, Tigert M, Agrawal S, Parks WA, Kingdom JC. Placental growth factor as a diagnostic tool for placental mediated fetal growth restriction. Pregnancy Hypertens 2021 Aug;25:123-128. [doi: 10.1016/j.preghy.2021.05.023] [Medline: 34119877]
19. Triunfo S, Lobmaier S, Parra-Saavedra M, Crovetto F, Peguero A, Nadal A, et al. Angiogenic factors at diagnosis of late-onset small-for-gestational age and histological placental underperfusion. Placenta 2014 Jun;35(6):398-403. [doi: 10.1016/j.placenta.2014.03.021] [Medline: 24746262]
20. Garcia-Manau P, Mendoza M, Bonacina E, Garrido-Gimenez C, Fernandez-Oliva A, Zanini J, et al. Soluble fms-like tyrosine kinase to placental growth factor ratio in different stages of early-onset fetal growth restriction and small for gestational age. Acta Obstet Gynecol Scand 2021 Jan;100(1):119-128 [FREE Full text] [doi: 10.1111/aogs.13978] [Medline: 32860218]
21. Savchev S, Figueras F, Cruz-Martinez R, Illa M, Botet F, Gratacos E. Estimated weight centile as a predictor of perinatal outcome in small-for-gestational-age pregnancies with normal fetal and maternal Doppler indices. Ultrasound Obstet Gynecol 2012 Mar;39(3):299-303 [FREE Full text] [doi: 10.1002/uog.10150] [Medline: 22102177]
22. NIETO A. Neonatal morbidity associated with disproportionate intrauterine growth retardation at term. Journal of Obstetrics and Gynaecology 2009 Jul 02;18(6):540-543. [doi: 10.1080/01443619866282]
23. Pilliod RA, Cheng YW, Snowden JM, Doss AE, Caughey AB. The risk of intrauterine fetal death in the small-for-gestational-age fetus. American Journal of Obstetrics and Gynecology 2012 Oct;207(4):318.e1-318.e6. [doi: 10.1016/j.ajog.2012.06.039]
24. Boers KE, Vijgen SMC, Bijlenga D, van der Post JAM, Bekedam DJ, Kwee A, et al. Induction versus expectant monitoring for intrauterine growth restriction at term: randomised equivalence trial (DIGITAT). BMJ 2010 Dec 21;341(dec21 1):c7087-c7087. [doi: 10.1136/bmj.c7087]
25. Figueras F, Savchev S, Triunfo S, Crovetto F, Gratacos E. An integrated model with classification criteria to predict small-for-gestational-age fetuses at risk of adverse perinatal outcome. Ultrasound Obstet Gynecol 2015 Jan 27;45(3):279-285. [doi: 10.1002/uog.14714]
26. Cruz-Martinez R, Savchev S, Cruz-Lemini M, Mendez A, Gratacos E, Figueras F. Clinical utility of third-trimester uterine artery Doppler in the prediction of brain hemodynamic deterioration and adverse perinatal outcome in small-for-gestational-age fetuses. Ultrasound Obstet Gynecol 2015 Jan 27;45(3):273-278. [doi: 10.1002/uog.14706]
27. DeVore GR. The importance of the cerebroplacental ratio in the evaluation of fetal well-being in SGA and AGA fetuses. American Journal of Obstetrics and Gynecology 2015 Jul;213(1):5-15. [doi: 10.1016/j.ajog.2015.05.024]
28. Martinez-Portilla RJ, Caradeux J, Meler E, Lip-Sosa DL, Sotiriadis A, Figueras F. Third-trimester uterine artery Doppler for prediction of adverse outcome in late small-for-gestational-age fetuses: systematic review and meta-analysis. Ultrasound Obstet Gynecol 2020 May;55(5):575-585 [FREE Full text] [doi: 10.1002/uog.21940] [Medline: 31785172]

29. Mure an D, Rotar IC, Stamatian F. The usefulness of fetal Doppler evaluation in early versus late onset intrauterine growth restriction. Review of the literature. Med Ultrason 2016 Mar;18(1):103-109 [FREE Full text] [doi: 10.11152/mu.2013.2066.181.dop] [Medline: 26962562]
30. Doctor BA, O'Riordan MA, Kirchner H, Shah D, Hack M. Perinatal correlates and neonatal outcomes of small for gestational age infants born at term gestation. Am J Obstet Gynecol 2001 Sep;185(3):652-659. [doi: 10.1067/mob.2001.116749] [Medline: 11568794]
31. Rizzo G, Mappa I, Bitsadze V, Słodki M, Khizroeva J, Makatsariya A, et al. Role of Doppler ultrasound at time of diagnosis of late-onset fetal growth restriction in predicting adverse perinatal outcome: prospective cohort study. Ultrasound Obstet Gynecol 2020 Jun;55(6):793-798 [FREE Full text] [doi: 10.1002/uog.20406] [Medline: 31343783]
32. Khalil A, Thilaganathan B. Role of uteroplacental and fetal Doppler in identifying fetal growth restriction at term. Best Pract Res Clin Obstet Gynaecol 2017 Jan;38:38-47. [doi: 10.1016/j.bpobgyn.2016.09.003] [Medline: 27720309]
33. Herraiz I, Simón E, Gómez-Arriaga PI, Quezada MS, García-Burguillo A, López-Jiménez EA, et al. Clinical implementation of the sFlt-1/PlGF ratio to identify preeclampsia and fetal growth restriction: A prospective cohort study. Pregnancy Hypertens 2018 Jul;13:279-285. [doi: 10.1016/j.preghy.2018.06.017] [Medline: 30177066]
34. Herraiz I, Quezada MS, Rodriguez-Calvo J, Gómez-Montes E, Villalaín C, Galindo A. Longitudinal change of sFlt-1/PlGF ratio in singleton pregnancy with early-onset fetal growth restriction. Ultrasound Obstet Gynecol 2018 Nov;52(5):631-638 [FREE Full text] [doi: 10.1002/uog.18894] [Medline: 28876491]
35. Kwiatkowski S, Bednarek-Jędrzejek M, Ksel J, Tousty P, Kwiatkowska E, Cymbaluk A, et al. sFlt-1/PlGF and Doppler ultrasound parameters in SGA pregnancies with confirmed neonatal birth weight below 10th percentile. Pregnancy Hypertens 2018 Oct;14:79-85. [doi: 10.1016/j.preghy.2018.08.448] [Medline: 30527123]
36. Gaccioli F, Sovio U, Cook E, Hund M, Charnock-Jones D, Smith G. Screening for fetal growth restriction using ultrasound and the sFLT1/PlGF ratio in nulliparous women: a prospective cohort study. Lancet Child Adolesc Health 2018 Aug;2(8):569-581 [FREE Full text] [doi: 10.1016/S2352-4642(18)30129-9] [Medline: 30119716]
37. Lees CC, Stampalija T, Baschat A, da Silva Costa F, Ferrazzi E, Figueras F, et al. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. Ultrasound Obstet Gynecol 2020 Aug;56(2):298-312 [FREE Full text] [doi: 10.1002/uog.22134] [Medline: 32738107]
38. Melamed N, Baschat A, Yinon Y, Athanasiadis A, Mecacci F, Figueras F, et al. FIGO (international Federation of Gynecology and obstetrics) initiative on fetal growth: best practice advice for screening, diagnosis, and management of fetal growth restriction. Int J Gynaecol Obstet 2021 Mar;152 Suppl 1:3-57 [FREE Full text] [doi: 10.1002/ijgo.13522] [Medline: 33740264]
39. Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennström M, et al. Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia. N Engl J Med 2016 Jan 07;374(1):13-22. [doi: 10.1056/NEJMoa1414838] [Medline: 26735990]
40. Zeisler H, Llurba E, Chantraine FJ, Vatish M, Staff AC, Sennström M, et al. Soluble fms-like tyrosine kinase-1 to placental growth factor ratio: ruling out pre-eclampsia for up to 4 weeks and value of retesting. Ultrasound Obstet Gynecol 2019 Mar;53(3):367-375 [FREE Full text] [doi: 10.1002/uog.19178] [Medline: 30014562]
41. Levine RJ, Maynard SE, Qian C, Lim K, England LJ, Yu KF, et al. Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med 2004 Feb 12;350(7):672-683. [doi: 10.1056/NEJMoa031884] [Medline: 14764923]
42. Signore C, Mills JL, Qian C, Yu K, Lam C, Epstein FH, et al. Circulating angiogenic factors and placental abruption. Obstet Gynecol 2006 Aug;108(2):338-344. [doi: 10.1097/01.AOG.0000216014.72503.09] [Medline: 16880304]
43. Chan A, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013 Feb 05;158(3):200-207 [FREE Full text] [doi: 10.7326/0003-4819-158-3-201302050-00583] [Medline: 23295957]
44. Robinson HP, Fleming JE. A critical evaluation of sonar "crown-rump length" measurements. Br J Obstet Gynaecol 1975 Sep;82(9):702-710. [doi: 10.1111/j.1471-0528.1975.tb00710.x] [Medline: 1182090]
45. Figueras F, Meler E, Iraola A, Eixarch E, Coll O, Figueras J, et al. Customized birthweight standards for a Spanish population. Eur J Obstet Gynecol Reprod Biol 2008 Jan;136(1):20-24. [doi: 10.1016/j.ejogrb.2006.12.015] [Medline: 17287065]
46. Papageorghiou AT, Ohuma EO, Altman DG, Todros T, Cheikh Ismail L, Lambert A, International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st). International standards for fetal growth based on serial ultrasound measurements: the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project. Lancet 2014 Sep 06;384(9946):869-879. [doi: 10.1016/S0140-6736(14)61490-2] [Medline: 25209488]
47. Mikolajczyk RT, Zhang J, Betran AP, Souza JP, Mori R, Gülmezoglu AM, et al. A global reference for fetal-weight and birthweight percentiles. Lancet 2011 May 28;377(9780):1855-1861. [doi: 10.1016/S0140-6736(11)60364-4] [Medline: 21621717]
48. Marsál K, Persson P, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. Acta Paediatr 1996 Jul;85(7):843-848. [doi: 10.1111/j.1651-2227.1996.tb14164.x] [Medline: 8819552]
49. Hadlock FP, Harrist R, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements--a prospective study. Am J Obstet Gynecol 1985 Feb 01;151(3):333-337. [doi: 10.1016/0002-9378(85)90298-4] [Medline: 3881966]

50. Ciobanu A, Wright A, Syngelaki A, Wright D, Akolekar R, Nicolaides KH. Fetal Medicine Foundation reference ranges for umbilical artery and middle cerebral artery pulsatility index and cerebroplacental ratio. Ultrasound Obstet Gynecol 2019 Apr 13;53(4):465-472 [FREE Full text] [doi: 10.1002/uog.20157] [Medline: 30353583]
51. Gómez O, Figueras F, Fernández S, Bennasar M, Martínez JM, Puerto B, et al. Reference ranges for uterine artery mean pulsatility index at 11-41 weeks of gestation. Ultrasound Obstet Gynecol 2008 Aug;32(2):128-132 [FREE Full text] [doi: 10.1002/uog.5315] [Medline: 18457355]
52. Arduini D, Rizzo G. Normal values of Pulsatility Index from fetal vessels: a cross-sectional study on 1556 healthy fetuses. J Perinat Med 1990;18(3):165-172. [doi: 10.1515/jpme.1990.18.3.165] [Medline: 2200862]
53. Baschat AA, Gembruch U. The cerebroplacental Doppler ratio revisited. Ultrasound Obstet Gynecol 2003 Feb 13;21(2):124-127 [FREE Full text] [doi: 10.1002/uog.20] [Medline: 12601831]
54. Overview | Inducing labour | Guidance | NICE. National Institute for Health and Care Excellence. URL: https://www.nice.org.uk/guidance/ng207 [accessed 2022-09-30]
55. Bishop EH. Pelvic scoring for elective induction. Obstet Gynecol 1964 Aug;24:266-268. [Medline: 14199536]
56. Overview | Intrapartum care for healthy women and babies | Guidance | NICE. National Institute for Health and Care Excellence. URL: https://www.nice.org.uk/guidance/cg190/ [accessed 2022-09-30]
57. Macones GA, Hankins GDV, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring: update on definitions, interpretation, and research guidelines. J Obstet Gynecol Neonatal Nurs 2008;37(5):510-515. [doi: 10.1111/j.1552-6909.2008.00284.x] [Medline: 18761565]
58. Bhide A, Acharya G, Baschat A, Bilardo CM, Brezinka C, Cafici D, et al. ISUOG Practice Guidelines (updated): use of Doppler velocimetry in obstetrics. Ultrasound Obstet Gynecol 2021 Aug;58(2):331-339 [FREE Full text] [doi: 10.1002/uog.23698] [Medline: 34278615]
59. Shrem G, Nagawkar SS, Hallak M, Walfisch A. Isolated oligohydramnios at term as an indication for labor induction: a systematic review and meta-analysis. Fetal Diagn Ther 2016;40(3):161-173 [FREE Full text] [doi: 10.1159/000445948] [Medline: 27160748]
60. Manning FA. Fetal biophysical profile. Obstet Gynecol Clin North Am 1999 Dec;26(4):557-77, v. [doi: 10.1016/s0889-8545(05)70099-1] [Medline: 10587955]
61. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013 Nov;122(5):1122-1131. [doi: 10.1097/01.AOG.0000437382.03963.88] [Medline: 24150027]
62. Sweet LR, Keech C, Klein NP, Marshall HS, Tagbo BN, Quine D, Brighton Collaboration Respiratory Distress in the Neonate Working Group. Vaccine 2017 Dec 04;35(48 Pt A):6506-6517 [FREE Full text] [doi: 10.1016/j.vaccine.2017.01.046] [Medline: 29150056]
63. Kumar A, Chakraborty B. Interim analysis: A rational approach of decision making in clinical trial. J Adv Pharm Technol Res 2016;7(4):118-122 [FREE Full text] [doi: 10.4103/2231-4040.191414] [Medline: 27833889]
64. Vall d'Hebron Research Institute (VHIR) Redcap installation. Vanderbilt University. URL: https://servirredcap.vhir.org/redcap/index.php? [accessed 2022-09-30]

Abbreviations

AF: angiogenic factors
CPR: cerebroplacental ratio
CTG: cardiotocography
EFW: estimated fetal weight
FGR: fetal growth restriction
MCA: middle cerebral artery
NICE: National Institute for Health and Care Excellence
NICU: neonatal intensive care unit
PE: preeclampsia
PI: pulsatility index
PlGF: placental growth factor
sFlt-1: soluble fms-like tyrosine kinase-1
SGA: small for gestational age
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
UA: umbilical artery
UtA: uterine artery

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Protocol

Program of Intensive Support in Emergency Departments for Care Partners of Cognitively Impaired Patients: Protocol for a Multisite Randomized Controlled Trial

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Abstract

Background: Older adults with cognitive impairment have more emergency department visits and 30-day readmissions and are more likely to die after visiting the emergency department than people without cognitive impairment. Emergency department providers frequently do not identify cognitive impairment. Use of cognitive screening tools, along with better understanding of root causes for emergency department visits, could equip health care teams with the knowledge needed to develop individually tailored care management strategies for post–emergency department care. By identifying and directly addressing patients' and informal caregivers' (or care partners') psychosocial and health care needs, such strategies could reduce the need for repeat acute care. We have used the terms "caregiver" and "care partner" interchangeably.

Objective: We aimed to describe the protocol for a randomized controlled trial of a new care management intervention, the Program of Intensive Support in Emergency Departments for Care Partners of Cognitively Impaired Patients (POISED) trial, compared with usual care. We described the research design, intervention, outcome measures, data collection techniques, and analysis plans.

Methods: Emergency department patients who were aged ≥75 years and screened positive for cognitive impairment via either the Mini-Cog or the proxy-reported Short Informant Questionnaire on Cognitive Decline in the Elderly, with a planned discharge to home, were recruited to participate with their identified informal (family or friend) caregiver in the 2-site POISED randomized controlled trial at New York University Langone Health and Indiana University. The intervention group received 6 months of care management from the POISED Care Team of registered nurses and specialty-trained paraprofessionals, who perform root

cause analyses, administer standardized assessments, provide advice, recommend appropriate referrals, and, when applicable, implement dementia-specific comorbid condition protocols. The control group received care as recommended at emergency department discharge (usual care) and were given information about resources for further cognitive assessment. The primary outcome is repeat emergency department use; secondary outcomes include caregiver activation for patient health care management, caregiver depression, anxiety, and experience of social support as important predisposing and time-varying enabling and need characteristics. Data were collected from questionnaires and patients' electronic health records.

Results: Recruitment was conducted between March 2018 and May 2021. Study findings will be published in peer-reviewed journals and presented to peer audiences, decision makers, stakeholders, and other interested persons.

Conclusions: The POISED intervention is a promising approach to tailoring care management based on root causes for emergency department admission of patients with cognitive impairment with the aim of reducing readmissions. This trial will provide insights for caregivers and emergency department and primary care providers on appropriate, personalized, and proactive treatment plans for older adults with cognitive impairment. The findings will be relevant to audiences concerned with quality of life for individuals with cognitive impairment and their caregivers.

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KEYWORDS

emergency department; cognitive impairment; dementia; care management; root cause analysis

Introduction

Background

An emergency department visit can be a "sentinel event" for an older adult; the need for urgent attention may signal a potentially serious new problem or failure in managing a chronic condition [1-3]. Although the presenting symptoms and medically related precipitation of acute decompensation are the focus for emergency department care, emergency departments do not typically deploy standardized strategies to uncover or address psychosocial and environmental underlying conditions, or patients' unmet needs or care process precipitants, including lifestyle or care factors that may be root causes of the need for acute care in older people. These root causes can include unrecognized cognitive impairment (often caused by Alzheimer disease or Alzheimer disease–related disorders) that increases the risk or impact of an injury or illness, unmet needs of caregivers, or an unsatisfactory home situation. We use the term, "caregiver" for someone (family or friend) we assume is giving care and "care partner" for someone (family or friend) where we do not make that assumption. Older adults visit emergency departments more frequently than younger adults and are more likely to experience adverse events after discharge [4]. They tend to present with greater acuity and clinical complexity, remain longer in the emergency department, and require more care coordination at discharge [5]. Older adults are also at greater risk of readmission and death after emergency department discharge; 20% of the older adults are readmitted and approximately 20% die within the first 3 months [6-8]. Risks are magnified by cognitive impairment in addition to age-related influences on symptom presentation and multiple comorbid conditions [9], polypharmacy [10], and higher risk of adverse drug events with increasing age [11,12]; presenting complaints and history may be vague or distorted by its effects on thinking, memory, and communication. As most emergency department physicians have little geriatric training, they may lack the expertise and skills to deal with these challenges and feel less comfortable caring for older than younger patients [13], increasing the potential for diagnostic errors and ineffective or inappropriate discharge plans [6,14]. Typical emergency department discharge plans do not account for the clinical complexity that is common in this patient group or organize effective follow-up for conditions not perceived as directly related to the visit, nor do they specifically address cognitive impairment or the help caregivers may need. Attention to recognizing and mitigating the risk of repeat emergency department visits is also not usual practice, and widely adopted care transition programs developed by Coleman [15] and Naylor [16] have not been adapted specifically for cognitively impaired patients or for the emergency department. Although some emergency department discharge approaches, such as follow-up phone calls, have had some success, they lack specificity for cognitively impaired individuals, cover only brief periods of follow-up [17], and do not target root causes [18].

Cognitive impairment is present in an estimated 25% to 40% of older patients in the emergency department [19-22] and is grossly underrecognized [20] as it is in primary care practice [23,24]. Affected individuals are at risk for poor disease management and accidental injuries that require acute care, and multiple comorbid conditions are common. In a study of emergency department use at Eskenazi Health (a site for this study), people with dementia had the highest mean number of comorbidities (mean 8, SD 2.5) of any patient subgroup, and their emergency department presentation was likely to be conditioned by this complexity [25]. In addition, caregivers may use the emergency department as a source of respite or general medical care that would be better provided in a different setting [26]. Importantly, emergency department use by people with cognitive impairment can signal unmet needs for treating ambulatory sensitive conditions or continuous medical management, for coaching or support for their caregivers at home, or for deployment of community-based services to sustain care in the home setting. Emergency departments are typically not equipped to identify reasons for visits owing to cognitive

impairment or unmet caregiver needs. Therefore, identifying cognitive impairment in the emergency department, coupled with planned postdischarge care management of associated medical and lifestyle risks, is clinically important and could mitigate the need for future emergency department care.

Most daily care needs of people with clinically significant cognitive impairment living in the community are provided for by unpaid caregivers, usually family or friends [27]. Caregivers report more emotional [28] and physical stress, more hours per week spent providing care, less time for themselves and other families, and had more work-related problems than caregivers of persons with noncognitive (physical) impairments [29]. In addition, emergency department use is associated with caregiver depression and care recipient functional, behavioral, and psychological symptoms [29,30]. Concerns about the needs of caregivers of persons with cognitive impairment, including dementia, have motivated the development of dementia care management programs [31,32], adult day centers, and community support services for people living with dementia and their caregivers. However, such programs do not focus specifically on high-risk or high-need patients, may not engage caregivers in health care management or even see them as partners with clinicians in managing overall medical care, or recognize the need for emergency department or other acute care as a possible signal of unmet needs. Although the patient is in the emergency department, purposeful identification of caregivers, who play indispensable roles in carrying out postdischarge care plans and assuring follow-up once the patient leaves the acute care setting, can occur only if cognitive impairment is first detected.

Our research team includes experienced investigators (JC, SB, NRF, KIC, CRG, and MAB) who have conducted trials of dementia detection and implemented dementia-specific collaborative care management programs. Our team also includes emergency department providers and international experts in psychosocial support for dementia caregivers and demonstrated an association between caregiver support and long-term reductions in nursing home placement [33]. We apply a method initially developed outside of health care—root cause analysis—to uncover potentially remediable but unrecognized factors that lead to emergency department visits. The goal is to inform and implement preventive, person-centered care strategies that may reduce the need for further emergency department care. This intervention is the first of its kind to determine the root causes of emergency department visits for patients who screen positive for cognitive impairment and provide tailored support for caregivers and patients (dyads) in post–emergency department care. In this study, we report the protocol for a randomized controlled trial of the care management intervention, Program of Intensive Support in Emergency Departments for Care Partners of Cognitively Impaired Patients (POISED) trial. POISED is the first caregiver-based intervention to look for and intervene on hidden factors that may contribute to emergency department visits among older people living with cognitive impairment.

Objectives

We aim to report the protocol for the design, implementation, and evaluation of a care management intervention, POISED, compared with usual care. The specific aims of this study are as follows:

1. To test whether the POISED intervention will reduce patients' recurrent acute care use over 6 months when compared with post–emergency department care for dyads not receiving POISED. We hypothesize that rates of recurrent acute care use over 6 months will be lower for patients whose family caregivers participate in POISED.
2. To test whether the 6-month POISED intervention will activate family care partners to improve management of care recipients' health care at 3 and 6 months compared with post–emergency department care without POISED. We hypothesize that POISED will increase family caregiver activation in managing the health care of patients.
3. To test whether POISED will improve care partner psychosocial outcomes compared with post–emergency department care without POISED at 3 and 6 months. We hypothesize that caregiver depression, anxiety, and experience of social support will improve more for caregivers who are enrolled in POISED than for those referred to other care management programs.

Methods

Trial Design

This is a 2-site single-blind randomized clinical trial. The randomized trial of the POISED intervention is conducted in 2 cities, New York City, New York, and Indianapolis, Indiana, and in the emergency departments of their respective academic institutions: New York University Langone Health and Indiana University Health and Eskenazi Health. Both emergency departments are academic teaching facilities used to participate in clinical trials. Both have multiple sites, which are in predominantly urban and racially diverse environments. Although these were the locations for recruitment, study procedures following consent occurred outside of the emergency department environment.

The 6-month intervention is led by the POISED Care Team, consisting of a registered nurse (the care manager) and a specially trained paraprofessional (care manager associate), who administer structured assessments and perform root cause analysis. These initial assessments are used to prepare the care management team with a comprehensive understanding of the problems leading to the emergency department visits and are the basis for creating a personalized, structured dyadic outpatient care management plan to address the needs of both patients and caregivers. The intervention is delivered via telephone or in person.

Participants

Patients in the emergency department, at New York University Langone Health and Indiana University Health and Eskenazi Health, aged ≥75 years, who screened positive for cognitive impairment and had a planned discharge to home, were recruited to participate with their identified informal care partner.

Potential participants were excluded if they lacked consent capacity and had no identified care partner, or were likely to be admitted to an inpatient service. Care partners were those persons who self-identified or were identified by the patient in the emergency department as the person most likely to assist with day-to-day activities if needed. Care partners had to (1) be English- or Spanish-speaking, (2) be able to speak by telephone, (3) have adequate hearing, (4) be at least 21 years old, and (5) demonstrate capacity to consent. If they did not meet all 5 criteria, they were excluded.

Procedure

This noninvasive health service intervention included cognitive screening administered by research staff at any point during their emergency department admission, which was inclusive of being in an observation unit. Each potential participant was screened with one of two screening tools: the Mini-Cog [34], for patients who could be interviewed directly, or the Short Informant Questionnaire on Cognitive Decline in the Elderly [35-37], given to their family care partner. A score of ≤3/5 on the Mini-Cog [38,39] or >3.4 on the Short Informant Questionnaire on Cognitive Decline in the Elderly (for those who could not complete the Mini-Cog [35-37]) was used to identify impairment. After identifying patients with probable cognitive impairment, the research staff approached them and offered participation to them and their care partners. When feasible, the research staff then conducted a baseline assessment in the emergency department or scheduled a baseline telephone interview with the care partner as soon as possible after discharge (preferably within 48 hours). Patients and care partners (dyads) were the unit of randomization to either POISED or usual care. Follow-up assessment surveys will occur at 3 and 6 months after baseline.

The POISED Model

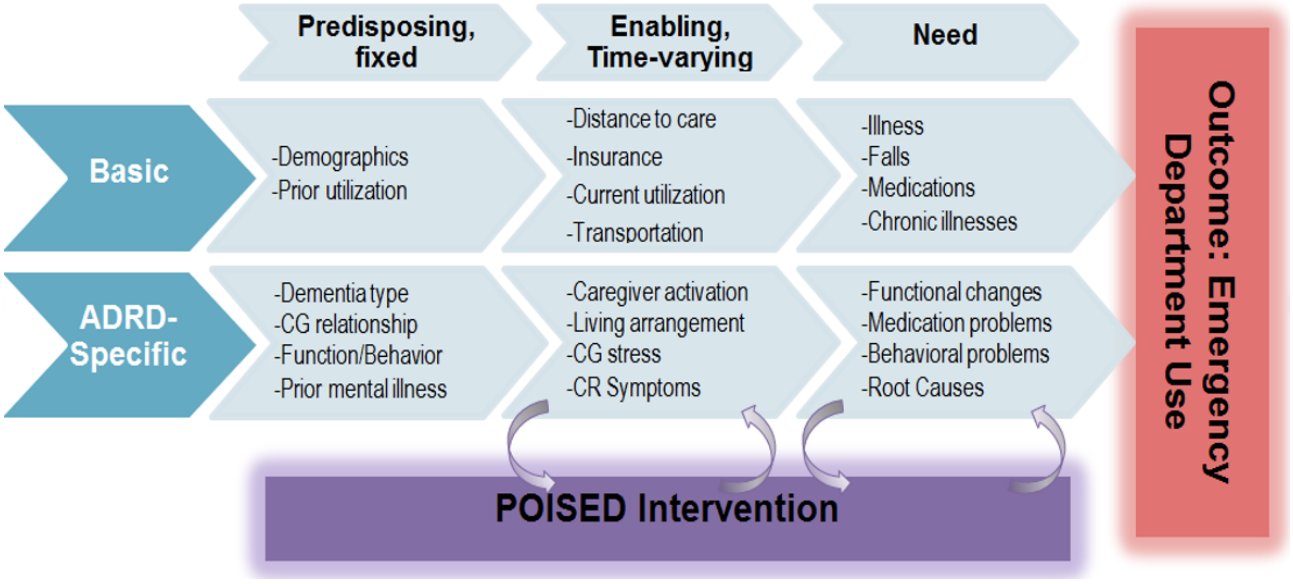
Overview

The POISED model is designed to maximize effectiveness, improve clinical outcomes, enhance family caregivers' skills in both self-management and health care management for the care recipient (ie, both members of the dyad), and to maximize their coping behaviors. The model is designed to promote reproducibility and has 3 main overlapping phases: the initial assessment phase, the collaborative care plan development phase, and ongoing collaborative care management.

Conceptual Framework

The POISED intervention was adapted from the Behavioral Model for Vulnerable Populations [40] originating from the Andersen behavioral model of health service use [41]. We reframed the "vulnerable" domain characteristics (Figure 1) as those particularly relevant to individuals with cognitive impairment that may substantially affect service use. These include *predisposing factors*, such as the care partner relationship (eg, spouse, child, or friend) with the care recipient, type and severity of cognitive impairment, and behavioral complications; *enabling factors*, such as care partner activation for health care management of the care recipient, in-home support resources, adequacy of the caregiving social network of family and friends); and *need factors*, such as specific treatment related to the care recipient's acute health conditions or lack of access to medication. The POISED intervention targets these basic factors and dementia-specific factors, including knowledge about dementia and other chronic comorbid conditions, social networks (mobilizing family and friends) and support, and perceptions about health states. Dementia-specific characteristics we targeted included care partner psychological factors, effective patient and care partner self-management skills (the foundation of optimal management of chronic diseases), health system navigation skills, and health perceptions.

Figure 1. Conceptual model. ADRD: Alzheimer disease/Alzheimer Disease–Related Disorders; CG: caregiver; CR: care recipient; POISED: Program of Intensive Support in Emergency Departments for Care Partners of Cognitively Impaired Patients. Please refer to Table 1 for a more detailed list of measured factors within each category.



Core Strategies: Basis for Program Components

The POISED model components were motivated by dementia care quality standards as developed by the American Medical Association Physician Consortium for Quality Practice-convened Dementia Measures Work Group [42] and supplemented with chronic disease management approaches primarily directed to family caregivers. POISED components were derived from several core strategies essential for successful care management: (1) building connection and trust with dyads to increase engagement; (2) using a shared decision-making framework to establish goals that make sense to care partners, care managers, and paraprofessional care manager associates; (3) using structured, validated assessments that are comprehensive but brief enough to limit care partner burden and increase scalability for future translation; (4) increasing "on-demand" care partner access to program resources; (5) ensuring flexibility in relationships with primary care physicians in establishing allocation of responsibility; and (6) ensuring minimum standards of expertise that cover the range of biopsychosocial needs of dyads through the use of interdisciplinary care management teams.

Collaborative Management of Dementia Care

The burden of dementia can be reduced with collaborative management of dementia care. In 2002, Boustani et al [43] at Indiana University conducted a randomized controlled trial to compare the efficacy of a collaborative care management program for persons with dementia with the efficacy of augmented usual care. Using the chronic care model framework [44,45], this program used guideline-based biopsychosocial interventions for patients with dementia and their family caregivers (dyads). Intervention patients had significantly fewer behavioral symptoms and showed a significant 18-month improvement in depression [43]. A care management intervention, Alzheimer's Disease Collaborative Care for San Diego Seniors, adapted a similar chronic care model framework to deliver a collaborative dementia care program within primary care and reduced dementia burden. On the basis of the mean percentage of per-patient guideline adherence, care quality for intervention group participants was better across 21 of the 23 guidelines; more dyads received community agency assistance, including respite care, than dyads in usual care [31,32]. In addition, a 3-year pragmatic cluster randomized telephone-only administered dementia care management trial within a Medicare Advantage plan improved care quality and caregiver confidence [46]. These collaborative dementia care programs, with similar chronic care model core components, were able to improve the quality of care, quality of life, and the behavioral and psychological symptoms of dementia among primary care patients and their family caregivers. The model continues to be spread in health systems for caregivers of patients already recognized as having dementia [47-49].

Transitioning From Acute to Postacute Settings

The Care Transitions Intervention, tested and implemented in >750 health care organizations in 40 states across the United States [50], was developed to assist vulnerable older adults in transitioning from acute to postacute settings and support increasing the capacity of patients and family caregivers in self-managing their care needs [50-52]. The Care Transitions Intervention focuses on "Four Pillars" of patient self-management: (1) medication management, (2) use of a personal health record, (3) appropriate medical follow-up, and (4) knowing how to identify and respond to a "red flag" indicative of a worsening chronic condition. We applied these strategies to the POISED intervention.

Preparation and Function of Care Manager Associates

Using paraprofessionals who are educated to support care management activities drives workforce development and ensures the scalability of the POISED model. Boustani et al [49] translated the collaborative dementia and depression care model into the Aging Brain Care Home funded by the Centers for Medicare and Medicaid Services Innovation Center to serve older adults in a safety net hospital system using care manager associate paraprofessionals educated in older adult care and screened for "caring." Care manager associates are required to possess specific attributes to be capable of delivering excellent care: the ability to express caring, compassion, and empathy to both care partners and care recipients [53].

POISED Intervention Description

The 6-month POISED care management intervention includes up to 2 in-person home visits between the dyad and the care manager and care manager associate (POISED Care Team), after an in-emergency department or phone call assessment and during the first 6 weeks after enrollment, supplemented by weekly care manager associate calls for the first month, twice-monthly calls during the second and third months, and monthly calls for the following 3 months. Although home visits are preferred, dyads remain in the intervention group even if all contacts are telephonic. Additional phone calls are scheduled with the care manager or care manager associate, as needed. A personalized dyadic care plan, "Our Action Plan," is prepared and placed in a Care Partner Notebook (3-ring health care binder) with appropriate disease-specific infographic educational materials to teach skills for managing the dyad's health needs on a day-to-day basis. "Our Action Plan" is a collaborative list of the care partner's priority problems or goals (in care partner's own words), titles of infographics, and next steps for the care partner and care manager to do. Care planning steps within the POISED disease-specific infographic educational sheets are as follows: (1) assess further; (2) inform by providing materials and education; (3) teach problem-solving and self-management or self-care; (4) make a clinical referral or follow-up appointment with a clinician; and (5) offer resources within New York University Langone Health or Indiana University Health and Eskenazi Health, or community social services in their respective regions. For clarity and usefulness, we prepared colorful infographics about disease-specific management designed to reflect the experience of caring for a person with cognitive impairment and written at an eighth grade reading level. The notebook also includes an "Introduction Letter," "POISED Care Team Contact Sheet," and other documents such as log sheets and an Advance Directive form, as appropriate. Supervision for the POISED Care Team is provided in twice-monthly team videoconferences with experienced dementia specialist clinicians who may help clarify root causes

and make other care management suggestions. Although POISED is not embedded within the primary care context, contact is made with the patient's primary care provider when necessary (eg, to share information relevant to medical treatment).

Intervention Group

POISED Initial Assessment Phase

The POISED Care Team is structured to maximize the skill sets of specialty-trained nurses functioning as care managers and paraprofessionals in the role of care manager associates in a collaborative model. The care manager and care manager associate conduct a biopsychosocial needs assessment by phone within 48 hours of emergency department discharge if not possible during the emergency department stay. This assessment includes a demographic and psychosocial interview focused on achieving problem identification. The program uses standardized assessment tools including "Managing Your Loved One's Health" for chronic disease management [54]. The care manager's interview also uses principles of root cause analysis to better understand the events and potential causes leading to the emergency department visit.

The POISED Care Team documents the initial and follow-up visits, focuses on problem clarification, and reviews the assessment findings, medical records, medication lists, emergency department discharge plans, and pharmacist consultation. The care manager also reviews any diagnostic testing, any brain imaging results, and functional details of the assessment to determine the presence or absence of a likely dementia diagnosis, identifying any reversible and comorbid conditions and, for complex cases, the need for referral for further evaluation at either New York University Langone Health's or Indiana University Health's or Eskenazi Health's well-developed dementia assessment centers. After reviewing the findings from prior data and the first encounter, the care manager and care manager associate create an initial plan and identify areas needing further assessment at the first home visit (within 2 weeks after enrollment). This visit enables the POISED Care Team to conduct additional cognitive and functional testing. In addition, the care manager uses the time to address more sensitive issues that the care partner may be uncomfortable discussing in the presence of the care recipient.

POISED Collaborative Care Plan Development Phase

This phase starts with the emergency department visit and concludes with the second home visit by the POISED care team. The goal of this phase is to create an individualized care plan through the lens of cognitive impairment, which aligns with the goals and capacities of the family care partner and care recipient. After the initial assessment is completed, any urgent issues are addressed, including consulting with the program geriatrician and primary care physician as needed. The POISED care team maps out a proposed care plan and schedules a second home visit to review the findings, discuss identified problems, and propose a collaborative plan of culturally sensitive interventions. During the second home visit, this team reviews the identified problem list, seeks input from the dyad on the continuing relevance of this list, and prioritizes the most important problems. From this consensus, the care manager discusses a proposed plan of care and customizes interventions to the dyad; explains the diagnosis, natural history, and the prognosis of dementia as necessary; and implements medical care protocols and connects patients and care partners to in-home services and community resources as needed. The POISED care team prepares and mails a personalized Care Partner 3-ring binder and follows up with a phone call to explain the binder and review materials with the care partner and patient, if able and appropriate.

POISED Follow-up Phase

This phase continues throughout the 6-month intervention or until the dyad is discharged from the program for reasons stipulated (see the *Criteria for Discharge From the POISED Intervention* section). During the follow-up phase, the POISED care team (primarily the care manager associate) continues to interact with the dyad by telephone, by video, by email, by fax, by mail, or face to face at their home, demonstrating a commitment to patient-centered care. The minimum amount of care manager associate contact during this time is weekly for the first month, twice-monthly calls during the second and third months, and monthly calls for the final 3 months. Interaction intensity is dictated by presenting needs and circumstances but is set at this minimum to reflect an anticipated high level of need. During these interactions, the care manager or care manager associate answers questions generated from previous visits, collects care recipient and care partner feedback, has the care partner complete a brief assessment to identify the need for specific care protocols, and facilitates care partner participation in community services already available in either the New York or Indianapolis areas. The care manager reconciles medication and reviews medication adherence at the initial and second home visit. Medication questions are referred to the study pharmacist. Throughout the follow-up phase, the team continues to work with the dyad, with contact with the patient's primary care provider as needed, to monitor, implement, and adjust the individualized care plan. Referrals are made to local support programs that include caregiver support groups and respite care.

Root Cause Analysis of the Index Emergency Department Visit

Both care manager and care manager associate members of the POISED care team are well-versed in root cause analysis strategies. Starting with the emergency department visit and working backward in time, the team explores and identifies problems or branch-point situations that progress to the need for emergency department care. Using a logic tree as a cause-and-effect approach to create a timeline of events leading to emergency department visits [55] and asking the question, "How could this occur?" or "Why?" based on the "five whys" strategy [56], the POISED care team asks "why" for each successive answer, starting with "Why did you come to the emergency department?" Answers are applied to medical record review looking for other possible triggers and opportunities for intervention.

POISED Care Team Support

Videoconference calls among the POISED care teams are regularly scheduled (weekly to biweekly) during the study period. These calls include at least one physician specializing in dementia care and a dementia nurse specialist to offer guidance on root cause analysis discussions of patients' emergency department visits. The root cause analysis review is structured across a 5-part domain dementia care model: (1) *body* or medical problems, (2) *behavior* or mental, (3) *brain* or cognition, (4) *buddy* or caregiver, and (5) *bank* or financial and social capital and resources. These calls also focus on ideas and methods to (1) involve the care partner and patient (as able) in goal setting and making plans to live as well as possible and (2) maximize collaboration to tailor patient-centered interventions to increase success for the care partner and patient throughout the 6-month intervention and the future. Another purpose for the video calls is to serve as an important collegial support mechanism within and across the New York University and Indiana University–based POISED care teams.

Criteria for Discharge From the POISED Intervention

The POISED care team used the following discharge criteria: (1) death of the patient, (2) patient or care partner declines to continue in the program, (3) primary care provider requests patient to be discharged from the program, (4) patient transitions to another health care system, (5) living situation or environment becomes unsafe for patient or care partner and therefore requires long-term skilled nursing home care, or (6) dyad completes the 6-month study.

Control Group

The comparison group are participants randomized to usual care. They receive referrals to services at the time of enrollment. The usual care group does not receive the POISED structured assessment, root cause analysis, or associated strategies for managing chronic disease in individuals with cognitive impairment. As for intervention dyads, usual care dyads receive a laminated card showing the stress thermometer [57] to be tracked in follow-up interview assessments. Usual care dyads might be referred to care management programs at New York University and Indiana University, but such programs are not focused on issues leading to emergency department care. Moreover, our experience is that wait times for engagement in these programs can take ≥2 months and should not reduce our ability to detect between-group differences should some control group participants become engaged in an alternate form of care management support.

Primary Outcome Measure

To assess for potential influence on any emergency department use after the index emergency department visit (primary outcome), we will use electronic medical records within each study site and identify all emergency department visits for 12 months before the index emergency department visit or study enrollment and 12 months after enrollment. We will also search all-payer databases in New York and the Indiana State Network for Patient Care (a fully operational Health Information Exchange) to identify any episode of ambulatory or acute care that occurred within the 12 months before and 12 months after enrollment (6-month intervention and 6-month follow-up). Finally, a one-item survey question will identify any additional visits that might have occurred outside the indicated state regions. For descriptive purposes, the International Classification of Diseases discharge diagnoses will be included for any emergency department use. We will structure continuous variables that describe the number of ambulatory or acute care episodes.

Secondary Outcome Measures

Specific Aim 2 Measures—Caregiver Activation in Health Care Management of Care Recipient

After consenting the care partner, we will measure caregiver activation, a multidimensional construct developed by Borson et al [54] that includes caregiver knowledge, skills, and confidence to manage a range of tasks and tackle challenges common to dementia health care management [54]. For what may be the central mediating influence on emergency department use within the domain of "need," this tool is a 29-item instrument with excellent internal consistency (Cronbach α=.95); good test-retest reliability, r=0.76; a strong factor structure; and strong construct validity by Rasch analysis. Domains include recognizing, anticipating, and managing day-to-day symptoms and challenges for care recipient health; managing care recipient medications; recognizing and managing sudden changes in care recipient health; accessing health services and advocating for the care recipient in the health care space; and managing caregiver self-care. Four-level item responses range from "agree completely" to "disagree completely" with an additional option, "not my job." We will use the total score to measure activation.

Specific Aim 3 Measures—Psychosocial States as Important Predisposing and Time-Varying Enabling and Need Characteristics

These include caregiver depression, anxiety, experience of social support, and stress. We will use the Patient Health Questionnaire–9 (PHQ-9; [58,59]) and the 7-item Generalized Anxiety Disorder (GAD-7) scale [60,61] to determine the impact of the POISED intervention on caregivers' mood and anxiety at baseline, 3 months, and 6 months. We have used both instruments in multiple research studies, including our dementia collaborative care trials [43,62,63]. The PHQ-9 is a 9-item depression scale with a total score from 0 to 27, and the GAD-7 is a 7-item anxiety scale with a total score from 0 to 21. Both scales have good internal consistency and test-retest reliability, as well as convergent, construct, criterion, procedural, and factorial validity for the diagnosis of major depression and general anxiety disorder [58-61]. Experience of social support will be measured using the Medical Outcomes Study (MOS) Social Support Survey—Abbreviated [64]. This is a 4-item survey that uses a 5-point Likert scale. Respondents are asked how often each kind of support is available if needed. The 4 elements of support are "someone to get together with for relaxation" (companionate support), "someone to help with daily chores if you were sick" (instrumental support), "someone to turn to for suggestions about how to deal with a personal problem" (informational with support), and "someone to love

and make you feel wanted" (emotional support). Analyses comparing the abbreviated version to the original version have shown strong similarities in performance and good psychometric properties based on confirmatory factor analyses [65]. The stress thermometer [57], a visual thermometer with a 5-level analog scale to indicate the level of stress chosen by the caregiver, measures caregiver stress. Every enrolled care partner will be given a laminated card with the stress thermometer at the time of emergency department discharge for use during interviews. Lost cards will be replaced. We will use the Healthy Aging Brain Care (HABC) monitor to adjust for dementia symptom severity [66]. The HABC monitor is a caregiver survey tool for monitoring 3 care recipient symptom domains (cognitive, functional, and behavioral or psychological) and a caregiver quality of life measure. It has good internal consistency (0.73-0.92) and construct validity compared with the Neuropsychiatric Inventory [67], and is sensitive to 3-month change compared with Neuropsychiatric Inventory "reliable change" groups [66].

Other Outcome Measures

Additional outcome measures (Table 1), in addition to primary and secondary measures, cover predisposing, enabling, and need characteristics and serve as important covariables within the regression model testing emergency department use as the primary outcome.

Table 1. Predisposing, enabling, and need characteristics.

Measure	Data source	Measure construction	Measures refer to CG[a] or CR[b]; assessment times: 0 or BL[c], 3, 6, and 12 months
Predisposing fixed characteristics			
Basic			
Age	EHR[d] or survey	Years	CG, CR; 0 months (BL)
Sex	EHR or survey	Categorical: Male or female	CG, CR; 0 months (BL)
Race or ethnicity	EHR or survey	Categorical: White, Black, Hispanic, other	CG, CR; 0 months (BL)
Education	Survey	Categorical: <High school, high school, some college, college graduate+	CG; 0 months (BL)
Prior (1-year) nonacute use	EHR or survey	Counts: Physician ambulatory visits	CR; 0 months (BL)
Prior (1-year) acute use	EHR or survey	Counts: ED[e], hospital visits or bed days	CR; 0 months (BL)
AD/ADRD[f] specific			
Dementia type	EHR	Categorical: Including Alzheimer disease, Lewy Body disease, Parkinson disease, vascular, frontotemporal, and mixed	CR; 0, 3, and 6 months
Caregiver relationship to CR	Survey	Categorical: Spouse, child, other relative, friend or other	CG, CR; 0 months
Functional state	Survey	14 items: Activities of Daily Living or Instrumental Activities of Daily Living [68] for CG; within HABC-M[g] [66] for CR	CG, CR; 0, 3, and 6 months
Marital status	Survey	Categorical: Single or never married, married, divorced, widowed	CG, CR; 0, 3, and 6 months
Substance use history	Survey	Current: Yes or no; past history: yes or no	CG, CR; 0, 3, and 6 months
Mental illness history	Survey	Yes or no: depression, schizophrenia, posttraumatic stress disorder, other	CG, CR; 0 months
Enabling time-varying effect characteristics			
Basic			
Distance to hospital (ED)	Calculated	Miles	CG, CR; 0, 3, and 6 months
Distance to usual source of care (USC)	Calculated	Miles	CG, CR; 0, 3, and 6 months
Difference in distance ED vs USC	Calculated	Miles (USC)—distance to hospital	CG, CR; 0, 3, and 6 months
Change in PCP[h]	Survey	Yes or no	CR; 0, 3, and 6 months
Insurance	EHR	Yes or no	CR; 0, 3, and 6 months
Current nonacute use	EHR or survey	Counts: physician ambulatory visits, in-home supportive services	CR; 0, 3, 6, and 12 months
Current acute use	EHR or survey	Counts: physician ambulatory visits, ED, hospital visits or bed days	CR; 0, 3, 6, and 12 months
AD/ADRD specific			
Mode of transportation	Survey	Categorical: personal car, taxi, train, bus, walk	CR; 0, 3, and 6 months
Caregiver living arrangement	Survey	Categorical: Live with subject, close proximity (miles), other	CG; 0, 3, and 6 months
Caregiver stress	Survey	Stress thermometer (scale), 5-level visual analog scale [57]	CG; 0, 3, 6, and 12 months
Dementia symptoms	Survey	HABC-M [66] (measuring severity of CR symptoms)	CR; 0, 3, and 6 months
Need characteristics			

Measure	Data source	Measure construction	Measures refer to CG[a] or CR[b]; assessment times: 0 or BL[c], 3, 6, and 12 months
Basic			
Acute illness	Survey	Counts: episodes by type (classification by study physicians)	CR; 0, 3, and 6 months
Falls, other injuries	Survey	Counts: episodes by type (classification by study physicians)	CR; 0, 3, and 6 months
Nonacute illness	Survey	Counts: episodes by type (classification by study physicians)	CR; 0, 3, and 6 months
Medication need for refill	Survey	Categorical: Yes or no	CR; 0, 3, and 6 months
Clinical comorbid conditions	EHR	Charlson comorbidity index [69]	CR; 0, 3, and 6 months
Satisfaction	Survey	Scale: 0-10 (worst possible care to best possible care [70])	CG; 0, 3, and 6 months
AD/ADRD specific			
Functional state	Survey	14 items: Activities of Daily Living or Instrumental Activities of Daily Living for CG [68]; within HABC-M [66] for CR	CG, CR; 0, 3, and 6 months
Caregiver activation	Survey	MYLOH[i] Instrument [71]	CR; 0, 3, 6, and 12 months
Social support	Survey	MOS[j] Abbreviated Social Support (4-item; 5-point Likert scale [64,72])	CG; 0, 3, and 6 months
Other root causes	EHR	Application of post hoc adjudication of root causes for ED use	CR; 0, 3, and 6 months

[a]CG: caregiver.

[b]CR: care recipient.

[c]BL: baseline.

[d]EHR: electronic health record.

[e]ED: emergency department.

[f]AD/ADRD: Alzheimer disease/Alzheimer Disease–Related Disorders.

[g]HABC-M: Healthy Aging Brain Care Monitor.

[h]PCP: primary care physician.

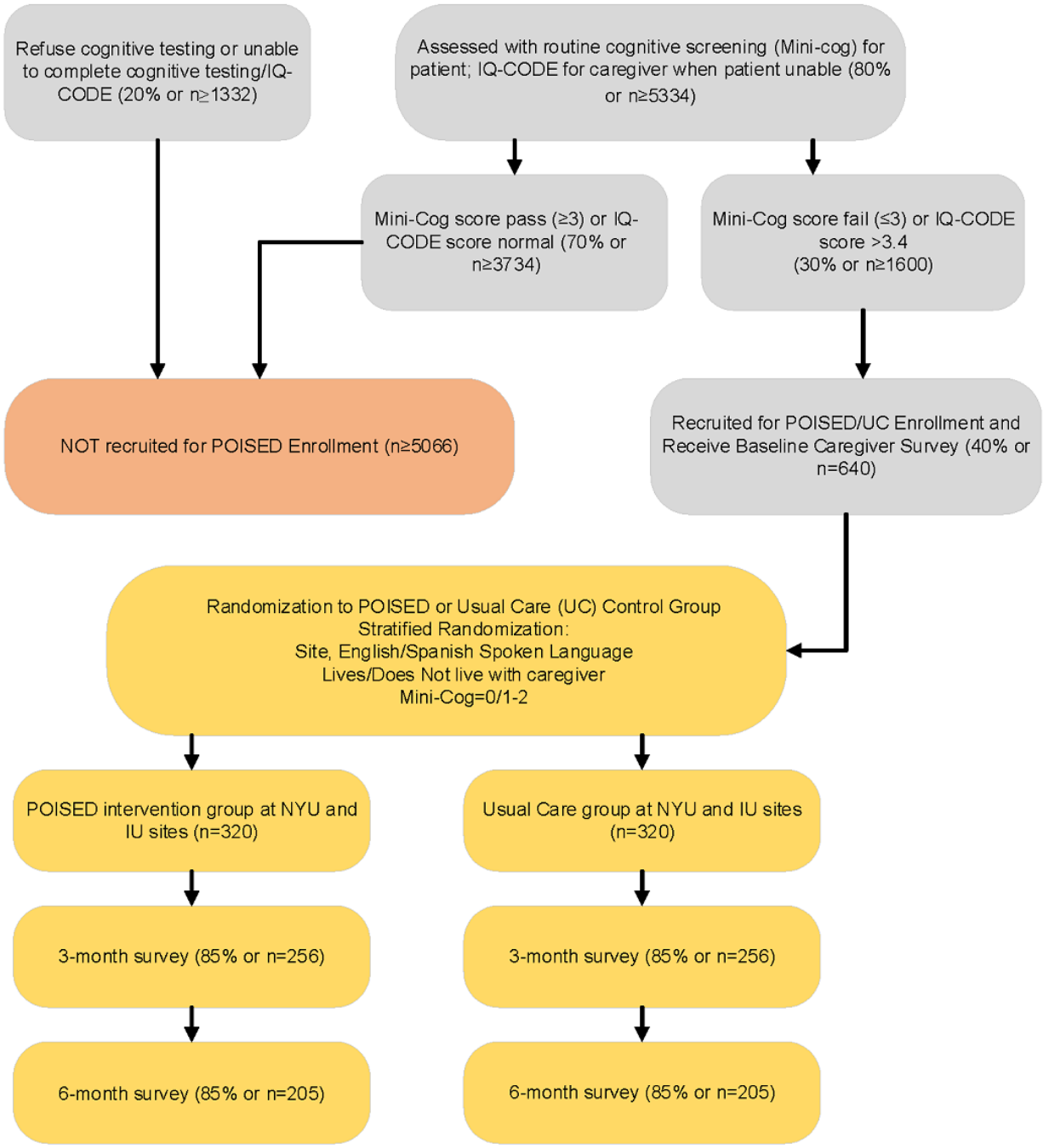
[i]MYLOH: Managing Your Loved One's Health.

[j]MOS: Medical Outcomes Study.

Sample Size Calculations

Using conservative prevalence statistics for cognitive impairment in patients presenting to the emergency department at New York University Langone Health, Indiana University Health, and Eskenazi Health, numbers (6100 patients in 2015) exceed those needed (Figure 2) to achieve 80% power for detecting reduction in acute care use in the POISED group compared with the usual care group in specific aim 1. A previous study reported a 30-day readmission rate of 58% in patients with dementia compared with 38% in those without dementia [26]. Given that our patient sample may include individuals with less severe cognitive impairment and less emergency department use, we assume, conservatively, that the rate of repeat emergency department visits in the usual care group is 40%. With 320 patients enrolled per group, we will have 82% power to detect an odds ratio of 0.62 for repeat emergency department visits in the POISED group compared with the usual care group at the 0.05 significance level. This detectable odds ratio is equivalent to reducing the emergency department visit rate to 29% or lower in the POISED group compared with the 40% assumed for the control group. The use of stratified randomization reduces the variance of the difference between the 2 group means and results in greater power than simple randomization [73,74]. Therefore, the actual power for our study will be higher than that projected here. As we will be using electronic health records for acute care data and phone follow-up to supplement out-of-network use, we anticipate complete data from all study participants for this aim.

Figure 2. Recruitment or enrollment flowchart. IQ-CODE: Informant Questionnaire on Cognitive Decline in the Elderly; IU: Indiana University; NYU: New York University; POISED: Program of Intensive Support in Emergency Departments for Care Partners of Cognitively Impaired Patients.



For aims 2 and 3, assuming that 205 (64%) dyads will complete the 6-month evaluation (Figure 2), we will have 80% power to detect an effect size ≥0.28 on the caregiver activation score, PHQ-9, GAD-7, and MOS scores between the POISED group and the control group using a 2-tailed *t* test at a .05 significance level. The detectable effect size of 0.28 used in our power estimation is reasonable and justified given that previous studies on collaborative care management of dementia patients have shown an effect size of 0.45 SD on a number of caregiver psychosocial outcomes [43]. Previous studies have found a mean PHQ-9 score of 4.4 (SD 5.6) and a mean GAD-7 score of 3.2 (SD 3.5 [43,58,59,61]). Thus, our projected effect size will allow us to detect a change as small as 1.6 on the PHQ-9 and 1 on the GAD-7. As described earlier, the use of stratified randomization will provide greater power than that projected here.

Randomization

To produce comparable groups and insure against accidental bias in treatment assignments, we used a computer-generated web-based stratified randomization scheme. Dyads were randomized to intervention or usual care groups in random blocks of 4 or 6 stratified by site (New York University Langone Health or Indiana University Health and Eskenazi Health).

Statistical Methods or Analysis Plan

Overview

We will compare randomization results to the preplanned schedule to ensure randomization integrity. To verify the comparability of the randomized groups, we will compare dyads between the 2 groups to identify differences in their baseline characteristics (age, sex, race, and education), care recipient comorbid medical conditions, and the Charlson comorbidity index [69,75]. We will also look for differences in the number of primary care visits and acute care use during the year before enrollment between the POISED group and the usual care group by using analysis of covariance models for continuous variables and the Cochran-Mantel-Hansel statistic for categorical variables controlling for the stratification variable of recruitment site. We will examine the distributions of continuous variables and use transformation or nonparametric methods in cases of violation to the normal distribution assumption. We will also examine the frequency distribution of all categorical variables and use exact inference procedures in cases of 0 or small cell size. We will use SAS (version 9.4; SAS Institute) for all the analyses.

Specific Aim 1

We will use logistic regression models to compare the rates of emergency department admission during the 6-month intervention period following the index (recruitment) emergency department visit. Emergency department readmission within 6 months will be used as a binary outcome in the logistic model, and the randomization group will be the independent variable while adjusting for site. Baseline characteristics that are shown to be unbalanced in univariate comparisons between the 2 groups will also be adjusted. Although not a primary outcome, we will also examine 12-month emergency department use data.

Specific Aim 2

We will use mixed effects models with caregiver activation scores at 3 months and 6 months as the outcome measure and randomization group as the independent variable while controlling for baseline activation score and site. We will conduct post hoc comparisons of the activation scores between the POISED group and the usual care group at 3 and 6 months using linear contrast from the mixed effects model following a significant group effect. To explore what changes are responsive to the POISED intervention, we will also use the mixed effects model to examine differences in activation domain scores between the 2 groups. The mixed effects model will account for potential correlations between repeated measures from the same individual and deal with missing data appropriately when the probability of missing data is unrelated to the missing observation.

Specific Aim 3

We will use mixed effects models with repeatedly measured PHQ-9, GAD-7, and MOS social support scores collected at 3 and 6 months as dependent variables. The independent variable for the mixed effects model will be the indicator variable for the randomization group while controlling for baseline scores and site. We will use post hoc analysis to determine group differences in these measures between the 2 groups at the 3- or 6-month evaluations. The modeling approach resembles that for aim 2.

Sensitivity Analysis for Missing Data

The analysis plan outlined above assumes that outcome measures at follow-up are missing at random with respect to demographic characteristics and baseline results. We will compare baseline characteristics of participants with missing outcomes because of death or withdrawal to detect potential violations of the missing-at-random assumption. Further sensitivity analyses will involve various imputation methods or a full parametric likelihood approach that assumes various patterns of missing data [58].

Data Monitoring

To proactively maintain high quality in data collection, data are routinely checked as they are stored within study databases. Data are quality-checked before analysis.

Data Collection

Data will come from 3 sources. First, the web-based tracking system of data entered by the POISED Care Team will use a REDCap (Research Electronic Data Capture; Vanderbilt University) database [76]. These data will provide us with extensive information on the process and content of care for those randomized to the POISED. This system is designed to support and monitor clinical care delivered by the POISED Care Team. We have fields to support the POISED intervention care processes, including results of assessment instruments, content of the tailored intervention, and clinical observations such as dyads' level of participation. Second, we will obtain data on health services use including all diagnostic testing and medication use and use of inpatient and outpatient services from 1 year before study enrollment to 1 year after enrollment (2-year duration) from the New York University Langone Health's Epic system and the Indiana Network for Patient Care [77]. Data are obtained from electronic medical records by a team of data managers employed by New York University (DataCore) and the Regenstrief Institute in support of clinical research. Third, the primary outcome measure data will come from telephone interviews and are entered in a separate REDCap database. A research interviewer collects complete telephone survey data from caregivers at baseline, 3 months, and 6 months using a 30-minute survey, blinded to randomization assignment. Care manager associates collect much briefer 12-month follow-up data (6 months after the intervention) from intervention and control caregivers as a measure of treatment effect sustainability. The interviewer enters deidentified survey data from each survey wave into a Health Insurance Portability and Accountability Act–compliant REDCap electronic database hosted at New York University [76]. REDCap baseline data are available to the POISED Care Team so that specific relevant data can inform care manager previsit data and limit redundancy in questions and caregiver interview burden.

Data Management

DataCore, a resource launched by the New York University Langone School of Medicine, housed within its Information Technology Department and formed in collaboration with the Clinical and Translational Science Institute, the Biomedical

Informatics and Translational Library Programs, and the Department of Population Health, will provide enterprise level support to ensure the integrity of electronic data during its capture, storage, management, extraction, and sharing. DataCore will merge these 3 data streams using unique identifiers assigned to the study participants and provide regular backups onto a secure server.

Ethical Considerations and Data Confidentiality

The Institutional Review Boards of New York University Langone Health and Indiana University Health provided permission on February 24, 2017, and April 27, 2017, respectively, to conduct the POISED study (approval number: i16-01473_CR2). The clinical trial registration (NCT03325608) was listed on October 30, 2017. At enrollment, we obtained consent from patients (or assent with care partner proxy consent when the patient lacked the capacity to consent) to enable the review of their medical records. The proxy consent was the next of kin using a defined hierarchy in the absence of a Durable Power of Attorney or by consenting the proxy who is the Durable Power of Attorney. Participants completed an "education session" during the consent process regarding the potential risks and benefits of participating in a noninvasive health services research study for valid informed consent. Electronic data are stored in password-protected files on secure servers at New York University and Indiana University. Research staff are trained in the institutional review board–approved methods for collecting, recording, storing, and reporting research data to protect the privacy of participants and maintain the confidentiality of data.

Results

Data collection began in March 2018 and was completed in February 2022. We have recruited 643 dyads (patients and care partners). Data are currently being analyzed. The study results will be published in peer-reviewed journals and presented to peer conferences, decision makers at the participating university medical centers, and other interested audiences.

Discussion

Potential Impact

Studying care management for older adults living with cognitive impairment and possible undetected dementia who are identified at emergency department visits may lead to low-cost strategies to reduce high-cost acute care. It may also improve caregivers' ability to optimally assist patients in the management of chronic disease that is particularly challenging in older adults with cognitive impairment. Related impacts may be improved health outcomes of patients and psychosocial well-being of caregivers.

Limitations (Threats to Validity)

The most significant limitation will be the dependence on one care management team at each site, as findings may reflect the personal qualities of the care manager and care manager associate. However, a clearly communicated and structured intervention protocol and standardized education and training program will limit the quality and reproducibility concerns. We may find no change in caregiver activation while demonstrating reductions in acute care use. An absence of change (aim 2) may reflect an inadequate measure or a factor that is not in the pathway of health service use. However, the opportunity to demonstrate a causal relationship between activation and use for this population is profoundly important. Given that usual care participants may receive dementia-specific resources given well-developed programs at both institutions, the comparative between-group differences might be diminished. However, engagement for usual care participants is not likely to occur for at least 2 months after the index emergency department visit and will not be focused on management strategies that reflect an applied root cause analysis for that visit. Although some emergency department patients will have a diagnosis of Alzheimer disease or Alzheimer disease–related dementia before their emergency department visit, some patients may not have Alzheimer disease or related dementia (even after a positive screen) and generalizability to future Alzheimer disease or related dementia patients might be questioned. However, the cognitive screener and older age group for inclusion should limit false positives, and diagnostic errors should be equivalent across groups.

Dissemination

Cognitive impairment is prevalent among older adults who visit the emergency department, but often this is unrecognized. Root cause analysis linked to care management strategies may better focus the intervention resulting in more reductions in acute care use while more directly addressing care partners' needs. This study may provide effective low-cost approaches for reducing high-cost acute care use and related improvements in care partners' abilities to optimize management of chronic diseases particularly challenging for care recipients with cognitive impairment. Moreover, this highly standardized and reproducible approach has the potential for direct application in large multisite clinical intervention trials. The use of paraprofessionals as care management assistants increases the scalability of this work and provides opportunities for large-scale implementation and dissemination if proven efficacious.

Conclusions

The POISED program is a promising approach to address the root causes for emergency department admission in older adults with cognitive impairment and prevent repeated readmissions. The results from this trial will provide insights for care partners and medical staff on proactive treatment plans with appropriate and personalized management plans for these older adults and for care partners themselves. These findings will be relevant to both professionals and nonprofessionals concerned with the quality of life for individuals with cognitive problems and their care partners.

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Data Availability

Data will be available upon request after the analyses are completed and the data are properly deidentified.

Conflicts of Interest

Several measures used in this research were developed by coauthors and were used without conditions in this study.

References

1. Kasper J, Freedman V, Spillman B. Disability and care needs of older Americans by dementia status: an analysis of the 2011 national health and aging trends study. ASPE. 2016. URL: https://aspe.hhs.gov/reports/disability-care-needs-older-americans-dementia-status-analysis-2011-national-health-aging-trends-1 [accessed 2016-01-10]
2. Gillespie R, Mullan J, Harrison L. Managing medications: the role of informal caregivers of older adults and people living with dementia. A review of the literature. J Clin Nurs 2014 Dec;23(23-24):3296-3308. [doi: 10.1111/jocn.12519] [Medline: 24354583]
3. Lowthian J, Straney LD, Brand CA, Barker AL, Smit PD, Newnham H, et al. Unplanned early return to the emergency department by older patients: the Safe Elderly Emergency Department Discharge (SEED) project. Age Ageing 2016 Mar;45(2):255-261. [doi: 10.1093/ageing/afv198] [Medline: 26764254]
4. Pines JM, Mullins PM, Cooper JK, Feng LB, Roth KE. National trends in emergency department use, care patterns, and quality of care of older adults in the United States. J Am Geriatr Soc 2013 Jan;61(1):12-17. [doi: 10.1111/jgs.12072] [Medline: 23311549]
5. Schumacher JG. Emergency medicine and older adults: continuing challenges and opportunities. Am J Emerg Med 2005 Jul;23(4):556-560. [doi: 10.1016/j.ajem.2004.12.011] [Medline: 16032631]
6. McCusker J, Roberge D, Vadeboncoeur A, Verdon J. Safety of discharge of seniors from the emergency department to the community. Healthc Q 2009;12 Spec No Patient:24-32 [FREE Full text] [doi: 10.12927/hcq.2009.20963] [Medline: 19667774]
7. Hastings SN, Schmader KE, Sloane RJ, Weinberger M, Goldberg KC, Oddone EZ. Adverse health outcomes after discharge from the emergency department--incidence and risk factors in a veteran population. J Gen Intern Med 2007 Nov;22(11):1527-1531 [FREE Full text] [doi: 10.1007/s11606-007-0343-9] [Medline: 17828432]
8. McCusker J, Cardin S, Bellavance F, Belzile E. Return to the emergency department among elders: patterns and predictors. Acad Emerg Med 2000 Mar;7(3):249-259 [FREE Full text] [doi: 10.1111/j.1553-2712.2000.tb01070.x] [Medline: 10730832]
9. Aminzadeh F, Dalziel W. Older adults in the emergency department: a systematic review of patterns of use, adverse outcomes, and effectiveness of interventions. Ann Emerg Med 2002 Mar;39(3):238-247. [doi: 10.1067/mem.2002.121523] [Medline: 11867975]
10. Banerjee A, Mbamalu D, Ebrahimi S, Khan A, Chan T. The prevalence of polypharmacy in elderly attenders to an emergency department - a problem with a need for an effective solution. Int J Emerg Med 2011 Jun 02;4(1):22 [FREE Full text] [doi: 10.1186/1865-1380-4-22] [Medline: 21635734]
11. Hohl CM, Dankoff J, Colacone A, Afilalo M. Polypharmacy, adverse drug-related events, and potential adverse drug interactions in elderly patients presenting to an emergency department. Ann Emerg Med 2001 Dec;38(6):666-671. [doi: 10.1067/mem.2001.119456] [Medline: 11719747]
12. Brown JD, Hutchison LC, Li C, Painter JT, Martin BC. Predictive validity of the beers and screening tool of older persons' potentially inappropriate prescriptions (STOPP) criteria to detect adverse drug events, hospitalizations, and emergency department visits in the United States. J Am Geriatr Soc 2016 Jan;64(1):22-30 [FREE Full text] [doi: 10.1111/jgs.13884] [Medline: 26782849]
13. Grief C. Patterns of ED use and perceptions of the elderly regarding their emergency care: a synthesis of recent research. J Emerg Nurs 2003 Apr;29(2):122-126. [doi: 10.1067/men.2003.65] [Medline: 12660693]
14. Meurer W, Potti T, Kerber K, Sasson C, Macy M, West B, et al. Potentially inappropriate medication utilization in the emergency department visits by older adults: analysis from a nationally representative sample. Acad Emerg Med 2010 Mar;17(3):231-237 [FREE Full text] [doi: 10.1111/j.1553-2712.2010.00667.x] [Medline: 20370754]
15. Coleman EA, Parry C, Chalmers S, Min S. The care transitions intervention: results of a randomized controlled trial. Arch Intern Med 2006 Sep 25;166(17):1822-1828. [doi: 10.1001/archinte.166.17.1822] [Medline: 17000937]
16. Naylor MD, Hirschman KB, Hanlon AL, Bowles KH, Bradway C, McCauley KM, et al. Effects of alternative interventions among hospitalized, cognitively impaired older adults. J Comp Eff Res 2016 May;5(3):259-272 [FREE Full text] [doi: 10.2217/cer-2015-0009] [Medline: 27146416]

17. Guttman A, Afilalo M, Guttman R, Colacone A, Robitaille C, Lang E, et al. An emergency department-based nurse discharge coordinator for elder patients: does it make a difference? Acad Emerg Med 2004 Dec;11(12):1318-1327 [FREE Full text] [doi: 10.1197/j.aem.2004.07.006] [Medline: 15576523]
18. Biese K, Lamantia M, Shofer F, McCall B, Roberts E, Stearns SC, et al. A randomized trial exploring the effect of a telephone call follow-up on care plan compliance among older adults discharged home from the emergency department. Acad Emerg Med 2014 Feb;21(2):188-195 [FREE Full text] [doi: 10.1111/acem.12308] [Medline: 24673675]
19. Hustey F, Meldon S. Prevalence and documentation of impaired mental status in elderly emergency department patients. Acad Emerg Med 2000 Oct;7(10):1166 [FREE Full text] [Medline: 11015259]
20. Hustey FM, Meldon SW, Smith MD, Lex CK. The effect of mental status screening on the care of elderly emergency department patients. Ann Emerg Med 2003 May;41(5):678-684. [doi: 10.1067/mem.2003.152] [Medline: 12712035]
21. Salen P, Heller M, Oller C, Reed J. The impact of routine cognitive screening by using the clock drawing task in the evaluation of elderly patients in the emergency department. J Emerg Med 2009 Jul;37(1):8-12. [doi: 10.1016/j.jemermed.2007.06.031] [Medline: 18065185]
22. Fonseca JA, Ducksbury R, Rodda J, Whitfield T, Nagaraj C, Suresh K, et al. Factors that predict cognitive decline in patients with subjective cognitive impairment. Int Psychogeriatr 2015 Oct;27(10):1671-1677. [doi: 10.1017/S1041610215000356] [Medline: 25812703]
23. Chodosh J, Petitti D, Elliott M, Hays R, Crooks V, Reuben D, et al. Physician recognition of cognitive impairment: evaluating the need for improvement. J Am Geriatr Soc 2004 Jul;52(7):1051-1059. [doi: 10.1111/j.1532-5415.2004.52301.x] [Medline: 15209641]
24. Callahan CM, Hendrie HC, Tierney WM. Documentation and evaluation of cognitive impairment in elderly primary care patients. Ann Intern Med 1995 Mar 15;122(6):422-429. [doi: 10.7326/0003-4819-122-6-199503150-00004] [Medline: 7856990]
25. LaMantia MA, Stump TE, Messina FC, Miller DK, Callahan CM. Emergency department use among older adults with dementia. Alzheimer Dis Assoc Disord 2016;30(1):35-40 [FREE Full text] [doi: 10.1097/WAD.0000000000000118] [Medline: 26523710]
26. Oliveira D, Zarit SH, Orrell M. Health-promoting self-care in family caregivers of people with dementia: the views of multiple stakeholders. Gerontologist 2019 Sep 17;59(5):e501-e511. [doi: 10.1093/geront/gnz029] [Medline: 30953585]
27. Schulz R, Martire LM. Family caregiving of persons with dementia: prevalence, health effects, and support strategies. Am J Geriatr Psychiatry 2004;12(3):240-249. [Medline: 15126224]
28. Cuijpers P. Depressive disorders in caregivers of dementia patients: a systematic review. Aging Ment Health 2005 Jul;9(4):325-330. [doi: 10.1080/13607860500090078] [Medline: 16019288]
29. Schubert CC, Boustani M, Callahan CM, Perkins AJ, Hui S, Hendrie HC. Acute care utilization by dementia caregivers within urban primary care practices. J Gen Intern Med 2008 Nov;23(11):1736-1740 [FREE Full text] [doi: 10.1007/s11606-008-0711-0] [Medline: 18690489]
30. Beck A, Jacobsohn G, Hollander M, Gilmore-Bykovskyi A, Werner N, Shah M. Features of primary care practice influence emergency care-seeking behaviors by caregivers of persons with dementia: a multiple-perspective qualitative study. Dementia (London) 2021 Feb;20(2):613-632 [FREE Full text] [doi: 10.1177/1471301220905233] [Medline: 32050779]
31. Vickrey B, Mittman B, Connor K, Pearson M, Della Penna RD, Ganiats T, et al. The effect of a disease management intervention on quality and outcomes of dementia care: a randomized, controlled trial. Ann Intern Med 2006 Nov 21;145(10):713-726. [doi: 10.7326/0003-4819-145-10-200611210-00004] [Medline: 17116916]
32. Chodosh J, Mittman BS, Connor KI, Vassar SD, Lee ML, DeMonte RW, et al. Caring for patients with dementia: how good is the quality of care? Results from three health systems. J Am Geriatr Soc 2007 Aug;55(8):1260-1268. [doi: 10.1111/j.1532-5415.2007.01249.x] [Medline: 17661967]
33. Gaugler JE, Reese M, Mittelman MS. Effects of the NYU caregiver intervention-adult child on residential care placement. Gerontologist 2013 Dec;53(6):985-997 [FREE Full text] [doi: 10.1093/geront/gns193] [Medline: 23339050]
34. Borson S, Scanlan J, Brush M, Vitaliano P, Dokmak A. The mini-cog: a cognitive 'vital signs' measure for dementia screening in multi-lingual elderly. Int J Geriatr Psychiatry 2000 Nov;15(11):1021-1027. [doi: 10.1002/1099-1166(200011)15:11<1021::aid-gps234>3.0.co;2-6] [Medline: 11113982]
35. Jorm AF, Jacomb PA. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): socio-demographic correlates, reliability, validity and some norms. Psychol Med 1989 Nov;19(4):1015-1022. [doi: 10.1017/s0033291700005742] [Medline: 2594878]
36. Jorm A. The Informant Questionnaire on cognitive decline in the elderly (IQCODE): a review. Int Psychogeriatr 2004 Sep;16(3):275-293. [doi: 10.1017/s1041610204000390] [Medline: 15559753]
37. Jorm A. A short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): development and cross-validation. Psychol Med 1994 Feb;24(1):145-153. [doi: 10.1017/s003329170002691x] [Medline: 8208879]
38. McCarten JR, Anderson P, Kuskowski MA, McPherson SE, Borson S, Dysken MW. Finding dementia in primary care: the results of a clinical demonstration project. J Am Geriatr Soc 2012 Feb;60(2):210-217. [doi: 10.1111/j.1532-5415.2011.03841.x] [Medline: 22332672]

39. Rosenbloom M, Barclay TR, Borson S, Werner AM, Erickson LO, Crow JM, et al. Screening positive for cognitive impairment: impact on healthcare utilization and provider action in primary and specialty care practices. J Gen Intern Med 2018 Oct;33(10):1746-1751 [FREE Full text] [doi: 10.1007/s11606-018-4606-4] [Medline: 30097978]
40. Gelberg L, Andersen R, Leake B. The Behavioral Model for Vulnerable Populations: application to medical care use and outcomes for homeless people. Health Serv Res 2000 Feb;34(6):1273-1302 [FREE Full text] [Medline: 10654830]
41. Andersen RM. Revisiting the behavioral model and access to medical care: does it matter? J Health Social Behav 1995 Mar;36(1):1. [doi: 10.2307/2137284]
42. Odenheimer G, Borson S, Sanders AE, Swain-Eng RJ, Kyomen HH, Tierney S, et al. Quality improvement in neurology: dementia management quality measures. Neurology 2013 Oct 22;81(17):1545-1549 [FREE Full text] [doi: 10.1212/WNL.0b013e3182a956bf] [Medline: 24068786]
43. Callahan C, Boustani M, Unverzagt F, Austrom M, Damush T, Perkins A, et al. Effectiveness of collaborative care for older adults with Alzheimer disease in primary care: a randomized controlled trial. JAMA 2006 May 10;295(18):2148-2157. [doi: 10.1001/jama.295.18.2148] [Medline: 16684985]
44. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness. JAMA 2002 Oct 09;288(14):1775-1779. [doi: 10.1001/jama.288.14.1775] [Medline: 12365965]
45. Williams JW, Plassman BL, Burke J, Benjamin S. Preventing Alzheimer's disease and cognitive decline. Evid Rep Technol Assess (Full Rep) 2010 Apr(193):1-727. [Medline: 21500874]
46. Chodosh J, Connor K, Vassar S, Pearson M, Lee M, Mittman B, et al. Implementing dementia care management in a Medicare managed care plan: a randomized controlled trial. J Am Geriatr Soc 2015;63.
47. Tan ZS, Jennings L, Reuben D. Coordinated care management for dementia in a large academic health system. Health Aff (Millwood) 2014 Apr;33(4):619-625 [FREE Full text] [doi: 10.1377/hlthaff.2013.1294] [Medline: 24711323]
48. Reuben DB, Evertson LC, Wenger NS, Serrano K, Chodosh J, Ercoli L, et al. The University of California at Los Angeles Alzheimer's and Dementia Care program for comprehensive, coordinated, patient-centered care: preliminary data. J Am Geriatr Soc 2013 Dec;61(12):2214-2218 [FREE Full text] [doi: 10.1111/jgs.12562] [Medline: 24329821]
49. Callahan CM, Sachs GA, Lamantia MA, Unroe KT, Arling G, Boustani MA. Redesigning systems of care for older adults with Alzheimer's disease. Health Aff (Millwood) 2014 Apr;33(4):626-632 [FREE Full text] [doi: 10.1377/hlthaff.2013.1260] [Medline: 24711324]
50. Coleman EA, Smith JD, Frank JC, Min S, Parry C, Kramer AM. Preparing patients and caregivers to participate in care delivered across settings: the Care Transitions Intervention. J Am Geriatr Soc 2004 Nov;52(11):1817-1825. [doi: 10.1111/j.1532-5415.2004.52504.x] [Medline: 15507057]
51. Parry C, Coleman E, Smith J, Frank J, Kramer A. The care transitions intervention: a patient-centered approach to ensuring effective transfers between sites of geriatric care. Home Health Care Serv Q 2003;22(3):1-17. [doi: 10.1300/J027v22n03_01] [Medline: 14629081]
52. Coleman EA, Roman SP, Hall KA, Min S. Enhancing the care transitions intervention protocol to better address the needs of family caregivers. J Healthc Qual 2015;37(1):2-11. [doi: 10.1097/01.JHQ.0000460118.60567.fe] [Medline: 26042372]
53. Cottingham AH, Alder C, Austrom MG, Johnson CS, Boustani MA, Litzelman DK. New workforce development in dementia care: screening for "caring": preliminary data. J Am Geriatr Soc 2014 Jul;62(7):1364-1368. [doi: 10.1111/jgs.12886] [Medline: 24916743]
54. Sadak T, Korpak A, Borson S. Measuring caregiver activation for health care: validation of PBH-LCI:D. Geriatr Nurs 2015;36(4):284-292. [doi: 10.1016/j.gerinurse.2015.03.003] [Medline: 25959036]
55. Latino R. Patient Safety The PROACT Root Cause Analysis Approach. Boca Raton, FL: Taylor and Francis; 2008.
56. The five whys technique. Asian Development Bank. 2016. URL: http://www.adb.org/publications/five-whys-technique [accessed 2016-01-25]
57. Borson S, Scanlan J, Sadak T, Lessig M, Vitaliano P. Dementia Services Mini-Screen: a simple method to identify patients and caregivers in need of enhanced dementia care services. Am J Geriatr Psychiatry 2014 Aug;22(8):746-755 [FREE Full text] [doi: 10.1016/j.jagp.2013.11.001] [Medline: 24315560]
58. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001 Sep;16(9):606-613 [FREE Full text] [doi: 10.1046/j.1525-1497.2001.016009606.x] [Medline: 11556941]
59. Löwe B, Unützer J, Callahan CM, Perkins AJ, Kroenke K. Monitoring depression treatment outcomes with the patient health questionnaire-9. Med Care 2004 Dec;42(12):1194-1201. [doi: 10.1097/00005650-200412000-00006] [Medline: 15550799]
60. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006 May 22;166(10):1092-1097. [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
61. Kroenke K, Spitzer RL, Williams JB, Monahan PO, Löwe B. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. Ann Intern Med 2007 Mar 06;146(5):317-325. [doi: 10.7326/0003-4819-146-5-200703060-00004] [Medline: 17339617]
62. Callahan CM, Boustani MA, Weiner M, Beck RA, Livin LR, Kellams JJ, et al. Implementing dementia care models in primary care settings: The Aging Brain Care Medical Home. Aging Ment Health 2011 Jan;15(1):5-12 [FREE Full text] [doi: 10.1080/13607861003801052] [Medline: 20945236]

63. Boustani MA, Sachs GA, Alder CA, Munger S, Schubert CC, Guerriero Austrom M, et al. Implementing innovative models of dementia care: The Healthy Aging Brain Center. Aging Ment Health 2011 Jan;15(1):13-22 [FREE Full text] [doi: 10.1080/13607863.2010.496445] [Medline: 21271387]
64. Sherbourne CD, Stewart AL. The MOS social support survey. Soc Sci Med 1991;32(6):705-714. [doi: 10.1016/0277-9536(91)90150-b] [Medline: 2035047]
65. Gjesfjeld C, Greeno CG, Kim KH. A confirmatory factor analysis of an abbreviated social support instrument: the MOS-SSS. Res Social Work Pract 2007 Nov 29;18(3):231-237. [doi: 10.1177/1049731507309830]
66. Monahan PO, Boustani MA, Alder C, Galvin JE, Perkins AJ, Healey P, et al. Practical clinical tool to monitor dementia symptoms: the HABC-Monitor. Clin Interv Aging 2012;7:143-157 [FREE Full text] [doi: 10.2147/CIA.S30663] [Medline: 22791987]
67. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994 Dec;44(12):2308-2314. [doi: 10.1212/wnl.44.12.2308] [Medline: 7991117]
68. Katz S. Assessing self-maintenance: activities of daily living, mobility, and instrumental activities of daily living. J Am Geriatr Soc 1983 Dec;31(12):721-727. [doi: 10.1111/j.1532-5415.1983.tb03391.x] [Medline: 6418786]
69. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373-383. [doi: 10.1016/0021-9681(87)90171-8] [Medline: 3558716]
70. HCAHPS Survey. HCAHPS. URL: https://hcahpsonline.org/globalassets/hcahps/survey-instruments/mail/effective-july-1-2020-and-forward-discharges/2020_survey-instruments_english_mail.pdf [accessed 2022-01-09]
71. Sadak T, Wright J, Borson S. Managing your loved one's health: development of a new care management measure for dementia family caregivers. J Appl Gerontol 2018 May;37(5):620-643. [doi: 10.1177/0733464816657472] [Medline: 27384048]
72. Dour HJ, Wiley JF, Roy-Byrne P, Stein MB, Sullivan G, Sherbourne CD, et al. Perceived social support mediates anxiety and depressive symptom changes following primary care intervention. Depress Anxiety 2014 May;31(5):436-442 [FREE Full text] [doi: 10.1002/da.22216] [Medline: 24338947]
73. Green SB, Byar DP. The effect of stratified randomization on size and power of statistical tests in clinical trials. J Chronic Dis 1978;31(6-7):445-454. [doi: 10.1016/0021-9681(78)90008-5] [Medline: 711836]
74. Kernan WN, Viscoli CM, Makuch RW, Brass LM, Horwitz RI. Stratified randomization for clinical trials. J Clin Epidemiol 1999 Jan;52(1):19-26. [doi: 10.1016/s0895-4356(98)00138-3] [Medline: 9973070]
75. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992 Jun;45(6):613-619. [doi: 10.1016/0895-4356(92)90133-8] [Medline: 1607900]
76. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009 Apr;42(2):377-381 [FREE Full text] [doi: 10.1016/j.jbi.2008.08.010] [Medline: 18929686]
77. McDonald C, Overhage J, Barnes M, Schadow G, Blevins L, Dexter P, INPC Management Committee. The Indiana network for patient care: a working local health information infrastructure. An example of a working infrastructure collaboration that links data from five health systems and hundreds of millions of entries. Health Aff (Millwood) 2005;24(5):1214-1220. [doi: 10.1377/hlthaff.24.5.1214] [Medline: 16162565]

Abbreviations

GAD-7: 7-item Generalized Anxiety Disorder
HABC: Healthy Aging Brain Care
MOS: Medical Outcomes Study
PHQ-9: Patient Health Questionnaire–9
POISED: Program of Intensive Support in Emergency Departments for Care Partners of Cognitively Impaired Patients
REDCap: Research Electronic Data Capture

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Protocol

Home-Based Respiratory Physiotherapy and Telephone-Based Psychological Support for COVID-19 Survivors in Peru: Protocol for a Randomized Controlled Trial

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Abstract

Background: Both pulmonary and mental health are affected following hospitalization for COVID-19 pneumonia. Pulmonary rehabilitation therapy has demonstrated benefits in improving mental health, but no validated combined programs that include mental health have been proposed.

Objective: This article presents the design of a trial that aimed to assess whether the participation in a combined rehabilitation program that includes home-based respiratory physiotherapy and telephone-based psychological support is associated with a greater improvement of pulmonary and mental health outcomes 7-12 weeks after COVID-19 hospitalization discharge compared with posthospital usual care provided by a public Peruvian hospital.

Methods: WAYRA (the word for air in the Quechua language) was an open-label, unblinded, two-arm randomized controlled trial. We recruited 108 participants aged 18-75 years who were discharged from the hospital after COVID-19 pneumonia that

required >6 liters/minute of supplemental oxygen during treatment. Participants were randomly assigned at a 1:1 ratio to receive the combined rehabilitation program or usual posthospital care provided by a public Peruvian hospital. The intervention consisted of 12 at-home respiratory rehabilitation sessions and 6 telephone-based psychological sessions. The primary outcome was the 6-minute walk distance. Secondary outcomes included lung function, mental health status (depression, anxiety, and trauma), and quality of life. Outcomes were assessed at baseline (before randomization) and at 7 and 12 weeks after hospital discharge to assess the difference between arms.

Results: This study was funded by the Peruvian National Council of Science Technology and Technology Innovation in July 2020. Ethics approval was obtained on September 2, 2020. Recruitment and data collection occurred between October 2020 and June 2021. Results are expected to be published by the end of 2022.

Conclusions: WAYRA was the first randomized controlled trial evaluating combined pulmonary-mental health rehabilitation for hospitalized COVID-19 survivors in resource-limited settings, potentially providing a foundation for the cost-effective scale-up of similar multidisciplinary rehabilitation programs.

Trial Registration: ClinicalTrials.gov NCT04649736; https://clinicaltrials.gov/ct2/show/NCT04649736

International Registered Report Identifier (IRRID): RR1-10.2196/36001

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KEYWORDS

COVID-19; pulmonary rehabilitation; psychiatric rehabilitation; mental health; clinical trial

Introduction

The COVID-19 pandemic is resulting in millions of survivors with long-term complications [1]. Complications are more frequent in patients who required hospitalization, affecting both physical and mental health [1]. Systematic reviews show that 24% to 36% and 40% to 58% of patients with COVID-19 report dyspnea and fatigue after acute illness, respectively [2,3]. The frequency of depression and anxiety in COVID-19 survivors ranges from 12% to 15% and 13% to 22%, respectively [2-5].

Although recommendations for post-COVID-19 rehabilitation already exist [6-9], the evidence is scarce from different aspects. First, most studies have focused on pulmonary rehabilitation [10-12], but no study has evaluated a rehabilitation program that integrates a psychological component. The high frequency of mental illness suggests that patients may benefit from physiological support. Second, no published clinical trial has evaluated a home-based rehabilitation program, an approach that could have advantages over inpatient programs and comparable efficacy [12]. After hospitalization, COVID-19 patients could have several health limitations that make it difficult to visit health care facilities for rehabilitation. Third, most strategies to address the sequelae of COVID-19 have been developed in high-income countries and therefore do not consider some of the challenges specific to developing countries, such as the availability and quality of professionals and infrastructure to carry out rehabilitation [13].

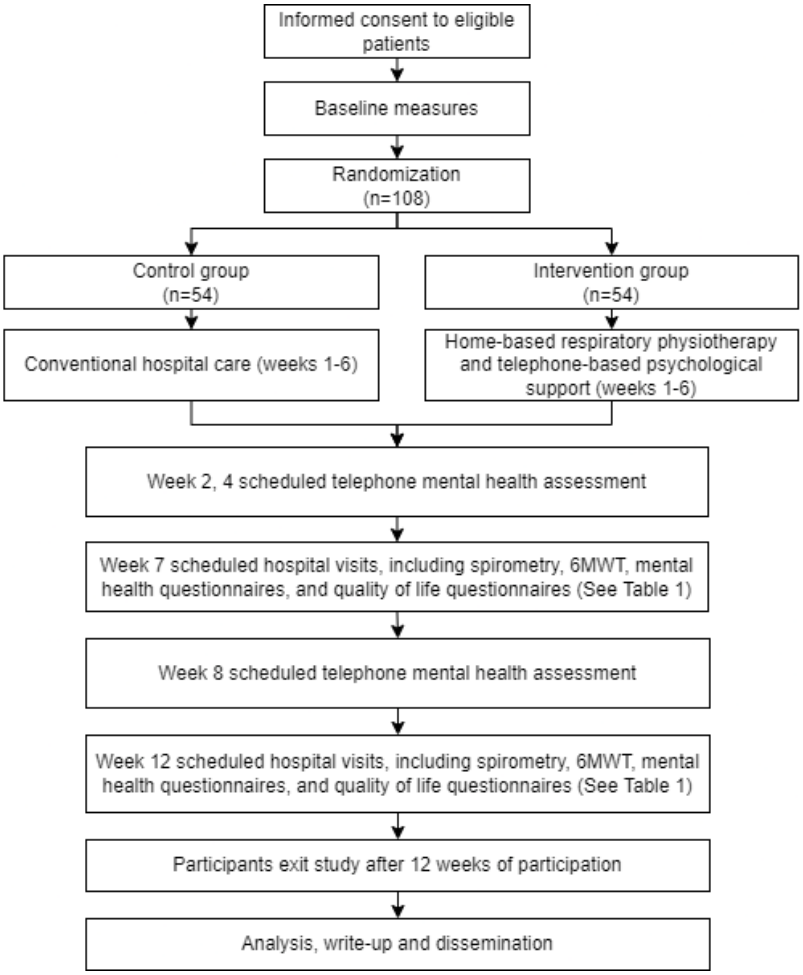
Considering that COVID-19 is a disease that results in short-, medium-, and long-term physical and mental impairment, and that limited rehabilitation strategies have been evaluated, this protocol describes the design and methodology of a randomized controlled trial that aimed to evaluate the effects of integrated home-based respiratory physiotherapy combined with a telephone-based psychological intervention on pulmonary and mental health–related outcomes at 7 and 12 weeks after hospital discharge in patients with COVID-19 pneumonia. The primary objective of the trial was to compare 6-minute walking distances at 7 and 12 weeks after hospital discharge among participants in a combined program versus those who received usual posthospital care provided by a Peruvian public hospital.

Methods

Study Design

WAYRA (the word for air in the Quechua language) was a randomized, controlled, open-label, two-arm clinical trial that evaluated the efficacy of a 6-week home-based respiratory physiotherapy and telephone-based psychological program compared to usual posthospital care provided by a public Peruvian hospital, aimed at improving exercise tolerance, lung function, mental health, and quality of life (QoL) outcomes. A baseline assessment was conducted at hospital discharge, with two follow-ups at week 7 and 12 (Figure 1). Due to the nature of the rehabilitation interventions, blinding of participants and the researchers was not possible; however, the data scientist conducting the data analysis was blinded. The trial was registered at ClinicalTrials.gov (NCT04649736).

Figure 1. Expected study enrollment and timeline diagram. 6MWT: 6-minute walk test.



Study Setting and Population

This study took place in the COVID-19 ward at Hospital Nacional Cayetano Heredia (HNCH), a public tertiary-care hospital and a major referral center that serves approximately 3 million people from underserved neighborhoods in the northern metropolitan area of Lima, the capital of Peru. HNCH has been one of the main COVID-19 national referral centers throughout the pandemic, with 241 hospitalization beds and 23 intensive care unit beds [14]. During the pandemic, more than half of Lima's population reported depressive symptoms, with increased rates of symptoms reported among young people with low income and without higher education [15].

The study population consisted of confirmed cases of COVID-19, diagnosed by serological or molecular tests, including members of both sexes, between 18 and 75 years of age, discharged from hospitalization, who received high-flow oxygen (>6 liters/minute) treatment at any point during hospitalization. Participants with prior respiratory pathology or psychiatric diagnoses were excluded. The complete eligibility criteria are provided in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Age between 18 and 75 years
- Discharged from hospitalization with a confirmed COVID-19 diagnosis
- Capable of understanding study procedures
- Capable of providing informed consent
- Required oxygen flow >6 liters/minute or through a high-flow device at any time during hospitalization
- Evaluated by the rehabilitation service at least once during hospitalization

Exclusion criteria

- Contraindications to the 6-minute walk test
- Contraindications to spirometry
- Complications during the baseline 6-minute walk test
- Neurological pathology, neuropathy, limb dysfunction, or other underlying physical disability that makes physical exercise impossible
- Pregnant or breastfeeding
- No access to the internet or a telephone line
- History or existing lung diseases such as asthma, chronic obstructive pulmonary disease, fibrosis, or tuberculosis
- Moderate or severe heart disease (Grade III or IV, New York Heart Association)
- Diagnosed with another severe disease in the last 6 months
- Severe depression or suicidal ideation
- Taking any medication for depression and/or anxiety, or another medication prescribed by a psychiatrist before the onset of COVID-19
- Cognitive impairment or sensory disturbance

Enrollment

A trained nurse made the initial contact and prescreening, starting with a daily review of the list of hospitalized patients during the enrollment period, to identify potentially eligible participants among newly discharged patients or those close to discharge in the following days. Potential participants were informed about the study and its procedures and were invited to participate. Those who accepted received a detailed explanation of the nature of the study, randomization, study procedures, their potential risks and benefits, their rights as participants, and the study timelines. Potential subjects were explicitly told that participation was not mandatory, that there was no penalty for refusing to participate, and that their clinical treatment at the hospital would not be compromised in any way if they refuse to participate or opt out of the study at any time. All interested patients received the screening informed consent form (Multimedia Appendix 1) for their review, and they provided a signature once all their questions and concerns were addressed.

After obtaining participant consent and signature, a trained nurse performed the screening assessments, including review of eligibility criteria compliance and baseline measurements. These included cognitive status (assessed using the Montreal Cognitive Assessment, visual impairment version [MoCA-BLIND] [16]), sociodemographic and clinical data, baseline respiratory symptoms (using the St. George's Respiratory Questionnaire [SGRQ]), depressive symptoms (using the Nine-Item Patient Health Questionnaire [PHQ-9]), anxiety symptoms (using the Generalized Anxiety Disorder Assessment [GAD-7]), posttraumatic stress disorder symptoms (Impact of Event Scale-Revised [IES-R]), and QoL (using the 36-Item Short Form Survey [SF-36] and EuroQuol-5D [EQ-5D]). Subsequently, a trained physician assessed the participants' exercise tolerance with the 6-minute walk test (6MWT) and pulmonary function with a spirometry test. Participants were screened for severe depressive symptoms. Those with a GAD-7 score ≥15 or IES-R score ≥37 were referred to a psychiatrist for evaluation and treatment. Participants with a PHQ-9 score ≥20 and self-reported suicidal ideation during the psychological evaluation were immediately referred to mental health services for treatment and were excluded from the study. Patients who completed the baseline assessments and met eligibility criteria were enrolled into the study. The recruitment team communicated with the study coordinator who performed a baseline data quality verification, the allocation to one of two arms (control or intervention), and assigned a participant ID code.

Randomization

We used a blinded list preuploaded in REDcap [17], which was created by a data administrator who was not involved in study recruitment. To achieve balance in the number of participants assigned to each study arm, the treatment arm was randomized at a 1:1 ratio using permuted blocks of variable size, randomly varying from 2, 4, and 6 participants. The blocks were randomized using the Stata v16.0 *ralloc* command (StataCorp). Finally, all participants were scheduled for follow-up visits as

described in Table 1. Sample selection and enrollment took place between the day before hospital discharge and up to 3 days after discharge.

Table 1. Data collection schedule.

Time point	Study period (week)												
	Enrollment (–1)	Baseline (0)	Postallocation										Close-out (12)
			1	2	3	4	5	6	7	8	9	10	11	
Enrollment														
Informed consent	✓													
Eligibility screen	✓													
Allocation		✓												
Interventions														
Intervention arm														
Home-based respiratory rehabilitation			✓	✓	✓	✓	✓	✓						
Telephone psychological support			✓	✓	✓	✓	✓	✓						
Control arm: conventional care			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Assessments														
Sociodemographic questionnaire	✓													
Primary outcome: 6MWT[a] distance		✓							✓					✓
Secondary outcomes														
Spirometry[b]		✓							✓					✓
Respiratory symptoms (SGRQ[c])		✓							✓					✓
Quality of life (SF-36[d], EQ-5D[e])		✓							✓					✓
Mental health (PHQ-9[f], GAD-7[g], IES-R[h])		✓		✓		✓			✓	✓				✓
Cognitive function (MoCA-BLIND[i], visual impairment)		✓		✓		✓			✓	✓				✓

[a]6MWT: 6-minute walk test.

[b]Includes forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC ratio.

[c]SGRQ: Saint George's Respiratory Questionnaire.

[d]SF-36: 36-Item Short Form Survey.

[e]EQ-5D: EuroQuol 5D.

[f]PHQ-9: Nine-Item Patient Health Questionnaire.

[g]GAD-7: Generalized Anxiety and Depression.

[h]IES-R: Impact of Event Scale-Revised.

[i]MoCA-BLIND: Montreal Cognitive Assessment visual impairment version.

Comparison Groups

Intervention Arm

The intervention consisted of 12 sessions of home-based respiratory rehabilitation and 6 sessions of weekly psychological support delivered through telephone home calls throughout a period of 6 weeks. Participants began the rehabilitation program no later than 1 week after hospital discharge.

Respiratory rehabilitation consisted of 12 sessions (1-3 per week depending on the participant's availability) performed at home under trained physiotherapist guidance. Each respiratory rehabilitation session lasted approximately 1 hour. In the first rehabilitation session, the physiotherapist brought the necessary equipment to perform the exercises (1-kilogram abdominal weight and a small rubber ball). In each session, the participant performed the following exercises: respiratory muscle training by breathing through pursed lips and breathing education exercises, coughing exercises to produce effective coughs, diaphragm training by teaching diaphragmatic contractions in the supine position with a light weight placed on the anterior abdominal wall, and stretching exercises whereby the participant was placed in a supine or lateral position with the knees bent to correct for lumbar lordosis. In addition, participants performed arm movements in flexion, horizontal extension, abduction, and external rotation. Participants were instructed to perform pursed-lip breathing and effective coughing on the days they did not receive assisted therapy, with a frequency of

30 times per day. The day of nonattendance at respiratory therapy was recorded. Given the risk of exposure to COVID-19, physiotherapists followed a strict biosafety protocol involving the use of personal protective equipment and a thorough disinfection process at each visit. In addition, rehabilitation was ideally performed in a well-ventilated room and the participant wore a surgical mask during visits as an extra protective measure.

The psychological support intervention consisted of an introductory session (Session 0) and 6 1-hour structured sessions based on emotion-centered problem-solving therapy (EC-PST). A trained licensed psychologist provided these sessions once a week by telephone home calls following the guidelines of the Inter-Agency Standing Committee (IASC) on Mental Health and Psychosocial Support in Humanitarian and Disaster Emergencies of the World Health Organization [18]. The EC-PST is an update of the classic problem-solving therapy that emphasizes guiding patients to better understand and manage their emotional reactions to stressful events as a means of coping with the negative effects of these stressors [19]. EC-PST reviews four components: (1) Planful Problem Solving, (2) Overcoming Brain Overload, (3) Enhancing Motivation for Action, and (4) Stop and Slow Down. In addition, we provided each participant with a printed workbook that included the themes and topics that were developed in each session, and the psychologist recorded the main points of the session using an adhoc evaluation form. Table 2 summarizes the objectives of each session.

Table 2. Psychological support objectives.

Session	Content	Objectives
0	Introductory session and psychological history	Take the participant's psychological medical history; evaluate stressful events, consequences, and the participant's perception of what they are experiencing, through the functional behavioral analysis
1	Psychoeducation session	Provide information on the types of problem orientation and problem-solving styles; identify the problem-solving style employed by the patient
2	Toolbox training 1 "Stop and Slow Down"	Teach the "Stop and Slow Down" tool to better modulate emotional reactions to stressful stimuli. Strategies included are counting, guided imagery or visualization, deep breathing, "fake" yawning, conscious meditation, relaxation exercises, deep-muscle exercise or conscious walking, talking to someone, prayer, and the DAPA[a] Method for Emotional Regulation
3	Toolbox training 2 "Overcome Brain Overload" and "Boost Motivation to Act"	Teach "Beat Brain Overload" tools to overcome barriers or obstacles to effective problem-solving, particularly when under stress, through three specific strategies: externalization, visualization, and simplification; orienting people to overcome low motivation and feelings of hopelessness through use of the "Power Motivation to Act" tool through externalization and visualization
4	Toolbox training 3 "Plan the Solution to Your Problems"	Explain and teach the four effective problem-solving steps: define the problem, generate solution alternatives, make the decision, and implement and verify the solution
5	Guided practice	Assist participants in adjusting the problem-solving skills they have acquired; monitor the application of these principles; help participants meaningfully integrate the various tools; reinforce the participant's progress as a means to further increase the sense of self-efficacy
6	Prognosis assessment and termination of the psychological therapy	Prognosis assessment: discuss possible difficulties that the participant may have to help them plan their actions; evaluate the possibility of using the tools taught in the possibility of managing these difficulties. Therapy termination: review the EC-PST[b] objectives established in the initial sessions; ask the patient for examples of how these objectives have been met

[a]DAPA: Dementia and Physical Activity: stop, walk slowly, think, act.

[b]EC-PST: emotion-centered problem-solving therapy.

Control Arm

Participants assigned to the control arm received posthospital usual care delivered by a Peruvian public hospital consisting of discharge recommendations and a telephone follow-up for 14 days provided by the same hospital. Although there are no national guidelines for standardized discharge indications in Peru, many hospitals recommended patients to perform home breathing exercises and symptomatic respiratory treatment. There are currently no diagnostic or follow-up plans for patients that experience or develop mental illness or a strategy for respiratory or psychological rehabilitation in most hospitals in Peru. We collected data about any additional nonstudy therapies that participants may have received from any internal or external health care provider.

Measured Outcomes

Primary Outcome

The primary health outcome was the change in 6-minute walk distance (6MWD) at 7 and 12 weeks after discharge compared to baseline. The 6MWT is a submaximal effort test of cardiorespiratory functional capacity with correlation to QoL and independence in activities of daily living [20]. The 6MWT is widely used for the follow-up of patients after hospitalization

because patients can self-regulate the intensity of the activity, resting as often as desired, leading to minimal risks of adverse events during the activity [20]. The test was performed in a 20-meter hospital aisle marked according to the recommendations of the American Thoracic Society [21,22]. Participants who demonstrated instability while standing, generalized weakness, or those with a decrease in oxygen saturation below 90% or increased heart rate of >130 beats per minute while standing did not perform the test. In this case, the participants were considered to have covered 0 meters. Each participant only attempted the test once. The number of meters walked in the 6MWT was calculated by the assessor and recorded in the data collection form.

Secondary Outcomes

A trained physician measured forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), and the FEV1/FVC ratio using a portable spirometer (Easy-On-PC). These spirometers are frequently used in pulmonary research because their calibration remains stable over time [23]. We aimed to obtain at least three acceptable and two reproducible tests following joint recommendations of the American Thoracic Society and European Respiratory Societies [24] or until the participant was no longer able to tolerate the procedure. Results were recorded on a secure interface (EasyOnConnect) on a personal computer.

For mental health and QoL assessments, participants responded to questionnaires administered by a trained health worker. We used PHQ-9, GAD-7, and IES-R questionnaires to assess mental health, including depression [25], anxiety [26], and posttraumatic stress disorder symptoms [27], respectively. Mental health questionnaires were administered at 2, 4, 7, 8, and 12 weeks after hospitalization by telephone home calls. We used the SF-36 v2 [28] and EQ-5D [29] questionnaires to measure QoL at 7 and 12 weeks after discharge. The psychometric properties of the SF-36 questionnaire have been widely studied and consist of 36 items assessing 8 dimensions: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health [30]. The details of the measurements for the primary and secondary outcomes are summarized in Table 3. We used the SGRQ to assess respiratory symptoms, an instrument recommended to measure changes in respiratory health following interventions [31]. We measured respiratory symptoms at 7 and 12 weeks after hospital discharge (Table 1).

Table 3. Outcomes and instruments in the WAYRA study.

Outcome	Instruments
Pulmonary function	6-minute walk test, spirometry [20]
Respiratory symptoms	St. George's Respiratory Questionnaire (SGRQ) [31]
Depressive symptoms	Patient Health Questionnaire (PHQ-9) [25]
Anxiety symptoms	Generalized Anxiety Disorder (GAD-7) [26]
Posttraumatic stress disorder	Impact Event Scale-Revised (IES-R) [27]
Quality of life	36-Item Short-Form Health Survey [28], EuroQol-5D (EQ-5D) [29]

Statistical Analyses

We will perform an intention-to-treat analysis of primary and secondary outcomes at 7 and 12 weeks after hospital discharge. The final analysis will be performed when all 108 participants completed the trial. We will compare the 6MWD (meters), FVC (liters), FEV1 (liters), and questionnaire scores at 7 and 12 weeks after hospitalization discharge between the intervention and control arms. In the secondary analyses, we will compare the proportion of participants with respect to restrictive spirometry pattern, depression, anxiety, and posttraumatic stress disorder at 7 and 12 weeks after hospital discharge between the intervention and control arms. In addition, following the recommendation by Cocks and Torgerson [32], we will use a one-sided 80% CI to determine if this trial should proceed to a phase III trial. As a sensitivity analysis, the association between the number of therapies received and outcomes will be examined, adjusting for potential confounders that will be identified by a causal acyclic diagram. There will be no formal interim analysis of the data.

Sample Size Calculation

We used STATA Version 16 (StataCorp) to calculate the ideal sample size. We attempted to enroll 108 participants in total, allocating 54 to each treatment arm. We estimate that a sample size of 86 participants would be sufficient to detect a mean difference between arms of 55.1 meters in the 6MWT according to the study by Liu et al [11] considering a 95% CI and 90% power. Assuming a potential 20% rate of rejection or loss to follow-up, we aimed to achieve a sample of 108 participants.

Ethics Approval

Ethical approval of the study protocol and informed consent form was obtained from the Institutional Review Board at Universidad Peruana Cayetano Heredia (#202852) and HNCH (#085-2020). Likewise, any changes in the protocol were reported to the mentioned ethics committees. Written informed consent was requested from all participants prior to any data collection. To protect participants' confidentiality, all collected data of clinical assessments were linked to a unique ID code. Data were registered in paper form and electronically. The electronic information was stored, backed-up, and secured by password protection in the RedCap server. Paper forms were archived in secure locked cabinets in the HNCH. All confidential information, including participants' contact details or other sensitive data, was only accessible to authorized staff from the project. Long-term data management complied with Universidad Peruana Cayetano Heredia research policy. The Peruvian

National Health Institute reviewed the protocol and determined that it was exempt from review by the Ethics Committee due to the nonpharmacological nature of the intervention.

Benefits and Risk of Participation

Both control- and intervention-arm participants benefited from the study. These benefits included education and counseling on respiratory disease risk factors, reporting of pulmonary function test results by a specialist physician, and referral to trained personnel if necessary.

Potential risks of respiratory rehabilitation were oxygen desaturation, palpitations, sweating, arrhythmias, chest tightness, shortness of breath, and muscle aches. Potential risks of psychological support were symptom substitution, dependence on the physiotherapist, stigmatization, problems in social relationships or even separation, as well as alcohol or drug abuse, deliberate self-harm, and suicidal ideation or attempts. Adverse events of the interventions were collected after participants provided informed consent and were duly enrolled in the study. If adverse events were detected, the field staff immediately notified the study coordinator and the management protocol was activated.

Results

The trial, which obtained funding in July 2020, was approved by the Institutional Review Board on September 2, 2020. Data collection began in October 2020. Enrollment of participants began in October 2020 and was completed in June 2021. Results of the study are expected to be published by the end of 2022.

Discussion

Summary

WAYRA is the first randomized controlled trial evaluating integrated pulmonary and mental health rehabilitation for hospitalized COVID-19 survivors in a low- and middle-income country setting. Through this trial, we gained experience in implementing a remote rehabilitation program in a resource-limited country and will generate evidence on pulmonary, mental health, and QoL alterations following COVID-19 the first 3 months after hospitalization. We hypothesize that participation in the combined program will improve pulmonary, physical, and mental health outcomes. We hope that our study will provide a reliable basis for further clinical trials focused on comprehensive rehabilitation in patients hospitalized for severe COVID-19 and other lung diseases.

The burden of long-term complications of COVID-19 will increase because, although several countries have achieved broad vaccination coverage, newly emerging variants may be resistant to vaccines [33]. The most frequently affected systems are respiratory and physical, although psychological symptoms are also common [3]. Despite this, there are still few published studies that have proposed strategies for COVID-19 survivors with long-term complications and far fewer that include mental health support. There are approximately 200 trials registered with ClinicalTrials.gov evaluating rehabilitation programs for COVID-19 survivors; most include pulmonary rehabilitation, whereas only a few have a psychological component [34].

Strengths and Limitations

The main strength of this study is that the calculated sample size has the power to detect a clinically significant difference between the groups. Nevertheless, this study has some limitations to be considered. First, mental health and QoL outcomes will be assessed with screening tools. Second, this trial has an open-label design due the nature of the intervention.

Conclusions

In conclusion, the COVID-19 pandemic will result in millions of people prone to develop respiratory and mental health sequelae worldwide, and health systems are not prepared to respond adequately to this situation. Little evidence exists on rehabilitation strategies, and most of the existing evidence does not come from low- and middle-income countries that face additional challenges compared with developed countries. The clinical trial described in this protocol will generate useful evidence to develop effective interventions to benefit patients after COVID-19, and will serve as a basis to help plan future studies evaluating pulmonary rehabilitation strategies and mental psychological support.

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Authors' Contributions

WC, AGL, SMH, and ANS conceived the original trial design. ECF, JAGB, RP, and SO designed the psychological rehabilitation program. WC, GEG, CYM, and AAD provided expertise to design the respiratory rehabilitation program. GM and EF guided the implementation of the study. ANS, AHCL, and AGL wrote the first draft of the paper. All authors contributed to the development of the study and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Informed consent form.
[PDF File (Adobe PDF File), 555 KB - resprot_v11i10e36001_app1.pdf]

Multimedia Appendix 2
CONSORT-eHEALTH v1.6.1
[PDF File (Adobe PDF File), 3130 KB - resprot_v11i10e36001_app2.pdf]

References

1. Chen C, Haupert SR, Zimmermann L, Shi X, Fritsche LG, Mukherjee B. Global prevalence of post COVID-19 condition or long COVID: a meta-analysis and systematic review. J Infect Dis 2022 Apr 16:online ahead of print [FREE Full text] [doi: 10.1093/infdis/jiac136] [Medline: 35429399]
2. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo P, Cuapio A, et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. Sci Rep 2021 Aug 09;11(1):16144. [doi: 10.1038/s41598-021-95565-8] [Medline: 34373540]
3. Nasserie T, Hittle M, Goodman SN. Assessment of the frequency and variety of persistent symptoms among patients with COVID-19: a systematic review. JAMA Netw Open 2021 May 03;4(5):e2111417 [FREE Full text] [doi: 10.1001/jamanetworkopen.2021.11417] [Medline: 34037731]
4. Michelen M, Manoharan L, Elkheir N, Cheng V, Dagens A, Hastie C, et al. Characterising long COVID: a living systematic review. BMJ Glob Health 2021 Sep 27;6(9):e005427 [FREE Full text] [doi: 10.1136/bmjgh-2021-005427] [Medline: 34580069]
5. Almas T, Malik J, Alsubai AK, Jawad Zaidi SM, Iqbal R, Khan K, et al. Post-acute COVID-19 syndrome and its prolonged effects: an updated systematic review. Ann Med Surg 2022 Aug;80:103995 [FREE Full text] [doi: 10.1016/j.amsu.2022.103995] [Medline: 35721785]
6. Living guidance for clinical management of COVID-19. World Health Organization. 2021. URL: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-2 [accessed 2022-09-16]
7. Maley JH, Alba GA, Barry JT, Bartels MN, Fleming TK, Oleson CV, et al. Multi-disciplinary collaborative consensus guidance statement on the assessment and treatment of breathing discomfort and respiratory sequelae in patients with post-acute sequelae of SARS-CoV-2 infection (PASC). PM R 2022 Jan 22;14(1):77-95. [doi: 10.1002/pmrj.12744] [Medline: 34902224]
8. Fine JS, Ambrose AF, Didehbani N, Fleming TK, Glashan L, Longo M, et al. Multi-disciplinary collaborative consensus guidance statement on the assessment and treatment of cognitive symptoms in patients with post-acute sequelae of SARS-CoV-2 infection (PASC). PM R 2022 Jan 12;14(1):96-111. [doi: 10.1002/pmrj.12745] [Medline: 34902226]
9. Webber SC, Tittlemier BJ, Loewen HJ. Apparent discordance between the epidemiology of COVID-19 and recommended outcomes and treatments: a scoping review. Phys Ther 2021 Nov 01;101(11):pzab155 [FREE Full text] [doi: 10.1093/ptj/pzab155] [Medline: 34160029]
10. Yang L, Yang T. Pulmonary rehabilitation for patients with coronavirus disease 2019 (COVID-19). Chronic Dis Transl Med 2020 Jun;6(2):79-86 [FREE Full text] [doi: 10.1016/j.cdtm.2020.05.002] [Medline: 32411496]
11. Liu K, Zhang W, Yang Y, Zhang J, Li Y, Chen Y. Respiratory rehabilitation in elderly patients with COVID-19: a randomized controlled study. Complement Ther Clin Pract 2020 May;39:101166 [FREE Full text] [doi: 10.1016/j.ctcp.2020.101166] [Medline: 32379637]
12. Fugazzaro S, Contri A, Esseroukh O, Kaleci S, Croci S, Massari M, Reggio Emilia COVID-19 Working Group. Rehabilitation interventions for post-acute COVID-19 syndrome: a systematic review. Int J Environ Res Public Health 2022 Apr 24;19(9):5185 [FREE Full text] [doi: 10.3390/ijerph19095185] [Medline: 35564579]
13. Bickton FM, Shannon H. Barriers and enablers to pulmonary rehabilitation in low- and middle-income countries: a qualitative study of healthcare professionals. Int J Chron Obstruct Pulmon Dis 2022;17:141-153. [doi: 10.2147/COPD.S348663] [Medline: 35046649]
14. Mejía F, Medina C, Cornejo E, Morello E, Vásquez S, Alave J, et al. Oxygen saturation as a predictor of mortality in hospitalized adult patients with COVID-19 in a public hospital in Lima, Peru. PLoS One 2020 Dec 28;15(12):e0244171 [FREE Full text] [doi: 10.1371/journal.pone.0244171] [Medline: 33370364]
15. Antiporta DA, Cutipé YL, Mendoza M, Celentano DD, Stuart EA, Bruni A. Depressive symptoms among Peruvian adult residents amidst a National Lockdown during the COVID-19 pandemic. BMC Psychiatry 2021 Feb 18;21(1):111 [FREE Full text] [doi: 10.1186/s12888-021-03107-3] [Medline: 33602157]

16. Dawes P, Pye A, Reeves D, Yeung WK, Sheikh S, Thodi C, et al. Protocol for the development of versions of the Montreal Cognitive Assessment (MoCA) for people with hearing or vision impairment. BMJ Open 2019 Mar 30;9(3):e026246 [FREE Full text] [doi: 10.1136/bmjopen-2018-026246] [Medline: 30928949]
17. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009 Apr;42(2):377-381 [FREE Full text] [doi: 10.1016/j.jbi.2008.08.010] [Medline: 18929686]
18. IASC Guidelines on mental health and psychosocial support in emergency settings. Inter-Agency Standing Committee. 2007. URL: https://interagencystandingcommittee.org/iasc-task-force-mental-health-and-psychosocial-support-emergency-settings/iasc-guidelines-mental-health-and-psychosocial-support-emergency-settings-2007 [accessed 2021-09-23]
19. Cuijpers P, de Wit L, Kleiboer A, Karyotaki E, Ebert DD. Problem-solving therapy for adult depression: an updated meta-analysis. Eur Psychiatry 2018 Feb 01;48(1):27-37. [doi: 10.1016/j.eurpsy.2017.11.006] [Medline: 29331596]
20. Diniz LS, Neves VR, Starke AC, Barbosa MP, Britto RR, Ribeiro AL. Safety of early performance of the six-minute walk test following acute myocardial infarction: a cross-sectional study. Braz J Phys Ther 2017 May;21(3):167-174 [FREE Full text] [doi: 10.1016/j.bjpt.2017.03.013] [Medline: 28473280]
21. Veloso-Guedes C, Rosalen S, Thobias C, Andreotti R, Galhardo F, Oliveira da Silva A, et al. Validation of 20-meter corridor for the 6-minute walk test in men on liver transplantation waiting list. Transplant Proc 2011 May;43(4):1322-1324 [FREE Full text] [doi: 10.1016/j.transproceed.2011.03.057] [Medline: 21620120]
22. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002 Jul 01;166(1):111-117. [doi: 10.1164/ajrccm.166.1.at1102] [Medline: 12091180]
23. Skloot GS, Edwards NT, Enright PL. Four-year calibration stability of the EasyOne portable spirometer. Respir Care 2010 Jul;55(7):873-877 [FREE Full text] [Medline: 20587099]
24. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med 2019 Oct 15;200(8):e70-e88 [FREE Full text] [doi: 10.1164/rccm.201908-1590ST] [Medline: 31613151]
25. Villarreal-Zegarra D, Copez-Lonzoy A, Bernabé-Ortiz A, Melendez-Torres GJ, Bazo-Alvarez JC. Valid group comparisons can be made with the Patient Health Questionnaire (PHQ-9): a measurement invariance study across groups by demographic characteristics. PLoS One 2019 Sep 9;14(9):e0221717 [FREE Full text] [doi: 10.1371/journal.pone.0221717] [Medline: 31498796]
26. García-Campayo J, Zamorano E, Ruiz MA, Pardo A, Pérez-Páramo M, López-Gómez V, et al. Cultural adaptation into Spanish of the generalized anxiety disorder-7 (GAD-7) scale as a screening tool. Health Qual Life Outcomes 2010 Jan 20;8(1):8 [FREE Full text] [doi: 10.1186/1477-7525-8-8] [Medline: 20089179]
27. Gargurevich R, Luyten P, Fils J, Corveleyn J. Factor structure of the Impact of Event Scale-Revised in two different Peruvian samples. Depress Anxiety 2009 Aug;26(8):E91-E98. [doi: 10.1002/da.20430] [Medline: 19180584]
28. Alonso J, Prieto L, Antó JM. The Spanish version of the SF-36 Health Survey (the SF-36 health questionnaire): an instrument for measuring clinical results. Med Clin 1995 May 27;104(20):771-776. [Medline: 7783470]
29. Konerding U, Elkhuizen SG, Faubel R, Forte P, Malmström T, Pavi E, et al. The validity of the EQ-5D-3L items: an investigation with type 2 diabetes patients from six European countries. Health Qual Life Outcomes 2014 Dec 05;12(1):181 [FREE Full text] [doi: 10.1186/s12955-014-0181-5] [Medline: 25479769]
30. Vilagut G, Ferrer M, Rajmil L, Rebollo P, Permanyer-Miralda G, Quintana J, et al. El Cuestionario de Salud SF-36 español: una década de experiencia y nuevos desarrollos. Gac Sanit 2005;19(2):135-150.
31. Jones PW. St. George's Respiratory Questionnaire: MCID. COPD 2005 Mar 24;2(1):75-79. [doi: 10.1081/copd-200050513] [Medline: 17136966]
32. Cocks K, Torgerson DJ. Sample size calculations for pilot randomized trials: a confidence interval approach. J Clin Epidemiol 2013 Feb;66(2):197-201. [doi: 10.1016/j.jclinepi.2012.09.002] [Medline: 23195919]
33. Wang Q, Guo Y, Iketani S, Nair MS, Li Z, Mohri H, et al. Antibody evasion by SARS-CoV-2 Omicron subvariants BA.2.12.1, BA.4 and BA.5. Nature 2022 Aug 05;608(7923):603-608 [FREE Full text] [doi: 10.1038/s41586-022-05053-w] [Medline: 35790190]
34. McGregor G, Sandhu H, Bruce J, Sheehan B, McWilliams D, Yeung J, et al. Rehabilitation Exercise and psycholoGical support After covid-19 InfectioN' (REGAIN): a structured summary of a study protocol for a randomised controlled trial. Trials 2021 Jan 06;22(1):8 [FREE Full text] [doi: 10.1186/s13063-020-04978-9] [Medline: 33407804]

Abbreviations

6MWT: 6-minute walk test
6MWD: 6-minute walk distance
EC-PST: emotion-centered problem-solving therapy
EQ-5D: EuroQol-5D
FEV1: forced expiratory volume in the first second.

FVC: forced vital capacity.
GAD-7: Generalized Anxiety Disorder
HNCH: Hospital Nacional Cayetano Heredia
IASC: Inter-Agency Standing Committee
IES-R: Impact Event Scale-Revised
MoCA-BLIND: Montreal Cognitive Assessment, visual impairment version
PHQ-9: Patient Health Questionnaire
QoL: quality of life
SF-36: 36-Item Short Form health survey
SGRQ: St. George's Respiratory Questionnaire

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Protocol

Preventing Revictimization Through a Web-Based Intervention for Primary Caregivers of Youth in Care (EMPOWERYOU): Protocol for a Randomized Factorial Trial

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Abstract

Background: Children in foster care are at a higher risk for relationship problems than their counterparts raised by their biological family because of higher exposure to or prevalence of neglect or maltreatment early in life. Consequently, these children may also show more challenging behavior in their foster families, which in turn increases the parental stress experience of foster caregivers. Furthermore, the children may engage in a vicious cycle of risky relationship behaviors and expectations that put them at a greater risk for revictimization.

Objective: To support foster caregivers in reducing the risk for revictimization, several intervention modules delivered via the internet were developed using a consumer-based approach (phase 1 of the multiphase optimization strategy). This project (phase 2 of the multiphase optimization strategy) aimed to develop a sustainable intervention by selecting promising intervention components based on their contribution to the outcome.

Methods: In a 2^4 factorial trial, a total of 317 foster caregivers with children aged 8 to 13 years are randomly assigned to 1 of 16 conditions. The primary outcome is the rate of revictimization from baseline to 3 months after intervention. Secondary outcomes include risk-taking and functional behaviors in relationships. All caregivers will receive access to all the intervention components after the follow-up assessment. The participants assigned to the condition with all component levels *on* are expected to show the best improvement in the primary and secondary outcomes.

Results: Recruitment and data collection for the factorial trial started in March 2022 and is ongoing. As of October 2022, we recruited 181 families. Although it is difficult to predict the exact study timeline owing to COVID-19 pandemic–related delays, results are expected in February 2024.

Conclusions: There is a need for easily accessible information related to raising children in foster care who have experienced early life adversities to interrupt the cycle of violence and enhance the developmental pathway of health and emotional stability. It might be useful, in addition to generally useful parenting information (eg, parental self-care or emotion regulation management), to specifically focus on the needs of these caregivers (eg, how to support the child to reduce dysfunctional relationship behaviors that may have developed because of early adverse experiences).

Trial Registration: ClinicalTrials.gov NCT05235659; https://clinicaltrials.gov/ct2/show/NCT05235659

International Registered Report Identifier (IRRID): DERR1-10.2196/38183

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KEYWORDS

multiphase optimization strategy; foster children; parenting; revictimization; web-based intervention; online intervention

Introduction

Background

Exposure to potentially traumatic events and being bullied by peers or siblings in childhood constitute forms of victimization or revictimization, which may be associated with severe long-term effects on mental health [1-3], including anxiety, depression, or suicidality [4]. We include the experience of different forms of maltreatment (emotional, physical, and sexual abuse; neglect; and intimate partner violence) as well as bullying experiences in the definition of revictimization in this trial.

Given that childhood victimization leads to an increased vulnerability for subsequent revictimization in adolescence [5,6], findings highlight a strong need for evidence-based prevention programs targeting children with a history of maltreatment or bullying as a high-risk population for revictimization. Although all types of maltreatment in childhood were found to be associated with revictimization [7] and mental health, one study with adolescent girls in child welfare found that the emotional type of maltreatment showed the strongest link to revictimization in a cross-sectional study using self-report of the types of child maltreatment experienced [8]. However, when using a population sample, sexual maltreatment increased the risk for revictimization the most [7]. In a recent meta-analysis, Scoglio et al [9] identified the following risk factors in most studies on the association between sexual victimization and revictimization: risky sexual behavior, further maltreatment experiences in childhood, presence of posttraumatic stress disorder (PTSD), and emotional dysregulation. In contrast, protective factors have rarely been examined. Only parental caregiving was identified as a protective factor. Unfortunately, many of the included studies were cross-sectional, and it is not always clear which key mechanism is driving the link (eg, why the presence of PTSD is increasing risk).

Children in Foster Care as an Example of a High-Risk Group for Revictimization

Children are often placed in foster care because of early adverse experiences in their family of origin, including maltreatment, with the majority experiencing neglect and emotional maltreatment, followed by physical and sexual abuse [10]. These children usually show comprehensive problems in relationships, including foster parent–child relationship, relationship with siblings [11], and peer relationships [12]. Furthermore, many children in foster care are affected by PTSD or attachment disorders [13] and show externalizing problem behaviors, which increase parental distress in (foster) parents [14]. The consequences of maltreatment (eg, PTSD-related symptoms and cognitions, such as negative self-appraisal; maladaptive cognitions of others and the world, eg, concerning the reliability and trustworthiness of others; and threat of harm) have been discussed to be causally involved in the risk for revictimization, although direct mediating effects were only established for threat of harm [15].

Interventions to Support Foster Caregivers

Many parenting programs are designed to equip (foster) parents with strategies for increasing positive behaviors in their children and to support them in appropriately managing externalizing problem behavior [16]. Although parenting programs, in general, are a very promising approach to changing child behavior (via changed parenting behavior and reduced parental stress [17]), it has rarely been investigated whether parents may also help to lower the risk for revictimization in children with high risk due to adverse (early) childhood experiences. Warm and responsive parenting is associated with protective effects on children's resilience to victimization [18], indicating that such parenting programs may be beneficial for coping with victimization and revictimization experiences. However, it is unclear whether parents could also be equipped with the knowledge and skills required to empower children with high risk for revictimization and thereby lower the risk for revictimizing experiences. Burke et al [19] outlined that *parental support* did not change the occurrence of victimization. Some authors also pointed out that some intervention components may be less effective than others in preventing or reducing child maltreatment experiences. Gubbels et al [20] concluded in their review and meta-analysis that "improving parental personal skills, improving problem-solving skills, and stimulating children's prosocial behavior should not be the main focus of parental training programs for preventing and reducing child maltreatment" [20]. However, many of these have been identified as promising components to successfully change child externalizing behavior [21], suggesting that the 2 different outcomes may be the result of different pathways of change. Child externalizing problem behavior could be driven by engines different from the risk for revictimization. The intervention model theory of change is key to determining the best intervention components that are most likely to cause changes in the preferred outcome domain [22]. Furthermore, there is some evidence that also challenges the impact (foster) parents may have on the developmental adaptation of their children in care, and the dynamic and reciprocal processes between children and parents that build the foundation for many social learning–based parenting approaches have not been fully supported in a sample of children in foster care in the Netherlands [14]. Although the children's behaviors affected the distress levels of the foster caregivers, the foster caregivers' stress did not affect the children's behaviors. Although this research group discussed a number of potential reasons for the lack of support for a transactional model (eg, foster parents may be expressing their distress less than biological parents, they could potentially give the child away, or children are less vulnerable to parental distress because they are accustomed to worse), this study may indicate that foster parent–child interactions may differ when children were maltreated in the past or at least the focus of the intervention may need to be shifted. For example, Burke et al [19] suggested teaching parents to "be more responsive and connected to their children when they are experiencing difficulties" [19] instead of equipping them with parent management skills more generally.

In sum, few evidence-based parenting programs for foster parents are available, and most of them include a package of

intervention strategies [20] and require comprehensive training and parental participation (eg, in-home training as in Attachment and Biobehavioral Catch-up or Keeping Foster Parents Trained and Supported [23,24]). However, (foster) parent participation is challenging [25]. Furthermore, the intervention model and key drivers of change are not specifically tailored to the factors that put children with maltreatment experiences at a higher risk for future revictimization [26]. There is a clear need to identify behaviors and pathways that are responsible for revictimization [27] in this population.

This Study

We use the multiphase optimization strategy (MOST) framework [22] to prepare and optimize an intervention for foster parents. The intervention components to be tested in phase 2 of MOST (this factorial study) were developed based on the phase 1 results. Multimedia Appendix 1 [27-32] provides a brief summary of the phase 1 results.

We built our conceptual model (Figure 1) and selected the following domains as targets for the intervention (*mediators* in the conceptual model):

1. Relationship-to-harm beliefs, which emphasize the degree to which a child believes that close relationships include harm
2. The threshold for risk detection, which, if lowered, leads to a delayed notice and, consequently, delayed response to danger cues in relationships

We combine these domains into 1 mediator called *relationship-related risk.*

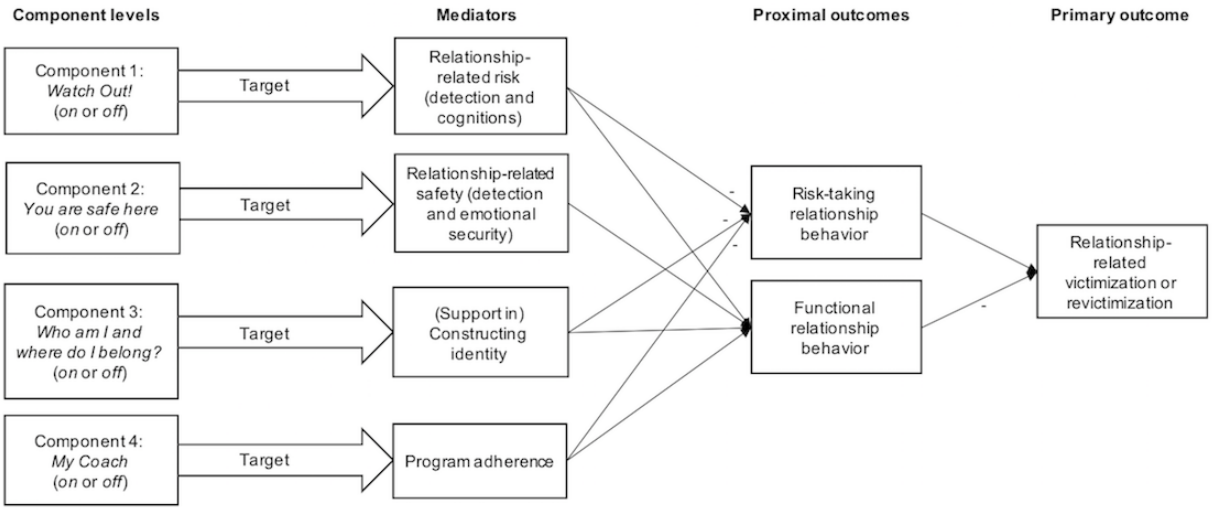
1. A lack of relationship skills to build up and maintain positive and safe relationships
2. Difficulties to detect safety signals and feeling emotionally secure in close relationships

We combine these domains into one mediator called *relationship-related safety.*

1. The emotional significance of a child's origins and the child's current foster family for *constructing a coherent identity*. This domain includes the recognition and sensitive responding of caregivers to the emotional significance of both families for the child's identity development.

We developed promising intervention components and specified how we expect these to change the risks of revictimization experiences and their consequences.

Figure 1. Conceptual model of the EMPOWERYOU intervention for primary caregivers of youth in care.



Objectives and Hypotheses (for Phase 2 of MOST)

The primary aim of this study is to examine the effects of each candidate component developed based on the conceptual model and delivered via an internet-based prevention program to the primary caregivers of preadolescent youth in care on revictimization in the form of conventional crime, child maltreatment, peer and sibling victimization, sexual victimization, witnessing and indirect victimization, and cyberbullying. The ultimate goal is to choose the candidates that best reduce and prevent revictimization from a set of *4 components* with *2 levels each (on/off)*. The primary and secondary research objectives are presented in Textbox 1.

We will examine the hypotheses specified in Textbox 2, which are related to the *main effects of the intervention components* (3 content components and 1 adherence component).

Textbox 1. Primary and secondary research objectives.

Primary research objectives

1. To examine the efficacy of the selected candidate components on the primary outcome, the risk of revictimization, at follow-up (ie, 3 months after intervention; approximately 24 weeks after baseline)
2. To examine the efficacy of the selected candidate components on the secondary outcomes (risk-taking behavior and functional behavior in relationships with the caregiver, siblings, peers, and others; Multimedia Appendix 2 [33-55] provides a full list of outcomes [Heinrichs, N, unpublished data, April 2021; Niestroj, S, unpublished data, September 2021; Zemp, M, unpublished data, 2011; Brühl, A, unpublished data, April 2021; Heinrichs, N, unpublished data, August 2020; Heinrichs, N, unpublished data, March 2021]) at posttest assessment (ie, 1 week after intervention; approximately 12 weeks after baseline)

Secondary research objectives

1. To test the enduring effects of the selected components on the secondary outcomes at 3-month follow-up
2. To test the mediating effects of theory-driven factors (Multimedia Appendix 2 provides a full list of potential mediators) on the relationship between the selected components and the secondary outcomes
3. To explore whether there are any interaction effects between components on the primary or secondary outcomes
4. To conduct exploratory analyses of potential moderators

Textbox 2. Hypotheses related to the main effects of the intervention components.

Hypotheses to be examined

1. Component *Watch Out!* deals with relationship-related risks, and we hypothesize that receiving this component will result in a better detection of risk signals in relationships and less risk-taking cognitions. This will lead to less relationship-related risk-taking behavior, which, in turn, will result in reductions in revictimization experiences and other secondary outcomes.
2. Component *You are safe here* deals with relationship-related safety, and we hypothesize that receiving this component will result in a better detection of relationship-related safety signals in relationships and more emotional security. This will lead to more functional relationship behavior, which, in turn, will result in reductions in revictimization experiences and other secondary outcomes.
3. Component *Who am I and where do I belong?* deals with the construction of identity, and we hypothesize that receiving this component will increase parental support for the child's efforts in constructing a coherent identity. This will lead to less risk-taking behavior and more functional relationship behavior, which, in turn, will result in reductions in revictimization experiences and other secondary outcomes.
4. Component *My Coach* deals with professional support, and we hypothesize that professional support from a parent coach who is facilitating each component will result in higher program adherence or engagement, which will yield larger intervention effects on the primary and secondary outcomes than without professional support.
5. We hypothesize that there will be an interaction effect between the relationship risk and relationship safety components. When both components are present, the effect will be larger compared with when only one of them is present.
6. We hypothesize that there will be an interaction effect between each component and the professional support component such that with professional support, the effects of each component will be larger than those without professional support via greater adherence of the caregiver.

We will also answer the following four questions to establish how well the conceptual model captures the relevant mechanisms of the intervention (mediation analyses, adapted from the study by Smith et al [56]): how well will the three mediators (relationship-related risk, relationship-related safety, and constructing an identity) predict the occurrence of revictimization, how well does each module content (*Watch Out*!, *You are safe here*, and *Who am I and where do I belong*?) and the coach evoke each of the 3 mediators, how much of the relationship between the intervention's content components and revictimization is explained by the 3 hypothesized mediators, and how much variability between the content components and revictimization will remain unexplained.

Furthermore, the following variables were identified as potential moderators of intervention (component) efficacy based on the literature review in phase 1:

1. Child executive functioning (ie, an impaired "ability to shift, inhibit, and focus attention; maintain focus in the face of distracting information" [28]): Reduced executive functioning will lead to smaller intervention effects.
2. Gender of the child [27,57]: We expect worse outcomes in girls than boys.
3. Type of maltreatment [7-9]: Sexual maltreatment experiences will lower the intervention effect compared with other types.
4. Contact with the family of origin [58]: We assume that conflictual contact may reduce intervention effects.
5. Caregiver's history of child maltreatment [59]: We expect caregivers with such a history to benefit less from the intervention.

Taken together, we use the MOST framework [22] to optimize a web-based program for foster parents, which comprises 4 intervention components. To optimize the program, the primary aim of this study is to examine the efficacy of each component on the primary and secondary outcomes. This paper outlines the protocol (version 01) or the factorial trial, following the

SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines for clinical trials (Multimedia Appendix 3 provides the SPIRIT checklist).

Methods

Ethics Approval

This study is conducted in accordance with the Declaration of Helsinki. This study was approved on September 1, 2021, by the University of Bremen Ethics Committee (no. 2021-09). Any changes to this protocol will be submitted to the institutional review board for notification and approval.

Study Design

The EMPOWERYOU project (funded by the German Ministry of Education and Research, Project code FKZ 01KR1806D) aims to develop and optimize a web-based parenting program by using the MOST framework [22]. This study will use a 2×2×2×2 full factorial design by randomly allocating participants to 1 of 16 experimental conditions (Table 1). To estimate the main effects of the 4 intervention components and their interactions, data from all the experimental conditions will be used. For example, the effect of the component *Relationship-related risk* will be estimated by comparing the mean of the experimental conditions 1 to 8 with the mean of the conditions 9 to 16 (Table 1). Families in the first condition will not receive any experimental component but will be delivered the 2 basic intervention modules that every caregiver receives. Families will be informed that everyone may access all modules and that the sequence and timing of each module will be based on a randomization procedure.

Table 1. Experimental intervention conditions (optimization schema).

Experimental condition	Component 1: *Watch Out*!—relationship-related risk	Component 2: *You are safe here*—relationship-related safety	Component 3: *Who am I and where do I belong?*—identity	Component 4: *My Coach*—professional support
1	Off[a]	Off	Off	Off
2	Off	Off	Off	On[b]
3	Off	Off	On	Off
4	Off	Off	On	On
5	Off	On	Off	Off
6	Off	On	Off	On
7	Off	On	On	Off
8	Off	On	On	On
9	On	Off	Off	Off
10	On	Off	Off	On
11	On	Off	On	Off
12	On	Off	On	On
13	On	On	Off	Off
14	On	On	Off	On
15	On	On	On	Off
16	On	On	On	On

[a]Not included in the intervention.

[b]Included in the intervention.

Sample Size Calculations

Anticipated effect sizes were estimated from the reported effect sizes for victimization and revictimization interventions, which also included (1) facilitating risk detection skills; (2) social skills, such as problem-solving or conflict management; (3) skills to build healthy relationships; and (4) the ability to reflect on own expectations that relationships will include harm [28,60,61]. We expect small to moderate effect sizes between Cohen *d*=0.28 and Cohen *d*=0.46 for the main effects of specific intervention components (component 3: 0.46, component 4: 0.28, and component 6: 0.32). Thus, a sample size of 317 was determined as necessary to detect the smallest anticipated effect size of Cohen *d*=0.28. To detect this difference with the analysis of covariance as the suggested method for component selection by the developer of the factorial design (groups=2, *df*=1, covariate=1) with 80% power at α=.10 per intervention component or interaction, a sample size of 317 is required (calculated with FactorialPowerPlan SAS Macro provided by Dr Collins [62]). We will use an intention-to-treat approach, although only one family dropped out during the intervention period in the pilot study. In contrast, findings from the pilot study showed that 26% (4/15) of the recruited caregivers that registered for the website dropped out before the intervention. Therefore, we consider a dropout rate (before the allocation to condition) of 26%. Therefore, we aim to recruit a total of 429

families. Recruitment will be stopped as soon as we reach the sample size needed for the analysis (N=317).

Procedure

Inclusion and Exclusion Criteria

We will only allow primary caregivers (foster or adoptive) of youth in care aged 8 to 13 years. Families indicating acute child endangerment during the web-based screening assessment (using 5 self-developed items) will be excluded. We will further exclude caregivers with an insufficient knowledge of German language, short-term foster families ("Bereitschaftspflege"), or kinship care ("Verwandtenpflege"). Excluded families will be provided with professional advice and referrals for services if desired.

Recruitment

We will recruit via a national association for foster and adoptive parents (Bundesverband der Pflege- und Adoptivfamilien), regional youth welfare institutions, and self-help organizations in Germany. Furthermore, we have active social media campaigns running to support recruitment.

Randomization and Blinding

Families will be randomized to 1 of the 16 experimental conditions via a database that uses concealed, computer-generated [63], permuted block randomization, with stratification by child's gender and with fixed block sizes of 16 (conditions were randomized within each block). Randomization procedures will be completed by another research group within the EMPOWERYOU consortium that is not associated with the intervention trial otherwise (Neuropsychology at the University Hospital Aachen, Germany) to minimize the occurrence of potential biases (eg, biases that may arise through primary caregivers' or researchers' preferences). Study staff at the University of Bremen will not view the allocation sequence to minimize researchers' prediction biases. The database will not reveal participants' treatment conditions to the study staff until after the family's eligibility is verified (after preintervention assessment). Families will be informed of their allocation status after baseline data collection is completed to ensure that participants are blind to allocation during the initial assessment. In the case of instances of harm or severe abuse to a child being reported by a participant, the allocation status of the participant will be unblinded. All cases of unblinding will be reported to the Data Safety and Monitoring Board (DSMB).

Informed Consent

Informed consent will be obtained from each participant (caregiver and child) on the web. Interested study participants can register on the website and then receive the information sheet and consent form on the web. The caregivers are informed about the objectives, study procedure, the rights and obligations of all those involved, and the procedure and data processing using the information and consent forms. If the participants have any questions about the documents or the study, they can call the study team at any time. The phone number will be clearly indicated on the website. Each caregiver is asked to provide active opt-in consent for their own participation and the participation of their child in care. Multimedia Appendix 4 provides the informed consent form in German language.

Intervention

Intervention Accessibility and Orientation

Caregivers will use a password to access the program (Figure 2). All parents will be offered to participate in a "welcome call" with the coach before starting with the first module. During the phone call, the procedure of the intervention and the adverse event assessment will be explained.

Figure 2. Website of the EMPOWERYOU program for caregivers.

Duration to Complete Each Module

During the program, parents will have 2 weeks to complete 1 module, with each module taking about 90 minutes to work through (including "homework" in the form of exercises with the child).

Duration of the Intervention Package

Caregivers can work through the web-based program for a maximum of 10 weeks (conditions with the 3 candidate components *on* resulting in 6 weeks plus 4 weeks for the 2 basic modules). The duration of the intervention is reduced by up to 4 weeks if caregivers receive the basic modules only (experimental condition 1; Table 1).

Content of Each Module

We have 6 intervention modules out of which only 4 will be put to test because modules 1 and 2 are already well investigated, with promising mental health benefits for the participants besides revictimization outcomes [20,21,64,65]. In addition to the 2 "basic modules," a website area with literature recommendations and information texts on child maltreatment, self-injury, and suicidal behavior allows us to offer some level of support across all conditions, including the condition with the lowest component level across all intervention modules. The 6 intervention modules are described in detail in Textbox 3.

The 6 modules are embedded in a common website and independent of family assessment. The assessment is conducted via a professional tool for web-based surveys (refer to the *Data Collection for the Primary and Secondary Outcomes* section). The web-based intervention includes various multimedia features (texts, slides, videos, fictional audio recordings, and interactive tasks) to make the program easily accessible and attractive.

Textbox 3. The intervention modules.

Module *My power, your power*—facilitating parental self-care and the self-worth of the child

- Caregivers learn how to recognize their own needs and how to implement resources-enhancing strategies in everyday life. Caregivers are encouraged and guided on how to facilitate their partnership quality (as an important resource for the caregiver and the child) and how to promote the child's self-worth.

Module *Our feelings*—facilitating the emotional regulation of the child and the caregiver

- The second module provides basic knowledge about emotions and their functions. Caregivers are supported in recognizing and communicating their emotions as well as the child's emotions. Parents are encouraged to attend to their child's emotional needs, reflect on their emotions, and learn to keep them separate from their own emotional state, or at least recognize the difference and attempt to understand their child's emotional reactions (eg, through storytelling and behavior attribution exercises). Emotional regulation strategies for the parent and the child are introduced and practiced.

Module *Watch Out!*—improving relationship-related risk detection and the self-protective behavior of the child

- Parents gain access to information on how they can support their child in noticing and processing risk signals (eg, combining risk signals). Exercises with the child that provide access to knowledge about children's rights, inhibit risk-taking behavior, and enhance self-protective behavior are included. Examples on how to talk (with the child) about victimization (eg, bullying experiences) are provided, and a brief section on media literacy completes this module.

Module *You are safe here*—improving relationship-related safety and facilitating solid relationships with family and peers

- This module includes knowledge about attachment and emotional security, and parents are supported in enhancing the child's feeling of safety in close relationships. Parents are encouraged to reflect on their own biography and that of their children to recognize functional or dysfunctional cognitions and assumptions about close relationships that may shape the way relationships are perceived or behaved in today.

Module *Who am I and where do I belong?*—supporting the child in constructing an identity

- The aim of this module is to support caregivers in helping their child develop an identity of their choice while providing the freedom to consider potential contributing influences of the family of origin, foster family, and peers. Caregivers are supported in facilitating a multidimensional, nonjudgmental picture of the biological parents that may allow the child to identify with their strengths. Parents are provided with practical assistance on how to reconcile the child's needs for social belonging and autonomy and how to prevent or reduce potential loyalty conflicts and associated distress across family members.

Module *My Coach*—providing professional support to the caregiver

- Professional support is provided to the caregiver in the form of 1 phone call per experimental module and 1 joint call for the basic modules with a coach. Coaching sessions include feedback on the caregivers' progress in enhancing the elaboration of module content and discussing related issues in the family. The coach answers questions about program content, homework, and the transfer of knowledge and activities in their everyday family life. The participants in conditions with coach assistance *on* receive 50 minutes of additional assistance via phone (per call) as well as either an SMS text message or an email with the core message of the module.

Data Collection for the Primary and Secondary Outcomes

Each participant will be assessed on the web using *SoSci Survey* [66] 3 times, that is, at preintervention assessment (week 1), postintervention assessment (week 12), and 3-month follow-up assessment (week 24). Families will complete a brief questionnaire (5 minutes) on adverse events and child behavior during the past 2 weeks at the beginning of each module on the program website to ensure a closely monitored adverse event assessment. Multimedia Appendix 5 outlines the SPIRIT-recommended schedule of enrollment, interventions, and assessments. Families will receive a reimbursement of €30 (US $29.32 in the form of 2 vouchers: €20 (US $19.55) for caregivers and €10 (US $9.77) for the child) for their study participation after follow-up assessments.

Data Management

To ensure data privacy, research data will be identified using pseudonyms and will be stored on 2 password-protected servers only accessible by approved study staff members. Personal data (ie, username, phone number, and email address) will be stored separately from research data. Personal data and the pseudonym codes will only be matched in a handwritten key code list to protect the confidentiality of data. Identifiable data (including the key code list) will be deleted 2 years after the end of the project. The research data will then be anonymized. The anonymized data set will be stored for 10 years and shared with other research teams upon request using a repository that will be chosen by the consortium (advised by the DSMB).

Data Monitoring

An independent DSMB will provide additional oversight on data safety, ethical procedures, and best clinical practices. A thorough data safety concept was developed and piloted in phase 1. This safety protocol outlines how adverse events will be identified, registered, acknowledged, and handled.

Measures

Primary Measures

To investigate the primary efficacy, we will use a revictimization score derived from 2 measures: the Juvenile Victimization Questionnaire [33] and the bullying screener [34]. We will assess the child and parent reports of each measure while using the parent report for the primary outcome. The Juvenile Victimization Questionnaire is a widely and internationally used self-report measure to assess victimization in children aged 8 to 17 years. It consists of 34 items in the child version and 37 items in the parent version spanning 5 domains, namely, crime, child maltreatment, peer and sibling victimization, sexual victimization, and witnessing crime, with follow-up questions that also assess the frequency and perpetrators of the victimization events. A total of 3 supplemental items on electronic victimization will be assessed. In our study, the participants (caregiver and child) will be asked whether the child was exposed to the respective event and, if yes, whether it happened during the last 3 months (primary outcome–assessment period). The participants will respond with yes (1) or no (0), leading up to a total score, with higher scores indicating greater victimization exposure. The bullying screener [34] is a 6-item screening tool that assesses bullying as victim and offender. After the respective definition of bullying type, the participants are asked how often these things happened to the child or how often they have done this to others in the last 3 months. The participants then respond on a 4-point scale from never to a lot (*at least once a week*).

Secondary Outcomes

Secondary outcomes include relationship-related risk-taking behaviors (questionnaire on risky situations in relationships; Heinrichs, N, unpublished data, April 2021). The questionnaire comprises 14 risky situations (eg, “How often has someone done something to your child even though he or she did not want that and said ‘no’?”). Caregivers and children will be asked how often the risky situation occurred during the last 3 months (frequency). Afterward, they will rate how likely it is that the situation is followed by a positive and negative consequence (child’s risk appraisal) on a scale from 1 (very unlikely) to 5 (very likely). The structure (frequency and appraisal of risky situations) is based on the Cognitive Appraisal of Risky Events [67]. In addition, 6 case vignettes for risky situations are currently being developed to administer at postintervention assessment. Risky situations include being persuaded by a friend to swim far out to sea, witnessing bullying behavior in school, or a stranger standing very close to a child at a swimming pool. To assess functional relationship behavior across relationships with caregivers, siblings, and others, we will use 3 well-established measures: (1) the subscales communication and involvement of the Parenting Relationship Questionnaire [35], (2) the 7 subscales referring to “warmth and closeness” of the Sibling Relationship Questionnaires [36-38], and (3) the Relationship Problems Questionnaire [39]. Further details are provided in Multimedia Appendix 2.

Mediators and Moderators

Caregivers and children will complete a battery of web-based questionnaires assessing potential moderators and mediators. Multimedia Appendix 2 provides the full list of measures. *Mediators* comprise a range of measures on relationship-related risk-taking cognitions, detection of risk and safety signals in relationships, emotional security, parental discord in front of the child, attachment, caregiver’s support with identity construction, program adherence, self-appraisal, belongingness, emotional regulation, parental self-care, and child behavior problems. Child’s gender, contact with the biological family, type of maltreatment, executive functioning, and parental childhood trauma will be assessed as *moderators*.

Statistical Analysis

Analyses

Before the analyses, missing data will be examined and appropriately handled using multiple imputation or full information maximum likelihood estimation. To investigate the effectiveness of each intervention component, the primary analyses will test the pre–follow-up change in children’s revictimization composite scores. The primary analysis will be conducted in an intention-to-treat sample. We will use the analysis of covariance with main and interaction effects on the

primary and secondary end points. The main effects and interactions are estimated based on aggregates (each reflecting the presence or absence of a specific component) across the 16 experimental conditions. The main effects will be modeled as a fixed effect with baseline levels of an outcome as a covariate and an assumed type I error of $P<.10$ (recommended for component selection [22]). To examine the hypotheses related to mediating and moderating effects, we will use regression analyses. Mediational analyses will be conducted by analyzing the indirect effects of each component on the primary outcome via the assumed mediators (Figure 1). Moderator analyses will be modeled in steps with baseline predictors (eg, type of maltreatment) and then as a second model including interactions with the main effect by condition.

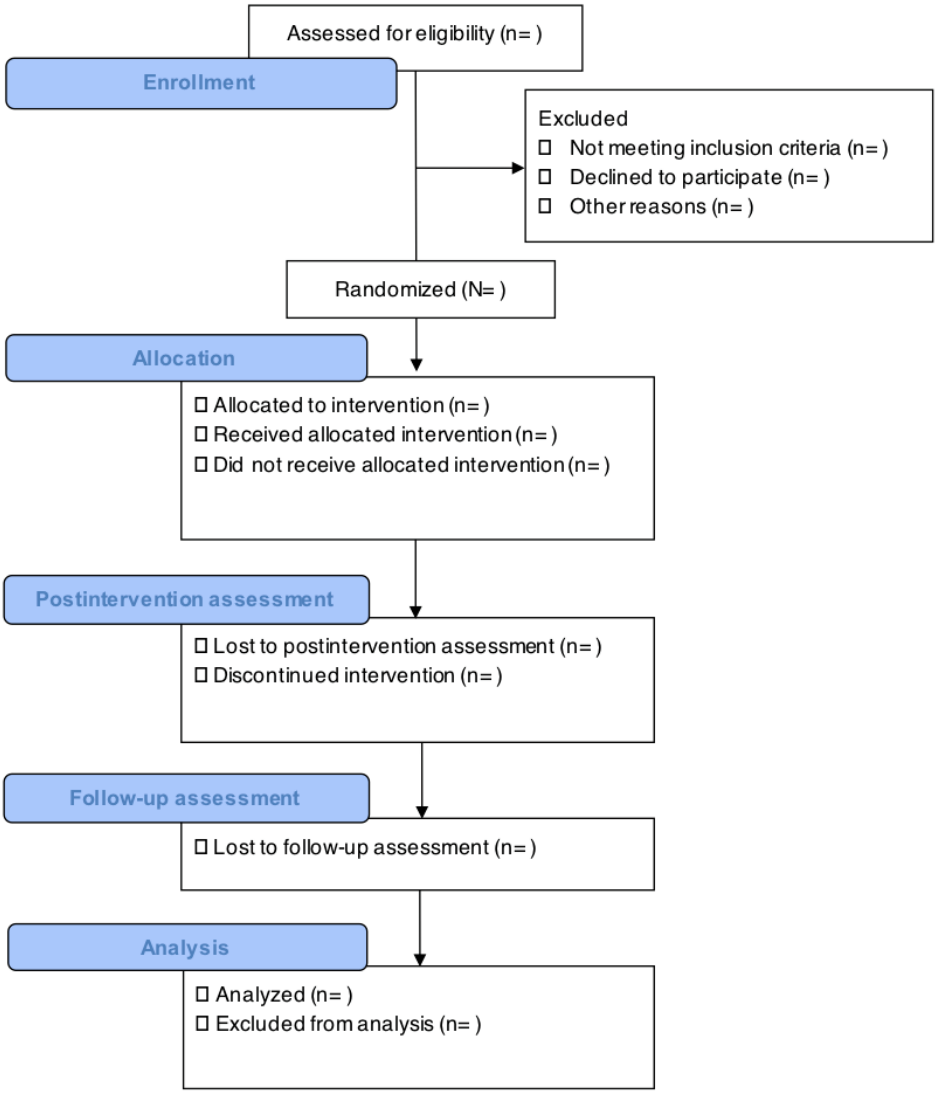
Decision-making Process

We will use the "all active components criterion" [22] for the selection of component levels. This means that we plan to include the component levels of the entire set of components that are associated with a better outcome, following an a priori decision-making process: (1) main effect on the primary outcome at follow-up; (2) if no significant main effect can be found, we will consider the interaction effect; and (3) if no main or interaction effects are found, we will consider the mediation models. If we do not find any significant main effect for any of the 4 factors on revictimization, we will choose the more cost-effective component levels. Before analysis, the assignment will be blinded in the data set. After completing the decision-making process, the assignment will be unblinded.

Results

The EMPOWERYOU project was funded in February 2019. Phase 1 (conducting focus groups and developing and piloting the intervention) was completed in September 2021. Afterward, the intervention was adapted based on the results of the pilot study. We started recruitment and data collection for phase 2 (factorial trial) in March 2022. Data collection is ongoing. As of October 2022, we recruited 181 families. Although it is difficult to predict the exact study timeline because of COVID-19 pandemic–related delays, preliminary results are expected in February 2024. Results will be published in peer-reviewed journals and presented at key conferences for researchers and stakeholders. Figure 3 shows the flow diagram of the study.

Figure 3. CONSORT (Consolidated Standards of Reporting Trials) flowchart for EMPOWERYOU Subproject 4.



Discussion

Caregivers in the foster care system take responsibility for children who are at risk of developing mental health problems because of their early life adversities. Therefore, it is important to provide support in an easy-to-access manner. For this purpose, we developed a consumer-informed e-parenting intervention that is meant to support foster caregivers in their important role of caring for these children. Scalability has been an important factor when developing the intervention (e-intervention will be accessible at any preferred time for caregivers, and costs will be—ignoring the professional support component—primarily driven by website hosting and maintenance), and this factorial trial can make a significant contribution to the optimization of an intervention package, which, after optimization, needs to be tested in a traditional randomized controlled trial (phase 3, evaluation) before being disseminated.

Acknowledgments

The EMPOWERYOU project is funded by the German Federal Ministry of Education and Research (grant FKZ 01KR1806D).

Data Availability

Data that can be fully anonymized are available from the corresponding author upon reasonable request. Access to data is restricted to the scientific community. The anonymized data set will be stored for 10 years and shared with other research teams upon request using a repository that will be chosen by the consortium (advised by the Data Safety and Monitoring Board, eg, Zenodo).

Authors' Contributions

NH prepared the first draft of the introduction and discussion and AB prepared the draft for the methods and results. Both authors contributed to the refinement of the full draft. AB took the lead during the editorial process. NH is the principal investigator, and AB is the project coordinator of this study.

Conflicts of Interest

NH and AB are the developers of the EMPOWERYOU program for primary caregivers of youth in care. NH is the principal investigator of the study and has received a research grant from the German Federal Ministry of Education and Research to conduct this work. NH is a member of the international scientific advisory board of the Positive Parenting Program (Triple P) and involved in a research project on the Parenting for lifelong Health program (PLH). She has expertise in cognitive behavior therapy and has received training in the Triple P, Paarlife, Parent-Child Interaction Therapy.

Multimedia Appendix 1
Prior work—development of a conceptual model (phase 1 of the multiphase optimization strategy).
[PDF File (Adobe PDF File), 78 KB - resprot_v11i10e38183_app1.pdf]

Multimedia Appendix 2
Outcomes and measures.
[PDF File (Adobe PDF File), 126 KB - resprot_v11i10e38183_app2.pdf]

Multimedia Appendix 3
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist for clinical trials.
[PDF File (Adobe PDF File), 136 KB - resprot_v11i10e38183_app3.pdf]

Multimedia Appendix 4
Informed consent form.
[PDF File (Adobe PDF File), 133 KB - resprot_v11i10e38183_app4.pdf]

Multimedia Appendix 5
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials)-recommended schedule of enrollment, interventions, and assessments.
[PDF File (Adobe PDF File), 81 KB - resprot_v11i10e38183_app5.pdf]

References

1. Bowes L, Wolke D, Joinson C, Lereya ST, Lewis G. Sibling bullying and risk of depression, anxiety, and self-harm: a prospective cohort study. Pediatrics 2014 Oct;134(4):e1032-e1039. [doi: 10.1542/peds.2014-0832] [Medline: 25201801]

2. Holmes K, Sher L. Dating violence and suicidal behavior in adolescents. Int J Adolesc Med Health 2013;25(3):257-261. [doi: 10.1515/ijamh-2013-0059] [Medline: 24006321]
3. Benedini KM, Fagan AA, Gibson CL. The cycle of victimization: the relationship between childhood maltreatment and adolescent peer victimization. Child Abuse Negl 2016 Sep;59:111-121. [doi: 10.1016/j.chiabu.2016.08.003] [Medline: 27568065]
4. Lee MA. Emotional abuse in childhood and suicidality: the mediating roles of re-victimization and depressive symptoms in adulthood. Child Abuse Negl 2015 Jun;44:130-139. [doi: 10.1016/j.chiabu.2015.03.016] [Medline: 25890665]
5. Widom CS, Czaja SJ, Dutton MA. Childhood victimization and lifetime revictimization. Child Abuse Negl 2008 Aug;32(8):785-796 [FREE Full text] [doi: 10.1016/j.chiabu.2007.12.006] [Medline: 18760474]
6. Blom H, Högberg U, Olofsson N, Danielsson I. Strong association between earlier abuse and revictimization in youth. BMC Public Health 2014 Jul 14;14:715 [FREE Full text] [doi: 10.1186/1471-2458-14-715] [Medline: 25018145]
7. Frugaard Stroem I, Aakvaag HF, Wentzel-Larsen T. Characteristics of different types of childhood violence and the risk of revictimization. Violence Against Women 2019 Nov;25(14):1696-1716. [doi: 10.1177/1077801218818381] [Medline: 30663527]
8. Auslander W, Tlapek SM, Threlfall J, Edmond T, Dunn J. Mental health pathways linking childhood maltreatment to interpersonal revictimization during adolescence for girls in the child welfare system. J Interpers Violence 2018 Apr;33(7):1169-1191. [doi: 10.1177/0886260515614561] [Medline: 26621036]
9. Scoglio AA, Kraus SW, Saczynski J, Jooma S, Molnar BE. Systematic review of risk and protective factors for revictimization after child sexual abuse. Trauma Violence Abuse 2021 Jan;22(1):41-53. [doi: 10.1177/1524838018823274] [Medline: 30669947]
10. Takayama JI, Wolfe E, Coulter KP. Relationship between reason for placement and medical findings among children in foster care. Pediatrics 1998 Feb;101(2):201-207. [doi: 10.1542/peds.101.2.201] [Medline: 9445492]
11. James S, Monn AR, Palinkas LA, Leslie LK. Maintaining sibling relationships for children in foster and adoptive placements. Child Youth Serv Rev 2008 Jan;30(1):90-106 [FREE Full text] [doi: 10.1016/j.childyouth.2007.07.001] [Medline: 19122749]
12. DeLuca HK, Claxton SE, van Dulmen MH. The peer relationships of those who have experienced adoption or foster care: a meta-analysis. J Res Adolesc 2019 Dec;29(4):796-813. [doi: 10.1111/jora.12421] [Medline: 29938859]
13. Lehmann S, Havik OE, Havik T, Heiervang ER. Mental disorders in foster children: a study of prevalence, comorbidity and risk factors. Child Adolesc Psychiatry Ment Health 2013 Nov 21;7(1):39 [FREE Full text] [doi: 10.1186/1753-2000-7-39] [Medline: 24256809]
14. Goemans A, van Geel M, Vedder P. Foster children's behavioral development and foster parent stress: testing a transactional model. J Child Fam Stud 2018;27(3):990-1001 [FREE Full text] [doi: 10.1007/s10826-017-0941-z] [Medline: 29568216]
15. Jaffe AE, DiLillo D, Gratz KL, Messman-Moore TL. Risk for revictimization following interpersonal and noninterpersonal trauma: clarifying the role of posttraumatic stress symptoms and trauma-related cognitions. J Trauma Stress 2019 Feb;32(1):42-55 [FREE Full text] [doi: 10.1002/jts.22372] [Medline: 30748027]
16. Golding K, Picken W. Group work for foster carers caring for children with complex problems. Adopt Foster 2004 Apr;28(1):25-37. [doi: 10.1177/030857590402800105]
17. Gray GR, Totsika V, Lindsay G. Sustained effectiveness of evidence-based parenting programs after the research trial ends. Front Psychol 2018 Oct 26;9:2035 [FREE Full text] [doi: 10.3389/fpsyg.2018.02035] [Medline: 30459680]
18. Lereya ST, Samara M, Wolke D. Parenting behavior and the risk of becoming a victim and a bully/victim: a meta-analysis study. Child Abuse Negl 2013 Dec;37(12):1091-1108. [doi: 10.1016/j.chiabu.2013.03.001] [Medline: 23623619]
19. Burke T, Sticca F, Perren S. Everything's gonna be alright! The longitudinal interplay among social support, peer victimization, and depressive symptoms. J Youth Adolesc 2017 Sep;46(9):1999-2014. [doi: 10.1007/s10964-017-0653-0] [Medline: 28315187]
20. Gubbels J, van der Put CE, Assink M. The effectiveness of parent training programs for child maltreatment and their components: a meta-analysis. Int J Environ Res Public Health 2019 Jul 06;16(13):2404 [FREE Full text] [doi: 10.3390/ijerph16132404] [Medline: 31284575]
21. Kaminski JW, Valle LA, Filene JH, Boyle CL. A meta-analytic review of components associated with parent training program effectiveness. J Abnorm Child Psychol 2008 May;36(4):567-589. [doi: 10.1007/s10802-007-9201-9] [Medline: 18205039]
22. Collins LM. Optimization of Behavioral, Biobehavioral, and Biomedical Interventions: The Multiphase Optimization Strategy (MOST). Cham, Switzerland: Springer; 2018.
23. Dozier M, Bick J, Bernard K. Intervening with foster parents to enhance biobehavioral outcomes among infants and toddlers. Zero Three 2011 Jan;31(3):17-22 [FREE Full text] [Medline: 23226918]
24. Price JM, Roesch S, Walsh NE, Landsverk J. Effects of the KEEP foster parent intervention on child and sibling behavior problems and parental stress during a randomized implementation trial. Prev Sci 2015 Jul;16(5):685-695 [FREE Full text] [doi: 10.1007/s11121-014-0532-9] [Medline: 25418812]
25. Dorsey S, Pullmann MD, Berliner L, Koschmann E, McKay M, Deblinger E. Engaging foster parents in treatment: a randomized trial of supplementing trauma-focused cognitive behavioral therapy with evidence-based engagement strategies. Child Abuse Negl 2014 Sep;38(9):1508-1520 [FREE Full text] [doi: 10.1016/j.chiabu.2014.03.020] [Medline: 24791605]

26. Gaviţa OA, David D, Bujoreanu S, Tiba A, Ionuţiu DR. The efficacy of a short cognitive–behavioral parent program in the treatment of externalizing behavior disorders in Romanian foster care children: building parental emotion-regulation through unconditional self- and child-acceptance strategies. Child Youth Serv Rev 2012 Jul;34(7):1290-1297. [doi: 10.1016/j.childyouth.2012.03.001]
27. Ruback RB, Clark VA, Warner C. Why are crime victims at risk of being victimized again? Substance use, depression, and offending as mediators of the victimization-revictimization link. J Interpers Violence 2014 Jan;29(1):157-185. [doi: 10.1177/0886260513504626] [Medline: 24097905]
28. DePrince AP, Chu AT, Labus J, Shirk SR, Potter C. Testing two approaches to revictimization prevention among adolescent girls in the child welfare system. J Adolesc Health 2015 Feb;56(2 Suppl 2):S33-S39. [doi: 10.1016/j.jadohealth.2014.06.022] [Medline: 25620452]
29. MAXQDA. VERBI Software. Berlin, Germany: VERBI Software; 2019. URL: https://www.maxqda.com/about [accessed 2021-07-01]
30. Mayring P. Qualitative Inhaltsanalyse: Grundlagen und Techniken. 12th Auflage. Weinheim, Germany: Julius Beltz; 2010.
31. Castro A, Ibáñez J, Maté B, Esteban J, Barrada JR. Childhood sexual abuse, sexual behavior, and revictimization in adolescence and youth: a mini review. Front Psychol 2019 Aug 30;10:2018 [FREE Full text] [doi: 10.3389/fpsyg.2019.02018] [Medline: 31543854]
32. Fraley RC, Roisman GI. Do early caregiving experiences leave an enduring or transient mark on developmental adaptation? Curr Opin Psychol 2015 Feb;1:101-106. [doi: 10.1016/j.copsyc.2014.11.007]
33. Finkelhor D, Ormrod R, Turner H, Hamby SL. The victimization of children and youth: a comprehensive, national survey. Child Maltreat 2005 Feb;10(1):5-25. [doi: 10.1177/1077559504271287] [Medline: 15611323]
34. Wolke D, Lereya ST. Long-term effects of bullying. Arch Dis Child 2015 Sep;100(9):879-885 [FREE Full text] [doi: 10.1136/archdischild-2014-306667] [Medline: 25670406]
35. Kamphaus RW, Reynolds CR. Parenting Relationship Questionnaire (PRQ). London, UK: Pearson; 2006.
36. Furman W, Buhrmester D. Children's perceptions of the qualities of sibling relationships. Child Dev 1985 Apr;56(2):448-461. [doi: 10.2307/1129733]
37. Bojanowski S, Riestock N, Nisslein J, Weschenfelder-Stachwitz H, Lehmkuhl U. Psychometrische Gütekriterien der deutschen Version des Sibling Relationship Questionnaire (SRQ-deu). Psychother Psychosom Med Psychol 2015 Sep;65(9-10):370-378. [doi: 10.1055/s-0035-1547228] [Medline: 26039367]
38. Bojanowski S, Riestock N, Nisslein J. Deutsche Version des Sibling Relationsship Questionnaire (SRQ-deu): Normierung an einer Schülerstichprobe. Psychother Psychosom Med Psychol 2019 Feb;69(2):81-86. [doi: 10.1055/a-0574-2306] [Medline: 29660750]
39. Minnis H, Rabe-Hesketh S, Wolkind S. Development of a brief, clinically relevant, scale for measuring attachment disorders. Int J Methods Psychiatr Res 2002;11(2):90-98 [FREE Full text] [doi: 10.1002/mpr.127] [Medline: 12459799]
40. Chodura S, Lohaus A, Symanzik T, Möller C, Heinrichs N, Konrad K. Demografische Eigenschaften von Pflegefamilien in Deutschland. Z Kinder Jugendpsychiatr Psychother 2019 May;47(3):211-227. [doi: 10.1024/1422-4917/a000620] [Medline: 30264651]
41. Schröder M, Fux E, Lüdtke J, Izat Y, Bolten M, Schmid M. German version of the relationship problems questionnaire: effective screening for attachment disorder. Psychopathology 2019;52(6):334-345. [doi: 10.1159/000504675] [Medline: 31865355]
42. von Stadler C, Janke W, Schmeck K. Inventar zur Erfassung von Impulsivität, Risikoverhalten und Empathie bei 9- bis 14-jährigen Kindern. Göttingen, Germany: Hogrefe Verlag; 2004.
43. Furman W, Buhrmester D. The network of relationships inventory: behavioral systems version. Int J Behav Dev 2009 Sep 01;33(5):470-478 [FREE Full text] [doi: 10.1177/0165025409342634] [Medline: 20186262]
44. Davies PT, Forman EM, Rasi JA, Stevens KI. Assessing children's emotional security in the interparental relationship: the Security in the Interparental Subsystem Scales. Child Dev 2002;73(2):544-562. [doi: 10.1111/1467-8624.00423] [Medline: 11949908]
45. Porter B, O'Leary KD. Marital discord and childhood behavior problems. J Abnorm Child Psychol 1980 Sep;8(3):287-295. [doi: 10.1007/BF00916376] [Medline: 7410730]
46. Mueller CE. Protective factors as barriers to depression in gifted and nongifted adolescents. Gifted Child Q 2009 Jan 01;53(1):3-14. [doi: 10.1177/0016986208326552]
47. Jacobson KC, Rowe DC. Genetic and environmental influences on the relationships between family connectedness, school connectedness, and adolescent depressed mood: sex differences. Dev Psychol 1999 Jul;35(4):926-939. [doi: 10.1037//0012-1649.35.4.926] [Medline: 10442862]
48. Resnick MD, Bearman PS, Blum RW, Bauman KE, Harris KM, Jones J, et al. Protecting adolescents from harm. Findings from the National Longitudinal Study on Adolescent Health. JAMA 1997 Sep 10;278(10):823-832. [doi: 10.1001/jama.278.10.823] [Medline: 9293990]
49. Anderman LH. Academic and social perceptions as predictors of change in middle school students' sense of school belonging. J Exp Educ 2003 Jan;72(1):5-22. [doi: 10.1080/00220970309600877]

50. Anderman EM. School effects on psychological outcomes during adolescence. J Educ Psychol 2002 Dec;94(4):795-809. [doi: 10.1037/0022-0663.94.4.795]
51. Drechsler R, Steinhausen HC. Verhaltensinventar zur Beurteilung exekutiver Funktionen: Deutschsprachige Adaptation des Behavior Rating Inventory of Executive Function (BRIEF). Göttingen, Germany: Hogrefe Publishing; 2013.
52. Bernstein DP, Fink L, Handelsman L, Foote J, Lovejoy M, Wenzel K, et al. Initial reliability and validity of a new retrospective measure of child abuse and neglect?: reply. Am J Psychiatry 1995 Oct;152(10):1535-1537. [doi: 10.1176/ajp.152.10.1535-a]
53. Greuel JF, Briegel W, Heinrichs N. Die Eltern-Kurzversion des Fragebogens zur Erhebung der Emotionsregulation bei Kindern und Jugendlichen (FEEL-KJ). Z Klin Psychol Psychother 2018 Jul 10;47(1):48-58. [doi: 10.1026/1616-3443/a000463]
54. Goodman A, Lamping DL, Ploubidis GB. When to use broader internalising and externalising subscales instead of the hypothesised five subscales on the Strengths and Difficulties Questionnaire (SDQ): data from British parents, teachers and children. J Abnorm Child Psychol 2010 Nov;38(8):1179-1191. [doi: 10.1007/s10802-010-9434-x] [Medline: 20623175]
55. Hurley SM. Parent Daily Report - Child Behavior Items. Fast Track Project Technical Report. 2000 Oct. URL: https://fasttrackproject.org/wp-content/uploads/sites/31/2021/07/pdr5tech.pdf [accessed 2022-10-13]
56. Smith RA, Coffman DL, Zhu X. Investigating an intervention's causal story: mediation analysis using a factorial experiment and multiple mediators. In: Collins LM, Kugler KC, editors. Optimization of Behavioral, Biobehavioral, and Biomedical Interventions: Advanced Topics. Cham, Switzerland: Springer; 2018:269-294.
57. Krahé B, Berger A. Gendered pathways from child sexual abuse to sexual aggression victimization and perpetration in adolescence and young adulthood. Child Abuse Negl 2017 Jan;63:261-272. [doi: 10.1016/j.chiabu.2016.10.004] [Medline: 27771010]
58. McKeough A, Bear K, Jones CJ, Thompson D, Kelly PJ, Campbell LE. Foster carer stress and satisfaction: an investigation of organisational, psychological and placement factors. Child Youth Serv Rev 2017 May;76:10-19. [doi: 10.1016/j.childyouth.2017.02.002]
59. Assink M, Spruit A, Schuts M, Lindauer R, van der Put CE, Stams GJ. The intergenerational transmission of child maltreatment: a three-level meta-analysis. Child Abuse Negl 2018 Oct;84:131-145. [doi: 10.1016/j.chiabu.2018.07.037] [Medline: 30086419]
60. Lind T, Bernard K, Ross E, Dozier M. Intervention effects on negative affect of CPS-referred children: results of a randomized clinical trial. Child Abuse Negl 2014 Sep;38(9):1459-1467 [FREE Full text] [doi: 10.1016/j.chiabu.2014.04.004] [Medline: 24814751]
61. Stormshak EA, Seeley JR, Caruthers AS, Cardenas L, Moore KJ, Tyler MS, et al. Evaluating the efficacy of the family check-up online: a school-based, eHealth model for the prevention of problem behavior during the middle school years. Dev Psychopathol 2019 Dec;31(5):1873-1886. [doi: 10.1017/S0954579419000907] [Medline: 31407644]
62. Dziak JJ, Collins LM, Wagner AT. FactorialPowerPlan SAS Macro Users' Guide. Version 1.0.: The Methodology Center, Penn State; 2013. URL: https://www.methodology.psu.edu/files/2019/03/factorial_power_plan_ug-1du7v00.pdf [accessed 2020-08-14]
63. Research Randomizer. URL: https://www.randomizer.org/ [accessed 2022-10-14]
64. Temcheff CE, Letarte MJ, Boutin S, Marcil K. Common components of evidence-based parenting programs for preventing maltreatment of school-age children. Child Abuse Negl 2018 Jun;80:226-237. [doi: 10.1016/j.chiabu.2018.02.004] [Medline: 29631254]
65. van der Put CE, Assink M, Gubbels J, Boekhout van Solinge NF. Identifying effective components of child maltreatment interventions: a meta-analysis. Clin Child Fam Psychol Rev 2018 Jun;21(2):171-202 [FREE Full text] [doi: 10.1007/s10567-017-0250-5] [Medline: 29204796]
66. Leiner DJ. SoSci Survey (Version 3.2.49). 2022. URL: http://www.soscisurvey.com [accessed 2022-10-13]
67. Fromme K, Katz EC, Rivet K. Outcome expectancies and risk-taking behavior. Cogn Ther Res 1997 Aug;21:421-442. [doi: 10.1023/A:1021932326716]

Abbreviations

DSMB: Data Safety and Monitoring Board
MOST: multiphase optimization strategy
PTSD: posttraumatic stress disorder
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

A Positive Emotion–Focused Intervention to Increase Physical Activity After Bariatric Surgery: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Physical activity levels after bariatric surgery are usually low, despite the significant protective health benefits of physical activity in this population. Positive psychological well-being is associated with improved adherence to health behaviors, but bariatric surgery patients often have negative associations with physical activity that prevent sustained engagement.

Objective: The Gaining Optimism After weight Loss Surgery (GOALS) pilot randomized controlled trial is aimed at testing a novel intervention to increase physical activity after bariatric surgery, which incorporates positive psychological skill-building with motivational interviewing and goal-setting.

Methods: The GOALS trial is a 2-arm, 24-week pilot randomized controlled trial that aims to enroll 58 adults who report less than 200 minutes per week of moderate to vigorous physical activity and a desire to become more active 6-12 months after bariatric surgery. GOALS is testing the feasibility, acceptability, and preliminary efficacy of a positive psychology–motivational interviewing telephone intervention targeting to increase physical activity and associated positive affect. Intervention components include positive psychology, goal-setting, self-monitoring via provided Fitbits, and motivational interviewing to overcome barriers and increase motivation. The intervention is compared to a physical activity education control that includes mailings with psychoeducation around physical activity and provision of a Fitbit. The primary outcomes of the pilot trial are feasibility and acceptability, measured as session completion rates and participant ratings of ease and helpfulness of each session. The main secondary outcome is change in accelerometer-measured moderate to vigorous physical activity post intervention and at 24-week follow-up. Additional outcomes include changes in attitudes related to physical activity, psychological well-being, and physical health measures.

Results: This multiphase project was funded in 2020 and institutional review board approval was obtained for the proposed trial in 2021. Recruitment for the randomized controlled trial began in July 2022. Upon completion of the pilot trial, we will examine the feasibility, acceptability, and preliminary efficacy of the intervention.

Conclusions: Although bariatric surgery is the most effective treatment available for severe obesity, weight regain occurs, often in the context of low psychological well-being. Many individuals would benefit from learning strategies to increase positive psychological well-being after bariatric surgery, which could help them maintain lifestyle changes. Positive psychology is a novel approach to improve adherence by increasing positive associations with health behaviors including physical activity. The GOALS pilot trial will determine whether this type of intervention is feasible and acceptable to this population and will provide a foundation for a future full-scale randomized controlled efficacy trial.

Trial Registration: ClinicalTrials.gov NCT04868032; https://clinicaltrials.gov/ct2/show/NCT04868032
International Registered Report Identifier (IRRID): PRR1-10.2196/39856

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KEYWORDS

behavioral intervention; physical activity; positive psychology; design; bariatric surgery; positive; psychological; well-being; weight loss; intervention; feasibility; acceptability; efficacy; effect; obesity; weight

Introduction

Bariatric surgery is the most effective treatment available for severe obesity, often resulting in cost-effective, sustained weight loss [1-3]. However, approximately 25% of surgical patients do not achieve long-term weight loss maintenance [2-4]. Weight loss is associated with remission of weight-related comorbidities (eg, type 2 diabetes, hypertension, and hypercholesterolemia), and weight loss maintenance is vital for preserving these improvements in health [3]. Physical activity is critical for weight loss maintenance and improved health after bariatric surgery, particularly given the increased risk of cardiometabolic disease in this population [5-7].

After bariatric surgery, experts recommend individuals to engage in at least 150 minutes per week of moderate to vigorous physical activity (MVPA), and even higher levels may be needed to control weight [8-10]. Unfortunately, a large majority of people who have bariatric surgery do not meet this recommendation [11-13]. Increasing physical activity, even without weight change, can improve insulin sensitivity, cardiorespiratory fitness, blood pressure, and blood lipid levels, all of which confer a lower risk for cardiac and metabolic disease in the general population [14-17]. Behavioral interventions to improve physical activity after bariatric surgery show promise, but the evidence is still limited by a lack of trials that do not include an in-person exercise program and are well-powered with long-term follow-up [18-20].

Emotional factors play a role in physical activity engagement and health outcomes. Psychological distress predicts lower physical activity levels and less weight loss after bariatric surgery [21], and these individuals are more likely to experience depressive symptoms than the general population [22,23]. Conversely, positive psychological constructs such as optimism and positive affect are associated with improved health independent of depression but have not been examined thoroughly in people who have bariatric surgery [24-26]. Further, positive affect during physical activity has been shown to predict future physical activity, supporting the “upward spiral” theory of lifestyle change [27,28]. This theory posits that by experiencing positive affect when performing a health behavior, nonconscious motives increase one’s likelihood of repeating that behavior. Over time, health behaviors become reinforcing rather than burdensome. However, most people experience a decrease in positive affect during exercise [29], and sedentary women with obesity have been found to experience even lower pleasure during physical activity than those with a BMI in the normal or overweight category [30]. People undergoing bariatric surgery may be missing out on this “upward spiral” owing to emotional barriers to physical activity, such as anxiety about getting injured, shame about appearance, and experiences of weight stigma, as well as physical barriers such as increased shortness of breath and discomfort [31-33]. This group would benefit from new skills to increase positive affect during physical activity as well increased psychological well-being in general.

Physical activity interventions that include positive psychology may be particularly effective after bariatric surgery. In addition to improving overall well-being, positive psychology interventions could improve physical activity by targeting positive affect during physical activity engagement [34,35]. Positive psychology may be more effective in combination with an adherence-based program such as motivational interviewing, a technique that focuses on clarifying motivation, addressing ambivalence, and setting achievable goals [36]. Indeed, a combined, remotely delivered positive psychology–motivational interviewing (PP-MI) intervention has shown preliminary efficacy in improving health behaviors in patients with type 2 diabetes and those with heart disease [37-39]. However, this intervention does not address the unique barriers that are common after bariatric surgery (eg, history of negative experiences with exercise due to injuries or weight stigma, adapting to a drastically changing body, and managing excess skin after weight loss) and does not directly address affect during physical activity.

The Gaining Optimism After weight Loss Surgery (GOALS) pilot randomized controlled trial (RCT) is testing an adapted PP-MI intervention promoting physical activity in individuals who have undergone bariatric surgery in the past 6-12 months. This paper describes the design and development of the intervention.

Methods

Overview

The GOALS trial is a 2-arm, 24-week pilot RCT that tests the feasibility, acceptability, and preliminary efficacy of a PP-MI telephone intervention, in comparison to a control arm, on physical activity and psychological, behavioral, and physical health outcomes immediately post intervention and at 24-week follow-up. The primary outcome of the trial is feasibility and acceptability of the intervention as measured by session completion rates and participant ease and utility ratings. The secondary outcomes are change at postintervention 10-14 weeks and 24-week follow-up in MVPA measured using an accelerometer. Additional outcomes include changes in light physical activity and steps per day, attitudes related to physical activity (enjoyment, self-efficacy, perceived barriers, and exercise identity), psychological well-being (symptoms of

depression and anxiety, optimism, positive affect, internalized weight bias, and general self-efficacy), and health measures (exercise capacity, BMI, bariatric surgery behavioral adherence, and general health status) post intervention and at 24-week follow-up.

Ethics Approval

The institutional review board of the Mass General Brigham initially approved the multiphase study in 2020 (2021P001006).

Study Development

The GOALS intervention and study protocol were developed and refined in accordance with the Obesity-Related Behavioral Intervention Trials (ORBIT) model [40]. The ORBIT model focuses specifically on early, pre-efficacy phases of intervention development and emphasizes a flexible, iterative approach to moving between phases. The GOALS intervention is based on a PP-MI intervention that was initially developed for people with heart disease [37]. To adapt the intervention for the unique experiences of those who have bariatric surgery, a qualitative study was performed to understand the emotional experiences of people with a recent history of bariatric surgery regarding physical activity (ORBIT phase 1a and 1b; design: define and refine) [33]. Results from this study informed adaptation from the original PP-MI intervention to develop the GOALS intervention. Next, a proof-of-concept trial of the newly developed intervention was completed in 12 participants with exit interviews to refine study procedures and intervention content (ORBIT phase IIa; preliminary testing: proof of concept). Results from this study phase led to further adjustments in the intervention that is now being tested in the described pilot RCT (ORBIT phase IIb; preliminary testing: pilots). These include content changes to address additional common barriers to physical activity (eg, history of injuries), adjusting the positive psychology content to include some general exercises in addition to those focused on physical activity, and some small changes to session order and organization.

Population

The GOALS trial is enrolling adults (age 18+ years) with a history of bariatric surgery in the prior 6-12 months. They also must self-report less than 200 minutes per week of MVPA and a desire to increase physical activity. While the physical activity recommendation is 150 minutes per week of MVPA, we chose a higher cutoff owing to a high likelihood of overestimation in self-reported physical activity [12], along with additional benefits of higher activity levels for weight loss promotion and maintenance [9,10]. Participants must have telephone access for study sessions and be able to read and speak English. Individuals are excluded from the study if they have cognitive deficits that preclude participation or informed consent assessed using a 6-item assessment tool designed to assess suitability for research participation [41], illness likely to lead to death in the next 6 months per chart review, inability to be physically active (eg, severe arthritis), severe psychopathology that may limit the ability to participate in the study per chart review, or current participation in another program targeting physical activity besides the standard care they receive at their surgery center.

Participant Recruitment

Our goal is to randomize 58 participants. We identify patients with surgery dates in the relevant time frame using the hospital system's Research Patient Data Registry, which allows for searching of electronic medical records to extract lists of patients who meet certain criteria. We send opt-out letters to patients from this list by mail and through the patient portal. Letters briefly describe the study and provide contact information if patients want to decline further contact. Letters are followed by a recruitment phone call 2 weeks later for those who do not opt out. We also can advertise for the study using a flyer to be distributed during postoperative groups and visits within the bariatric surgery clinic. These recruitment methods have been used successfully in prior studies [33].

Participant Screening

Interested participants complete a screening phone call that includes a version of the International Physical Activity Questionnaire–Short Form modified to include brisk walking as a form of moderate activity [42], a 6-item cognitive deficit assessment [41], and questions about interest and ability to increase physical activity and participation in any other physical activity program. If eligible, their baseline visit is scheduled at this time.

Assessment Visits

Participants attend assessment visits at baseline, end of treatment (10-14 weeks), and follow-up (24 weeks) at the hospital's translational clinical research center. Assessment visit timing is designed to assess both the immediate and sustained intervention impact. Informed consent is obtained at the baseline visit. At each assessment, participants provide demographic and medical information (eg, medical comorbidities and weight history) and complete self-report measures via REDCap. Physiological measures are obtained by a trained translational clinical research center staff member, and 5-mL samples of blood are drawn. Staff also perform a 6-minute walk test to assess functional exercise capacity [43]. Participants are asked to wear an ActiGraph GT3X-BT accelerometer [44] for 7 days (minimum acceptable use is 4 days with 10 hours of recorded data) at each assessment. Participants are paid US $100 for completing each assessment visit.

Randomization Visit

After wearing the accelerometer for 7 days following the baseline visit, participants return the accelerometer and are randomized 1:1 with a random number generator to a study condition (PP-MI or control) after sufficient wear time is confirmed. Only participants who complete accelerometry and return for this visit are randomized. At this time, study staff provide the participant a Fitbit to aid with self-monitoring physical activity and helps them set it up with a study-created account. If they are randomized to PP-MI, they are given the study manual and meet with a study interventionist for approximately 45 minutes for an in-person discussion of the introduction and first session of the program, including setting a long-term physical activity goal to reach by the end of the program. If they are randomized to the control group, they are provided an educational handout about physical activity.

Intervention Components

The GOALS intervention was adapted and refined on the basis of results from the formative qualitative study and from interventionist experience and participant feedback from a proof-of-concept trial of the intervention [33]. It is delivered over 10 weeks via weekly 30-45–minute phone calls supported by a written participant manual. A window of 14 weeks for intervention completion allows for flexibility in the timing of weekly sessions. Each week includes a topic related to increasing physical activity and a positive psychology skill that is focused on increasing positive emotions in general and during physical activity (see Table 1). Participants are assigned pages in the manual to read and worksheets to complete each week. The physical activity portion of the call includes a review of the prior week's physical activity topic and of their activity levels from the prior week, including whether they met their goal based on Fitbit data or other methods of self-monitoring, and noting positive emotions experienced during physical activity that week. Furthermore, a new topic is assigned to be completed over the subsequent week and a new physical activity goal is collaboratively set for the upcoming week on the basis of their activity level in the prior week. This goal is customized to each participant's current activity level and interest, and is primarily self-determined with input from the interventionist as needed. The positive psychology portion includes a review of written assignments from the prior week and associated positive thoughts and feelings identified, followed by introduction to the next week's topic and assignment. Reviewing, reflecting, and planning for the future sessions encourage integration of positive psychology skills learned into daily life by developing a specific plan to build a habit. All content is delivered using a motivational interviewing approach. The specific weekly topics are described in Table 1. Participants are also sent psychoeducation about physical activity via mail or email as in the control condition (see the *Control Content* section for details).

Table 1. Weekly intervention topics.

Week	Physical activity topic	Positive psychology topic
1	*Getting started with increasing activity*: benefits of physical activity, importance and confidence in making a change, and setting an overall program goal	*Identifying positive feelings during exercise*:[a] pay attention to and write down specific positive emotions during and after physical activity
2	*Pros and cons of change/SMART*[b]*goals*: consider pros and cons of making a behavior change and of staying the same, setting goals that are specific, measurable, attainable, relevant, and time-based	*Gratitude for positive events*: identify 3 good things that happen this week, one related to exercise and two broadly, write about them and associated positive thoughts and feelings
3	*Barriers and problem-solving*: identify barriers to physical activity and brainstorm ways to overcome them	*Positive reappraisal – general*: learn about positive reappraisal as a way of seeing the silver lining in a negative situation, use it in response to a situation this week following guided prompts
4	*Strength training and equipment resources*: set a strength-training goal in addition to general physical activity goal; identify and use exercise equipment	*Positive reappraisal for physical activity*: consider common negative experiences with physical activity and how to positively reappraise; use positive reappraisal for one situation related to physical activity this week
5	*Neighborhood, online, and social resources*: brainstorm resources for increasing activity and use a new one this week	*Using perseverance*: review benefits of perseverance, pick physical activity-related goal to achieve using perseverance this week
6	*Reviewing and reflecting*: review progress so far, adjust long-term goals if needed, and reassess importance and confidence	*Reviewing and reflecting*: review skills learned so far, make a plan to integrate one into daily life this week to build a habit
7	*Reducing sedentary time*: assess most sedentary activities and make a plan to incorporate standing breaks and small increases in movement throughout the day	*Focusing on meaning during physical activity*: identify nonweight reasons for physical activity and practice thinking of these motivators when making the decision to be active and during activity this week
8	*Managing slips*: normalize slips, plan how to avoid long-term decreases after slips	*Remembering past successes*: write about a time in the past when you were successful with exercise, and about the qualities that were helpful in succeeding
9	*Finding new routes*: assess walking environment while trying a new local walking route	*Using personal strengths*: identify a "signature strength" and use it to help promote physical activity this week
10	*Planning for the future*: review progress, set goals for future increase or maintenance of physical activity	*Planning for the future*: choose 2 positive psychology skills that were most helpful, make plan to integrate moving forward

[a]Participants are asked to identify positive emotions during exercise every week throughout the intervention.

[b]SMART: specific, measurable, attainable, relevant, and time-based.

Intervention Delivery and Fidelity

Interventionists are doctoral level psychologists or psychology doctoral students. All sessions are audio-recorded, and at least 25% of calls are reviewed for fidelity by the principal investigator using a fidelity scale developed for the trial to ensure consistency in intervention delivery. The scale measures mention of session-specific topics and procedures (eg, review of the prior week's physical activity), use of motivational interviewing techniques, and that other psychological techniques are not used. Cases are reviewed and discussed in weekly supervision.

Control Content

Participants randomized to the control condition receive a Fitbit and instructions for its use at their randomization visit. They are also provided with educational information about physical activity and its benefits at 4 time points throughout the intervention period (in person at randomization visit, mailed or emailed at weeks 3, 6, and 9). The study research assistant calls control participants at the midpoint of the intervention period to ensure they are receiving educational materials. These include publicly available infographics from the Centers for Disease Control and Prevention and psychoeducation material used in primary care offices affiliated with this hospital discussing overcoming barriers to physical activity and giving instruction for simple strength exercises to be completed at home. Specific physical activity goals are not provided for control participants. Fitbits are provided to all participants to ensure that group differences are not simply due to Fitbit use.

Outcome Assessments

The primary outcomes of this study are feasibility and acceptability. Feasibility of the intervention is measured as the number of sessions attended by each participant. The intervention will be considered feasible if at least 7 of the 10 sessions are completed, on average. Intervention acceptability is measured using participant ratings on ease and utility of each intervention topic on a scale from 0 to 10 (0="not at all easy/helpful"; 10="very easy/helpful"). The intervention will be considered acceptable if average ratings are ≥7 out of 10.

Physical activity is assessed using accelerometers (ActiGraph GT3X-BT). At least 4 days of at least 600 minutes of wear time are required for data to be considered valid, according to established recommendations [45,46]. We will calculate average MVPA in terms of minutes per day (1952 counts per minute) and light physical activity (100-1951 counts per minute) and the daily step count. Raw data are analyzed using ActiLife (version 6.13.14; ActiGraph) in 60-second epochs. The International Physical Activity Questionnaire–Short Form is used to assess self-reported physical activity [42]. Self-efficacy for exercise is measured with the Self-Efficacy for Exercise Scale [47], exercise identity is measured with the Exercise Identity Scale [48], exercise enjoyment is measured with the Physical Activity Enjoyment Scale [49], and barriers to being active are measured with the Barriers to Being Active Quiz [50].

Psychological outcomes include positive affect measured using the Positive and Negative Affect Scale [51], optimism with the Life Orientation Test–Revised [52], symptoms of depression and anxiety with the Hospital Anxiety and Depression Scale [53], internalized weight bias with the Weight Bias Internalization Scale–Modified [54], and general self-efficacy with the General Self-Efficacy Scale [55].

Health-related outcomes include BMI, waist circumference (broadest hip and midpoint between last rib and iliac crest), percent body fat assessed with the RJL Systems Quantum IV Bioelectrical Impedance Analyzer, exercise capacity assessed using the 6-minute walk test [43], adherence to the MBS diet and vitamin regimen assessed with the Bariatric Surgery Self-Management Questionnaire [56], and general health status measured with the Short Form-12 [57]. All self-report measures have been validated in large samples.

Several physiological markers of cardiometabolic health are also measured at assessment points to test procedural feasibility in preparation for a future fully powered trial. These include blood pressure measured in mm Hg, blood lipids (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, and triglycerides), HbA1c, and high-sensitivity c-reactive protein. We do not anticipate meaningful changes in these measures in this pilot trial; hence, we have not included them as formal outcomes. Table 2 summarizes the timing of the assessments.

Table 2. Timing of assessments [56].

Measure	Screening	Visit 1 (week 0)	Visit 2 (week 2)	10 weekly intervention calls	Visit 3 (week 14)	Visit 4 (week 28)
Primary outcomes						
Feasibility	N/A[a]	N/A	N/A	Completion rate	N/A	N/A
Acceptability	N/A	N/A	N/A	Weekly ratings	N/A	N/A
Secondary outcome						
Objective moderate to vigorous physical activity	N/A	Actigraph given	Actigraph returned	N/A	Actigraph mailed 1 week prior	Actigraph mailed 1 week prior
Additional outcomes						
Objective light physical activity	N/A	Actigraph given	Actigraph returned	N/A	Actigraph mailed 1 week prior	Actigraph mailed 1 week prior
Objective steps per day	N/A	Actigraph given	Actigraph returned	N/A	Actigraph mailed 1 week prior	Actigraph mailed 1 week prior
Self-reported physical activity	X[b]	X	N/A	Reported weekly from Fitbits and self-monitoring	X	X
Self-efficacy for exercise	N/A	X	N/A	N/A	X	X
Exercise identity	N/A	X	N/A	N/A	X	X
Physical activity enjoyment	N/A	X	N/A	N/A	X	X
Barriers to being active	N/A	X	N/A	N/A	X	X
Positive affect	N/A	X	N/A	N/A	X	X
Optimism	N/A	X	N/A	N/A	X	X
Depression	N/A	X	N/A	N/A	X	X
Anxiety	N/A	X	N/A	N/A	X	X
Internalized weight bias	N/A	X	N/A	N/A	X	X
MBS diet and vitamin adherence	N/A	X	N/A	N/A	X	X
BMI	N/A	X	N/A	N/A	X	X
Waist circumference	N/A	X	N/A	N/A	X	X
Body fat percentage	N/A	X	N/A	N/A	X	X
Exercise capacity	N/A	X	N/A	N/A	X	X
General health status	N/A	X	N/A	N/A	X	X

[a]N/A: not applicable.

[b]X: measure assessed at this timepoint.

Analytical Approach

Power and Sample Size

This feasibility study is not designed to detect significant between-group differences in physical activity and other outcomes; rather, its primary aim is to estimate feasibility and acceptability of the intervention. With 29 subjects receiving the intervention, we will be able to estimate the proportion who complete the intervention (feasibility) with a CI width of approximately ±0.2. We will examine the effect sizes of the intervention outcomes in addition to *P* values owing to low power.

Statistical Analysis Plan

We will calculate the average proportion of sessions completed to measure feasibility. The study will be considered feasible if at least 7 of 10 sessions are completed on average. Acceptability will be measured with means and SDs of participants' ratings of session ease and utility, compared to our hypothesized target of ≥7 out of 10 for each rating. For physical activity and other psychological, behavioral, and physiological outcomes, we will model changes in each outcome using a repeated measures regression model with a fixed effect of treatment condition, a categorical effect of time, and a time by treatment interaction. The interaction will estimate the difference in the change with time comparing the treatment groups. To account for the repeated measures on each participant, we will use an

unstructured covariance matrix. In addition to tests of statistical significance, which will be exploratory, given the sample size, we will calculate effect sizes to estimate the magnitude of effect of the intervention. The effect size will be estimated as the difference in the mean change with time between the groups from the interaction term divided by the estimated SD of the change with time from the unstructured covariance matrix. All tests will be considered significant based on a 2-tailed α level of .05.

Results

Funding for this multiphase project was awarded in July 2020. The first 2 years of the award were developmental. Approval from the institutional review board for the proof-of-concept trial and RCT was attained in May 2021. The proof-of-concept trial was conducted from July 2021 through June 2022. Recruitment for the RCT began in July 2022, and study completion is anticipated by July 2024. The trial is registered at ClinicalTrials.gov [NCT04868032].

Discussion

We hypothesize that the GOALS intervention will be feasible and acceptable and will improve physical activity and psychological well-being. After bariatric surgery, patients typically do not meet physical activity recommendations, and they receive little guidance and support to help them succeed [13]. The GOALS trial addresses this need by testing a PP-MI intervention for physical activity, which is specifically customized to the needs of this population.

While health behavior change interventions are common, the PP-MI approach is novel in its additional focus on addressing the lack of positive reinforcement that may be restraining many from developing and maintaining a consistent physical activity routine and enhancing positive psychological well-being more broadly [33]. By incorporating positive psychological skill development with motivational interviewing, self-monitoring, and goal-setting for physical activity, we hope to build participants' self-efficacy for being active while also teaching them how to make exercise a more enjoyable experience that they will want to continue doing. Results from other versions of PP-MI interventions in other medical populations suggest that this approach is generally accepted and leads to greater well-being and MVPA, even compared to active controls [37-39]. The GOALS intervention aims to further integrate the positive psychology approach with physical activity engagement by focusing specifically on the identification and building of positive affect during physical activity and by addressing psychological barriers to being active consistently.

Another strength of the GOALS intervention is its remote delivery. In-person postoperative interventions have struggled with attendance, with common barriers including living long distances from the clinic and lack of time off from work [58-61]. By using a written manual along with weekly phone calls, participants are able to complete GOALS assignments flexibly and can more easily fit in weekly sessions from work or home. They also learn how to build physical activity into their routines in a sustainable way by finding resources in their own environments to facilitate activity rather than attending a prescribed exercise training program that has an end date.

We chose to focus the GOALS intervention on physical activity exclusively rather than also including a diet component. This was in part because patients typically receive more guidance about the postoperative diet from their surgical center than they do about physical activity. Further, we decided to focus more on the direct mental and physical health benefits of physical activity instead of encouraging exercise as a tool to lose more weight. While dietary changes are more strongly associated with weight loss than with increasing physical activity [62], patients can achieve significant health benefits from increasing physical activity independent of their weight [14-17]. By focusing on these nonweight motivators, physical activity may be more likely to improve body image [63]. When considering that long-term maintenance of physical activity after weight loss from surgery is complete, building motivators separate from weight loss is critical.

We chose the time window of 6-12 months post bariatric surgery for study enrollment based on careful consideration of several factors. By 6 months, most patients have completed standard postoperative group sessions and other care, so they may have time and interest in additional support at that time. This also allows us to target patients who have not been able to sufficiently increase physical activity on their own, as by 6 months, their physical recovery from surgery should be complete, as should their adaptation to the new diet. We limited the maximum time since surgery to 12 months to identify people who still have high motivation to make weight-related behavioral changes following their surgery.

Strengths of the study include an iteratively developed intervention incorporating patient preferences and feedback, remote delivery, randomized design, and objective measurement of physical activity and biometric outcomes. Study limitations include a small sample size with insufficient power to detect significant effects at this pilot stage and single-site delivery, which may reduce the generalizability of our results.

If the GOALS pilot RCT is feasible, acceptable to patients, and leads to improvements in physical activity and psychological outcomes, the next step will be to test the efficacy of GOALS on physical activity in a full-scale trial. Ultimately, a program such as GOALS could be integrated into clinical postoperative care as a remotely delivered, longer-term approach to promote physical activity and psychological well-being after bariatric surgery.

Data Availability

The data sets generated during and analyzed in this study will be available from the corresponding author on reasonable request at study completion.

Conflicts of Interest

None declared.

References

1. Alsumali A, Eguale T, Bairdain S, Samnaliev M. Cost-effectiveness analysis of bariatric surgery for morbid obesity. Obes Surg 2018 Aug;28(8):2203-2214 [FREE Full text] [doi: 10.1007/s11695-017-3100-0] [Medline: 29335933]
2. Adams T, Davidson L, Litwin S, Kim J, Kolotkin R, Nanjee M, et al. Weight and metabolic outcomes 12 years after gastric bypass. N Engl J Med 2017 Sep 21;377(12):1143-1155 [FREE Full text] [doi: 10.1056/nejmoa1700459]
3. Courcoulas A, King WC, Belle SH, Berk P, Flum DR, Garcia L, et al. Seven-year weight trajectories and health outcomes in the longitudinal assessment of bariatric surgery (LABS) study. JAMA Surg 2018 May 01;153(5):427-434 [FREE Full text] [doi: 10.1001/jamasurg.2017.5025] [Medline: 29214306]
4. Clapp B, Wynn M, Martyn C, Foster C, O'Dell M, Tyroch A. Long term (7 or more years) outcomes of the sleeve gastrectomy: a meta-analysis. Surg Obes Relat Dis 2018 Jun;14(6):741-747 [FREE Full text] [doi: 10.1016/j.soard.2018.02.027] [Medline: 29625744]
5. Livhits M, Mercado C, Yermilov I, Parikh JA, Dutson E, Mehran A, et al. Exercise following bariatric surgery: systematic review. Obes Surg 2010 May;20(5):657-665 [FREE Full text] [doi: 10.1007/s11695-010-0096-0] [Medline: 20180039]
6. Egberts K, Brown WA, Brennan L, O'Brien PE. Does exercise improve weight loss after bariatric surgery? A systematic review. Obes Surg 2012 Mar;22(2):335-341 [FREE Full text] [doi: 10.1007/s11695-011-0544-5] [Medline: 22038571]
7. Carnero E, Dubis GS, Hames KC, Jakicic JM, Houmard JA, Coen PM, et al. Randomized trial reveals that physical activity and energy expenditure are associated with weight and body composition after RYGB. Obesity (Silver Spring) 2017 Jul;25(7):1206-1216 [FREE Full text] [doi: 10.1002/oby.21864] [Medline: 28558160]
8. Saris WHM, Blair SN, van Baak MA, Eaton SB, Davies PSW, Di Pietro L, et al. How much physical activity is enough to prevent unhealthy weight gain? Outcome of the IASO 1st Stock Conference and consensus statement. Obes Rev 2003 May;4(2):101-114 [FREE Full text] [doi: 10.1046/j.1467-789x.2003.00101.x] [Medline: 12760445]
9. Donnelly J, Blair S, Jakicic J, Manore M, Rankin J, Smith B. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. Med Sci Sports Exerc 2009;41(2):459-471 [FREE Full text] [doi: 10.1249/mss.0b013e3181949333]
10. Mechanick J, Youdim A, Jones DB, Timothy Garvey W, Hurley DL, Molly McMahon M, et al. Surg Obes Relat Dis 2013;9(2):159-191 [FREE Full text] [doi: 10.1016/j.soard.2012.12.010] [Medline: 23537696]
11. King W, Hsu JY, Belle SH, Courcoulas AP, Eid GM, Flum DR, et al. Pre- to postoperative changes in physical activity: report from the longitudinal assessment of bariatric surgery-2 (LABS-2). Surg Obes Relat Dis 2012;8(5):522-532 [FREE Full text] [doi: 10.1016/j.soard.2011.07.018] [Medline: 21944951]
12. Bond D, Jakicic JM, Unick JL, Vithiananthan S, Pohl D, Roye GD, et al. Pre- to postoperative physical activity changes in bariatric surgery patients: self report vs. objective measures. Obesity (Silver Spring) 2010 Dec;18(12):2395-2397 [FREE Full text] [doi: 10.1038/oby.2010.88] [Medline: 20379143]
13. King W, Chen JY, Bond DS, Belle SH, Courcoulas AP, Patterson EJ, et al. Objective assessment of changes in physical activity and sedentary behavior: Pre- through 3 years post-bariatric surgery. Obesity (Silver Spring) 2015 Jun;23(6):1143-1150 [FREE Full text] [doi: 10.1002/oby.21106] [Medline: 26010326]
14. Friedenreich C, Neilson H, Woolcott C, McTiernan A, Wang Q, Ballard-Barbash R, et al. Changes in insulin resistance indicators, IGFs, and adipokines in a year-long trial of aerobic exercise in postmenopausal women. Endocrine Related Cancer 2011 Apr 11;18(3):357-369 [FREE Full text] [doi: 10.1530/erc-10-0303]
15. Mann S, Beedie C, Jimenez A. Differential effects of aerobic exercise, resistance training and combined exercise modalities on cholesterol and the lipid profile: review, synthesis and recommendations. Sports Med 2014 Mar;44(2):211-221 [FREE Full text] [doi: 10.1007/s40279-013-0110-5] [Medline: 24174305]
16. Conn V, Koopman RJ, Ruppar TM, Phillips LJ, Mehr DR, Hafdahl AR. Insulin sensitivity following exercise interventions: systematic review and meta-analysis of outcomes among healthy adults. J Prim Care Community Health 2014 Jul;5(3):211-222 [FREE Full text] [doi: 10.1177/2150131913520328] [Medline: 24474665]
17. Cornelissen V, Smart N. Exercise training for blood pressure: a systematic review and meta‐analysis. JAHA 2013 Jan 23;2(1):A [FREE Full text] [doi: 10.1161/jaha.112.004473]
18. Rudolph A, Hilbert A. Post-operative behavioural management in bariatric surgery: a systematic review and meta-analysis of randomized controlled trials. Obes Rev 2013 Apr;14(4):292-302 [FREE Full text] [doi: 10.1111/obr.12013] [Medline: 23294936]

19. Herring L, Stevinson C, Carter P, Biddle SJH, Bowrey D, Sutton C, et al. The effects of supervised exercise training 12-24 months after bariatric surgery on physical function and body composition: a randomised controlled trial. Int J Obes (Lond) 2017 Jun;41(6):909-916 [FREE Full text] [doi: 10.1038/ijo.2017.60] [Medline: 28262676]
20. David LA, Sijercic I, Cassin SE. Preoperative and post-operative psychosocial interventions for bariatric surgery patients: a systematic review. Obes Rev 2020 Apr 22;21(4):e12926 [FREE Full text] [doi: 10.1111/obr.12926] [Medline: 31970925]
21. Rosenberger P, Henderson KE, White MA, Masheb RM, Grilo CM. Physical activity in gastric bypass patients: associations with weight loss and psychosocial functioning at 12-month follow-up. Obes Surg 2011 Oct;21(10):1564-1569 [FREE Full text] [doi: 10.1007/s11695-010-0283-z] [Medline: 20890771]
22. Mitchell J, King WC, Chen JY, Devlin MJ, Flum D, Garcia L, et al. Course of depressive symptoms and treatment in the longitudinal assessment of bariatric surgery (LABS-2) study. Obesity (Silver Spring) 2014 Aug;22(8):1799-1806 [FREE Full text] [doi: 10.1002/oby.20738] [Medline: 24634371]
23. Switzer N, Debru E, Church N, Mitchell P, Gill R. The impact of bariatric surgery on depression: a review. Curr Cardiovasc Risk Rep 2016 Feb 15;10(3):A [FREE Full text] [doi: 10.1007/s12170-016-0492-7]
24. Rasmussen H, Scheier MF, Greenhouse JB. Optimism and physical health: a meta-analytic review. Ann Behav Med 2009 Jun;37(3):239-256 [FREE Full text] [doi: 10.1007/s12160-009-9111-x] [Medline: 19711142]
25. Chida Y, Steptoe A. Positive psychological well-being and mortality: a quantitative review of prospective observational studies. Psychosom Med 2008 Sep;70(7):741-756. [doi: 10.1097/PSY.0b013e31818105ba] [Medline: 18725425]
26. Feig E, Golden J, Huffman JC. Emotional impact on health behavior adherence after bariatric surgery: what about positive psychological constructs? Obes Surg 2019 Jul;29(7):2238-2246 [FREE Full text] [doi: 10.1007/s11695-019-03833-4] [Medline: 30887307]
27. Van Cappellen P, Rice EL, Catalino LI, Fredrickson BL. Positive affective processes underlie positive health behaviour change. Psychol Health 2018 Jan;33(1):77-97 [FREE Full text] [doi: 10.1080/08870446.2017.1320798] [Medline: 28498722]
28. Rhodes R, Kates A. Can the affective response to exercise predict future motives and physical activity behavior? A systematic review of published evidence. Ann Behav Med 2015 Oct;49(5):715-731 [FREE Full text] [doi: 10.1007/s12160-015-9704-5] [Medline: 25921307]
29. Backhouse S, Ekkekakis P, Bidle SJH, Foskett A, Williams C. Exercise makes people feel better but people are inactive: paradox or artifact? J Sport Exerc Psychol 2007 Aug;29(4):498-517 [FREE Full text] [doi: 10.1123/jsep.29.4.498] [Medline: 17968050]
30. Ekkekakis P, Lind E, Vazou S. Affective responses to increasing levels of exercise intensity in normal-weight, overweight, and obese middle-aged women. Obesity (Silver Spring) 2010 Jan;18(1):79-85 [FREE Full text] [doi: 10.1038/oby.2009.204] [Medline: 19556979]
31. Ball K, Crawford D, Owen N. Too fat to exercise? Obesity as a barrier to physical activity. Aust N Z J Public Health 2000 Jun;24(3):331-333 [FREE Full text] [doi: 10.1111/j.1467-842x.2000.tb01579.x] [Medline: 10937415]
32. Han S, Agostini G, Brewis AA, Wutich A. Avoiding exercise mediates the effects of internalized and experienced weight stigma on physical activity in the years following bariatric surgery. BMC Obes 2018;5:18 [FREE Full text] [doi: 10.1186/s40608-018-0195-3] [Medline: 29988619]
33. Feig E, Harnedy LE, Golden J, Thorndike AN, Huffman JC, Psaros C. A qualitative examination of emotional experiences during physical activity post-metabolic/bariatric surgery. Obesity surgery 2022;32(3):660-670.
34. Labarthe D, Kubzansky LD, Boehm JK, Lloyd-Jones DM, Berry JD, Seligman MEP. Positive cardiovascular health: a timely convergence. J Am Coll Cardiol 2016 Aug 23;68(8):860-867 [FREE Full text] [doi: 10.1016/j.jacc.2016.03.608] [Medline: 27539179]
35. Van Cappellen P, Rice EL, Catalino LI, Fredrickson BL. Positive affective processes underlie positive health behaviour change. Psychol Health 2018 Jan;33(1):77-97 [FREE Full text] [doi: 10.1080/08870446.2017.1320798] [Medline: 28498722]
36. Safren S, Bedoya C, O'Cleirigh C, Biello K, Pinkston M, Stein M, et al. Cognitive behavioural therapy for adherence and depression in patients with HIV: a three-arm randomised controlled trial. The Lancet HIV 2016 Nov;3(11):e529-e538 [FREE Full text] [doi: 10.1016/s2352-3018(16)30053-4]
37. Huffman J, Feig EH, Millstein RA, Freedman M, Healy BC, Chung WJ, et al. Usefulness of a positive psychology-motivational interviewing intervention to promote positive affect and physical activity after an acute coronary syndrome. Am J Cardiol 2019 Jun 15;123(12):1906-1914 [FREE Full text] [doi: 10.1016/j.amjcard.2019.03.023] [Medline: 30979409]
38. Huffman JC, Golden J, Massey CN, Feig EH, Chung W, Millstein RA, et al. A positive psychology–motivational interviewing intervention to promote positive affect and physical activity in type 2 diabetes: the BEHOLD-8 controlled clinical trial. Psychosom Med 2020 Jul 14;82(7):641-649 [FREE Full text] [doi: 10.1097/psy.0000000000000840]
39. Celano CM, Freedman ME, Harnedy LE, Park ER, Januzzi JL, Healy BC, et al. Feasibility and preliminary efficacy of a positive psychology-based intervention to promote health behaviors in heart failure: The REACH for Health study. J Psychosom Res 2020 Dec;139:110285 [FREE Full text] [doi: 10.1016/j.jpsychores.2020.110285] [Medline: 33160091]
40. Czajkowski S, Powell LH, Adler N, Naar-King S, Reynolds KD, Hunter CM, et al. From ideas to efficacy: the ORBIT model for developing behavioral treatments for chronic diseases. Health Psychol 2015 Oct;34(10):971-982 [FREE Full text] [doi: 10.1037/hea0000161] [Medline: 25642841]

41. Callahan C, Unverzagt FW, Hui SL, Perkins AJ, Hendrie HC. Six-item screener to identify cognitive impairment among potential subjects for clinical research. Med Care 2002 Sep;40(9):771-781 [FREE Full text] [doi: 10.1097/00005650-200209000-00007] [Medline: 12218768]
42. Lee P, Macfarlane DJ, Lam TH, Stewart SM. Validity of the International Physical Activity Questionnaire Short Form (IPAQ-SF): a systematic review. Int J Behav Nutr Phys Act 2011 Oct 21;8:115 [FREE Full text] [doi: 10.1186/1479-5868-8-115] [Medline: 22018588]
43. Enright P. The six-minute walk test. Respir Care 2003 Aug;48(8):783-785 [FREE Full text] [Medline: 12890299]
44. Copeland J, Esliger DW. Accelerometer assessment of physical activity in active, healthy older adults. J Aging Phys Act 2009 Jan;17(1):17-30 [FREE Full text] [doi: 10.1123/japa.17.1.17] [Medline: 19299836]
45. Cain K, Geremia C. University California San Diego; San Diego State University. 2012. URL: http://www.ipenproject.org/documents/methods_docs/Accelerometer_Data_Collection_and_Scoring_Manual_Updated_June2012.pdf [accessed 2022-09-29]
46. Keadle S, Shiroma EJ, Freedson PS, Lee IM. Impact of accelerometer data processing decisions on the sample size, wear time and physical activity level of a large cohort study. BMC Public Health 2014 Nov 24;14:1210 [FREE Full text] [doi: 10.1186/1471-2458-14-1210] [Medline: 25421941]
47. Resnick B, Jenkins LS. Testing the reliability and validity of the self-efficacy for exercise scale. Nurs Res 2000;49(3):154-159 [FREE Full text] [doi: 10.1097/00006199-200005000-00007] [Medline: 10882320]
48. Anderson D, Cychosz CM. Development of an exercise identity scale. Percept Mot Skills 1994 Jun;78(3 Pt 1):747-751 [FREE Full text] [doi: 10.2466/pms.1994.78.3.747] [Medline: 8084685]
49. Kendzierski D, DeCarlo KJ. Physical activity enjoyment scale: two validation studies. J Sport Exerc Psychol 1991;13(1):50-64. [doi: 10.1123/jsep.13.1.50]
50. Barriers to being active quiz. 1999. URL: https://www.cdc.gov/diabetes/ndep/pdfs/8-road-to-health-barriers-quiz-508.pdf [accessed 2022-09-29]
51. Watson D, Clark L, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 1988;54(6):1063-1070 [FREE Full text] [doi: 10.1037/0022-3514.54.6.1063]
52. Scheier M, Carver C, Bridges M. Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the Life Orientation Test. J Pers Soc Psychol 1994;67(6):1063-1078 [FREE Full text] [doi: 10.1037/0022-3514.67.6.1063]
53. Bjelland I, Dahl A, Haug T, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. J Psychosom Res 2002 Feb;52(2):69-77 [FREE Full text] [doi: 10.1016/s0022-3999(01)00296-3]
54. Pearl R, Puhl RM. Measuring internalized weight attitudes across body weight categories: validation of the modified weight bias internalization scale. Body Image 2014 Jan;11(1):89-92 [FREE Full text] [doi: 10.1016/j.bodyim.2013.09.005] [Medline: 24100004]
55. Sherer M, Maddux J, Mercandante B, Prentice-Dunn S, Jacobs B, Rogers R. The Self-Efficacy Scale: construction and validation. Psychol Rep 2016 Aug 31;51(2):663-671 [FREE Full text] [doi: 10.2466/pr0.1982.51.2.663]
56. Welch G, Wesolowski C, Piepul B, Kuhn J, Romanelli J, Garb J. Physical activity predicts weight loss following gastric bypass surgery: findings from a support group survey. Obes Surg 2008 May;18(5):517-524 [FREE Full text] [doi: 10.1007/s11695-007-9269-x] [Medline: 18365295]
57. Ware J, QualityMetric Incorporated, New England Medical Center Hospital. How to score version 2 of the SF-12 health survey (with a supplement documenting version 1). WorldCat. 2005. URL: https://www.worldcat.org/title/how-to-score-version-2-of-the-sf-12-health-survey-with-a-supplement-documenting-version-1/oclc/60577051 [accessed 2022-09-29]
58. Bradley L, Forman EM, Kerrigan SG, Butryn ML, Herbert JD, Sarwer DB. A pilot study of an acceptance-based behavioral intervention for weight regain after bariatric surgery. Obes Surg 2016 Oct;26(10):2433-2441 [FREE Full text] [doi: 10.1007/s11695-016-2125-0] [Medline: 26964997]
59. Jennings N, Boyle M, Mahawar K, Balupuri S, Small P. The relationship of distance from the surgical centre on attendance and weight loss after laparoscopic gastric bypass surgery in the United Kingdom. Clin Obes 2013 Dec;3(6):180-184 [FREE Full text] [doi: 10.1111/cob.12031] [Medline: 25586734]
60. Kalarchian M, Marcus MD, Courcoulas AP, Cheng Y, Levine MD, Josbeno D. Optimizing long-term weight control after bariatric surgery: a pilot study. Surg Obes Relat Dis 2012;8(6):710-715 [FREE Full text] [doi: 10.1016/j.soard.2011.04.231] [Medline: 21719357]
61. Sarwer D, Moore RH, Spitzer JC, Wadden TA, Raper SE, Williams NN. A pilot study investigating the efficacy of postoperative dietary counseling to improve outcomes after bariatric surgery. Surg Obes Relat Dis 2012;8(5):561-568 [FREE Full text] [doi: 10.1016/j.soard.2012.02.010] [Medline: 22551576]
62. Johns D, Hartmann-Boyce J, Jebb SA, Aveyard P, Behavioural Weight Management Review Group. Diet or exercise interventions vs combined behavioral weight management programs: a systematic review and meta-analysis of direct comparisons. J Acad Nutr Diet 2014 Oct;114(10):1557-1568 [FREE Full text] [doi: 10.1016/j.jand.2014.07.005] [Medline: 25257365]

63. Homan K, Tylka TL. Appearance-based exercise motivation moderates the relationship between exercise frequency and positive body image. Body Image 2014 Mar;11(2):101-108 [FREE Full text] [doi: 10.1016/j.bodyim.2014.01.003] [Medline: 24529336]

Abbreviations

GOALS: Gaining Optimism After weight Loss Surgery
MVPA: moderate to vigorous physical activity
ORBIT: Obesity-Related Behavioral Intervention Trials
PP-MI: positive psychology–motivational interviewing
RCT: randomized controlled trial

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Protocol

Providing Accessible ReCreation Outdoors–User-Driven Research on Standards: Protocol for Mobile and Web-Based Interviews for Winter Assessments

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Abstract

Background: Although there have been recent efforts to improve access to Canadian national parks, many remain not fully accessible to people with disabilities. Winter conditions, in particular, present challenges that limit their participation in outdoor activities.

Objective: This study aimed to develop a novel method to assess park access during winter, which will inform recommendations for national park standards to meet the needs of all park visitors (regardless of ability) during winter conditions.

Methods: A larger participatory mixed methods research project exploring park access was adapted. A 3-phase approach has already been proposed to achieve the study objectives. In the first phase, a scoping review of the existing accessibility standards will be conducted. In the second phase, objective audits of trails and features in 6 parks, 3 in western Canada and 3 in eastern Canada, will be conducted, as well as mobile interviews with 24 various participants in each region regarding their experiences of and recommendations for improving the park's accessibility. In the final phase, a Delphi participatory consensus development process will be used, based on the data gathered in the first 2 phases, to prioritize recommendations for standards. This paper will focus on the second phase of the study, specifically on whether the in-person winter mobile interviews (ie, walking and wheeling interviews) with people who have a wide range of disabilities while visiting 3 parks in 2 provinces were modified. Changes were made to accommodate the extreme winter weather conditions in Quebec while using safe and informative data collection methods.

Results: In Quebec, one park, where winter conditions are safer, has been assessed in person (n=4). Web-based interviews were used to facilitate the assessment of other winter and summer conditions in two other parks (n=8). Winter and web-based interviews were completed in April 2022. Data are currently being collected and analyzed, and results will be completed by December 2022.

Conclusions: We expect that adapting the protocol to gather further information on winter conditions and access to parks will provide high-quality and rich data to better inform park access standards. This participatory mixed methods research will inform the development of park standards that consider the accessibility needs of all people.

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KEYWORDS

parks; accessibility; standards; user-oriented research; winter; disability; access; participatory; national parks; barriers; participation; Canada; national park; participation; outdoor; activity; standard; interview; safe; virtual; summer; data; mix-method; development

Introduction

Background

The purpose of this study is to inform accessibility standards in Canadian national parks. Such technical standards do not exist. The protocol, which was previously published [1], reported a participatory approach that will be used with people with disabilities in British Columbia (BC) and Quebec, Canada. A 3-phase approach has already been proposed to achieve the study objectives. In the first phase, a scoping review of the existing accessibility standards will be conducted. In the second phase, objective audits of trails and features in 6 parks, 3 in western Canada and 3 in eastern Canada, will be conducted, as well as mobile interviews with 24 various participants in each region regarding their experiences of and recommendations for improving the park's accessibility. In the final phase, a Delphi participatory consensus development process will be used, based on the data gathered in the first 2 phases, to prioritize recommendations for standards.

This paper describes the modifications made to address specific challenges related to extreme winter conditions that were experienced at the beginning of the study and, thus, the second phase of the study.

Winter conditions can present serious obstacles for individuals living with a wide range of disabilities (snow and ice made walking dangerous, tires and casters becoming stuck in the snow, difficulty ascending inclines or ramps, and cold hands while using controls or pushing rims, frozen batteries, seat cushions or backrests, or electronics) [2-6]. Having initiated our research activities, we have identified some challenges in carrying out interviews with certain disability groups during winter weather conditions. For example, in discussions with walker and cane users, we learned that the distances and unsafe trail conditions during winter were key barriers to completing the in-person mobile interviews as originally proposed. Thus, our data collection will be incomplete if we rely solely on in-person interviews at the park. We found that even moderate to easy park conditions can be too challenging for some participants, in all weather conditions. As a result, the distances participants can travel limits the number of features they are able to assess and provide feedback on. This is intensified in cold winter conditions where the health risks to participants and the reduction in distances they are able to travel will significantly reduce the breadth and depth of data we are able to collect.

Objectives

The overall goals of the main study remain the following: (1) to identify park accessibility standards that exist internationally, (2) to identify the accessibility challenges that people with disabilities face in park environments, and (3) to prioritize and recommend accessibility standards for national parks.

The specific objective of this paper is to describe the modified protocol that will be used to inform park standards in summer and winter conditions in Quebec. These protocol modifications will only be made in Quebec, where winter conditions pose more difficult or dangerous experimental conditions, including the transportation risks owing to driving to the mountain parks at this time of the year.

Advisory committees were created in both provinces (Quebec and BC), including individuals with a variety of disabilities (one in each province) to ensure the consideration of inputs or concerns of these individuals in the research project through a participatory research approach. These committees include individuals with mobility, visual, and hearing disabilities; intellectual disabilities; autism spectrum disorder; dementia; and Alzheimer disease. Quebec's committee was specifically solicited to validate the proposed modifications to the protocol described in this paper.

Methods

Overview

Modifications have been made to the second phase of the project that involves in-person mobile interviews. The proposed mobile interview protocol was previously published [1]. Interviews will take place in the park assigned to the participants. The interviews will be administered by trained researchers. The mobile interview will take approximately 2 hours along 3 predetermined routes of 500-1300–m length during both summer and winter.

In Quebec, 2 of 3 parks will be evaluated through web-based interviews in winter (n=8 participants). One park, located in an urban location with nearby amenities, will be evaluated using the initial in-person mobile interview protocol format (n=4 participants), as participant safety can be assured.

Web-based interviews facilitate the collection of feedback on features that were planned and, beyond this, by including footage of park elements that are not in the parks, which we selected to be assessed in person. This approach will allow us to collect data when we otherwise might not be able to because most mobility-aid users will be unable to get to or use the trails in winter.

Web-based interviews will also be used to explore access issues in summer conditions with participants who will take part in web-based interviews to allow for comparison. This will ensure comparable results, help inform national standards more effectively, retain methodological consistency, and enable us to gather data from people who would not be able to participate in our original protocol. These adaptations are an example of the participatory nature of the study where the concerns of participants were considered to refine the mechanisms for data collection.

Mobile Versus Web-Based Interviews

In Fall 2021, the weather became very cold with snow accumulation in Quebec. Four in-person mobile interviews were conducted as originally planned, at which time we observed that participants provided fewer details when answering questions during the in-person winter mobile interviews because they felt uncomfortable (eg, too cold). To address this challenge, we attempted to reduce burden on participants by focusing on questions about features that were altered owing to weather.

The data collection plan retains the preinterview survey from the original protocol and adapts the in-person mobile interview to take into consideration participant burden [1]. Participants who take part in the in-person winter mobile interviews will also complete a summer in-person mobile interview. This strategy will allow us to collect rich data in both winter and summer conditions, while ensuring the comfort and safety of the participants. Table 1 presents a summary of each step.

In addition to the in-person mobile interviews, we will perform web-based interviews. Videos and pictures of trails and features that are similar to those found in national parks were collected from parks in the Quebec City region (eg, Parc Jacques Cartier, Forêt Montmorency, and Plaines of Abraham) both in summer and winter as well as web-based images from national parks to depict the breadth of potential activities available in parks across seasons and the potential for accessibility barriers. Web-based summer interviews will be conducted at the same time for methodological consistency by using the same approach as the web-based winter interviews.

The web-based interviews will not be mobile interviews. The aim is not to comment on a trail as we view it in its entirety but rather to show participants various park features in different contexts to obtain as much feedback as possible on them. The videos and pictures will elicit impressions and opinions to complete a semistructured interview. The web-based interviews will be conducted in the participants' home or at the research center depending on participant preference. Participants will review videos and pictures of features and trails on a computer monitor or electronic device. Blind and low-vision individuals will not take part in web-based interviews; the in-person mobile interviews allow them to better experience the environment, which could only be described at great lengths to provide sufficient details to truly inform them. A similar set of questions as those in the in-person interviews will be used in the web-based interviews. This will include items from the Stakeholders' Walkability/Wheelability Audit in Nature (SWAN-PARKS) instrument and open-ended questions to assess trail and feature accessibility and conditions and explore the positive and negative impressions of the experience. Participants will also be asked to provide recommendations for improving the interview experience.

However, way-finding exercises as described in the original protocol, such as estimating distance and slope, pointing to the origin of the route, and sketching maps of the route, which are part of the in-person mobile interviews, will not be conducted during the web-based interviews [1].

Table 1. Summary of steps of in-person mobile interviews from the original protocol and modifications for web-based interviews.

Step and summary	Status of modification
1. Preinterview survey	
Web-based questionnaire (Qualtrics) about sociodemographic characteristics (eg, age and sex), disability and mobility status (eg, diagnoses and assistive aids used), subjective wayfinding skills, preferences for park settings and activities, and transport mode to parks	Unchanged, will be done for web-based interviews in the same manner as the in-person mobile interviews
2. Mobile interviews	
Interviews in the park assigned to the participant [7-9] (administered by trained researchers) along 3 predetermined routes of 500-1300–m length (recorded audio and film)	Unchanged for in-person summer and winter mobile in-person interviews
Map of the intended route of exercise to ask for expectations	In-person summer and winter mobile interviews
Structured questions (presence or absence of features or characteristics): Stakeholders' Walkability/Wheelability Audit in Nature (SWAN-PARKS) tool	Only for in-person summer mobile interviews
Semistructured questions (about their experiences related to way-finding and wayfaring)	In-person summer and winter mobile interviews
3. Postroute interview questions (for each of the 3 routes)	
Objective spatial skills test: orientation and estimation skills. Participants will be positioned at a predefined location and asked to point a compass in the direction of the origin of the route. They will also be asked to estimate the distance and slope to a predefined landmark in the distance [10,11]	Only for in-person summer mobile interviews
Rate the route on a 7-point Likert scale: perceived physical demand, mental demand, safety, enjoyment, and confidence to find their way independently	In-person summer and winter mobile interviews
Recall the route verbally or by drawing the route and all its features onto a route map [12]	Only for in-person summer mobile interviews
Describe the wayfaring and wayfinding experiences overall and provide additional feedback and recommendations	In-person summer and winter mobile interviews. For winter, changes due to seasonality will be noted

Types of Interviews

Participants of the web-based interviews will complete the data evaluations for both summer and winter conditions using the methods described above. As for the in-person mobile interviews, including those conducted during winter, there are no changes to the protocol followed in BC (the second site), and all interviews will be conducted on site. In Quebec, 4 in-person winter mobile interviews will be conducted at Plains of Abraham (the participants are already recruited), where conditions can be mitigated more easily. The remaining 8 will be web-based interviews.

Sample Distribution

The number of people to be interviewed and the distribution of participants by disability or mobility type will remain unchanged; that is, a purposive sample of 48 people (24 at each site) with a broad range of disabilities, who use a variety of mobility devices, will be recruited. To be included, participants will need to be at least 18 years of age, able to travel approximately 3 km with rests over a 2-3–hour period, and able to communicate directly with researchers (verbally) or indirectly through an assistant or attendant. Participants will be recruited through partners and participants from previous studies and selective advertising if necessary.

We intend to recruit 24 participants for summer (3 manual wheelchair users, 3 power wheelchair users, 3 scooter users, 3 people who use walkers, 3 people who use canes or crutches, 2 people who are D/deaf and hard of hearing, 3 people who are blind, and 4 people with cognitive impairments) and 12 for winter interviews at each site.

Participants

Table 2 presents an overview of the participants' distribution in Quebec. Overall, 24 participants will be recruited in Quebec (8 for Plains of Abraham—4 of whom will participate in both the in-person summer and the winter mobile interviews and 4 will participate in only the summer interviews; 4 in-person summer mobile interviews each for Jacques-Cartier National Park and Forêt Montmorency; and 8 web-based interviews that include both summer and winter conditions).

Table 2. Sample distribution (Quebec) according to participants characteristics.

	In-person mobile interview at Plains of Abraham during summer	In-person mobile interview at Plains of Abraham during winter	In-person mobile interview at Jacques-Cartier National Park during summer	In-person mobile interview at Forêt Montmorency during summer	Web-based interview
Wheeled mobility	1 with a scooter, 1 with a power wheelchair (PWC), and 1 with a manual wheelchair (MWC)	1 with a PWC and 1 with an MWC	1 with a scooter and 1 with a PWC	1 with a PWC	1 with a scooter and 2 with MWCs
Walkers, canes, or crutches	1 with a walker and 1 with a cane	None	None	1 with a cane	2 with walkers and 1 with a cane
Visual disability	1	1	1	1	None
Hearing disability	1	None	None	1	None
Cognitive disability	1	1	1	None	2
Total	8	4 of the 8	4	4	8
Total during summer (n=24)	8	None	4	4	8
Total during winter (n=12)	None	4	None	None	8

Data Analysis: Descriptive Analysis

Transcripts generated from the in-person mobile and web-based interviews will document what was being said or observed and by whom. Pertinent quotes will be coded to reflect the feature or experience being explained (way-finding or wayfaring) by the participant and any observation made by the researchers [1].

For in-person mobile interviews, the quotes and their codes will be digitized in the geographical information system (GIS) at the location that it occurred. This will be linked to the participant survey responses through their ID as a separate file in the GIS (delimited file without spatial information) [1].

For the web-based interviews, as for the in-person mobile interviews, a mixed methods coding process will be used. We identified a list of codes in accordance with the content of the web-based interview guides, and we will adjust the codes in accordance with the emerging data [13]. According to Linneberg and Korsgaard [14], "As the research process develops, so does the type of coding, which also allows the researcher to move from basic descriptive codes toward answering the research question posed." Web-based interviews will not be analyzed using the spatial transcript method as described in the original protocol because the activity will not occur in the parks; therefore, there will be no geospatial contextual information available.

Ethical Considerations

The study was approved by Behaviour Research Ethics Boards at the Centre intégré universitaire de santé et de services sociaux de la Capitale-Nationale (Project #2021-2120) and the Research Ethics Board at the University of British Columbia (H20-04036). Approval was also obtained from the regional health authorities at each site. All study participants will provide informed consent. Evaluation in parks started in August 2021, and web-based interviews started in March 2022.

Results

Funding for this study was obtained from Accessibility Standards Canada. Using the web-based interviews along with the already proposed in-person mobile interviews allows us to examine features that participants would not be able to comment on because of topography or weather conditions. The results support the development of a spatial transcript and thematic analysis that helps decipher patterns of park experiences between participants across diverse variables such as gender, mobility device use, way-finding abilities, and season. A grounded visualization approach will be used to examine the qualitative and quantitative data derived from the in-person and web-based methods. This involves an iterative analysis of the results, including topographical data derived from open data and the environmental audit such as slope, cross slope, and trail surface conditions to gain a better understanding of the park experience [15,16]. This approach provides a thick, spatially contextualized description of the interactions and perceptions that people with disabilities have with the natural environment and provides the funding agency with more information for the identification of accessibility standards in a park context. Data collection, analysis, and results will be completed by the end of 2022.

Discussion

Principal Findings

The purpose of the original protocol previously published [1] was to describe the methodology for informing park accessibility standards. The modified approach proposed in this paper will facilitate data collection on park access for people with diverse disabilities during winter months, as well as the rest of the year, while reducing discomfort and risk. Not everyone has the ability or the capacity to use park installations as they are currently built, regardless of weather conditions. Additionally, cold temperatures, snow accumulation, and icy roads and trails make

it difficult to move around parks. As a result, the area that can be assessed in the park would be reduced, and this would limit our ability to collect data. This will also allow us to obtain feedback about features and activities that people with disabilities have never been able to participate in because of accessibility issues. This would assist with site planning (placement of features), which is a significant concern of the Accessibility Standards Canada's Outdoors Accessibility Committee that is currently developing standards (which author MP is a member).

In addition to allowing us to obtain feedback about more features in the park, web-based interviews may make recruitment more successful. Many of the challenges that limit mobility also affect decisions regarding study participation. Conducting interviews in participants' homes or at the laboratory will reduce travel demands on participants and mitigate the impact of being outdoors for several hours during the in-person mobile interview.

To our knowledge, this is the first study to leverage a web-based interface for collecting data about outdoor environments with people with disabilities. The potential impacts generated by the modification of the original protocol include the possibility of exploring more barriers and access issues in a wider range of parks and conditions. Most people with disabilities avoid going out in the winter but would still like to be active [4,17]. They might not be aware of the potential opportunities that exist. Using the web-based method allows us to explore these features and better inform accessibility standards. Without the web-based method, this exploration would not be possible.

Limitations

This project targets national parks. It is hoped that the obtained finding could also be useful in the design of community parks, but these kinds of parks were not specifically targeted in this project. The limitations of this approach are a modest reduction of insights on the real-world experiences of people with disabilities travelling along winter trails and limited feedback about wayfinding requirements. However, these changes are proposed to maximize participant safety, while no adapted equipment is available on site. These limitations are mitigated by the fact that we will complete these activities in the winter in 1 park in Quebec and all 3 parks in BC.

Conclusions

People with disabilities' valuable insights on winter conditions and parks will inform accessibility standards to be used in national parks and beyond. Accessibility in winter conditions can be very difficult to attain and very difficult to assess in real-life situations for certain groups. This also applies to certain individuals in summer conditions. By gathering individuals with disabilities' opinions using a variety of methods that allow individuals to participate in the discussion regarding park access during all seasons while respecting their capacities can provide a solid basis on which to better plan park design to overcome obstacles during all seasons.

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Conflicts of Interest

None declared.

References

1. Prescott M, Routhier F, Labbé D, Grandisson M, Mahmood A, Morales E, et al. Providing Accessible Recreation Outdoors-User-Driven Research on Standards (PARCOURS): Protocol for a multiphase study. JMIR Res Protoc 2022 Mar 31;11(3):e33611 [FREE Full text] [doi: 10.2196/33611] [Medline: 35357324]
2. Montgomery RE, Li Y, Dutta T, Holliday PJ, Fernie GR. Quantifying mobility scooter performance in winter environments. Arch Phys Med Rehabil 2021 Oct;102(10):1902-1909 [FREE Full text] [doi: 10.1016/j.apmr.2021.06.005] [Medline: 34237307]
3. Morales E, Lindsay S, Edwards G, Howell L, Vincent C, Yantzi N, et al. Addressing challenges for youths with mobility devices in winter conditions. Disabil Rehabil 2018 Jan;40(1):21-27. [doi: 10.1080/09638288.2016.1239768] [Medline: 27927034]
4. Li Y, Hsu JA, Fernie G. Aging and the use of pedestrian facilities in winter-the need for improved design and better technology. J Urban Health 2013 Aug 28;90(4):602-617 [FREE Full text] [doi: 10.1007/s11524-012-9779-2] [Medline: 23188551]
5. Ripat JD, Brown CL, Ethans KD. Barriers to wheelchair use in the winter. Arch Phys Med Rehabil 2015 Jun;96(6):1117-1122. [doi: 10.1016/j.apmr.2015.01.020] [Medline: 25666785]
6. Morales E, Gamache S, Edwards G. Winter: public enemy #1 for accessibility EXPLORING NEW SOLUTIONS. J Access Des All 2014;4(1):52. [doi: 10.17411/jacces.v4i1.57]
7. Parent L. The wheeling interview: mobile methods and disability. Mobilities 2016 Oct 31;11(4):521-532. [doi: 10.1080/17450101.2016.1211820]

8. Evans J, Jones P. The walking interview: methodology, mobility and place. Applied Geography 2011 Apr;31(2):849-858. [doi: 10.1016/j.apgeog.2010.09.005]
9. Wästerfors D. Required to be creative. Everyday ways for dealing with inaccessibility. Disabil Soc 2020 Feb 04;36(2):265-285. [doi: 10.1080/09687599.2020.1720610]
10. Fajen B, Phillips F. Spatial Perception and Action. In: Waller D, Nadel L, editors. Handbook of Spatial Cognition. Washington, DC: American Psychological Association; 2013:67-80.
11. Hochmair H, Frank A. Influence of estimation errors on wayfinding-decisions in unknown street networks – analyzing the least-angle strategy. Spat Cogn Comput 2000;2(4):313. [doi: 10.1023/A:1015566423907]
12. Boschmann EE, Cubbon E. Sketch maps and qualitative GIS: using cartographies of individual spatial narratives in geographic research. The Professional Geographer 2013 Apr 19;66(2):236-248. [doi: 10.1080/00330124.2013.781490]
13. Elliott V. Thinking about the Coding Process in Qualitative Data Analysis. TQR 2018 Nov 24. [doi: 10.46743/2160-3715/2018.3560]
14. Skjott Linneberg M, Korsgaard S. Coding qualitative data: a synthesis guiding the novice. QRJ 2019 Jul 24;19(3):259-270. [doi: 10.1108/qrj-12-2018-0012]
15. Jones P, Evans J. The spatial transcript: analysing mobilities through qualitative GIS. Area 2012;44:92-99 [FREE Full text] [doi: 10.1111/j.1475-4762.2011.01058.x]
16. Knigge L, Cope M. Grounded visualization: integrating the analysis of qualitative and quantitative data through grounded theory and visualization. Environ Plan A 2016 Jul 24;38(11):2021-2037. [doi: 10.1068/a37327]
17. Ripat J, Sibley KM, Giesbrecht E, Curtis B, Touchette A, Borisoff J, et al. Winter mobility and community participation among people who use mobility devices: a scoping review. Arch Rehabil Res Clin Transl 2020 Mar;2(1):100018 [FREE Full text] [doi: 10.1016/j.arrct.2019.100018] [Medline: 33543060]

Abbreviations

BC: British Columbia
GIS: geographical information system
SWAN-PARKS: Stakeholders' Walkability/Wheelability Audit in Nature

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Protocol

The PharmNet Harm Reduction Intervention for Community Pharmacies: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: The overdose epidemic in the United States has continued to worsen despite substantial efforts to mitigate its harms. The opioid antagonist naloxone has been identified as a key means of reducing the prevalence of fatal overdoses. An important evidence-based approach to optimizing naloxone's impact is to seed it throughout the community, because bystanders are often able to reverse overdoses more quickly than first responders and sometimes are the only possible means of overdose reversal. As part of a multipronged approach to distributing naloxone nationwide, community pharmacies have been identified as ideal venues for naloxone dispensing, especially under standing orders. However, dispensing rates remain surprisingly low, and there is a need to understand how best to engage community pharmacies in naloxone-based harm reduction services.

Objective: The objective of this trial is to determine whether a tailored, pragmatic pharmacy intervention (PharmNet) results in greater naloxone dispensing relative to baseline (the prior 3 months) compared to a control condition. This pilot trial is intended to determine whether it is appropriate to invest the substantial resources that would be required to conduct a full-scale, randomized controlled study of PharmNet.

Methods: We will conduct a 3-month randomized controlled pilot trial consisting of 2 parallel groups with a 4:3 allocation ratio. A group of 7 independent pharmacies from rural areas in Indiana will be randomly assigned to either the PharmNet intervention arm (n=4) or the control arm (n=3). The primary outcome will be overall naloxone dispensing (both at cost and free), and secondary outcomes will include the distribution of referral cards and multiple variables at the level of individual staff members. Dispensing data will be collected for the 3 months prior to the intervention and the 3 months of the intervention, and all other data will be collected using a pretest-posttest design. The primary analysis will be a generalized linear mixed model with a Poisson distribution with fixed effects for group, time, and their interaction and a random effect for pharmacy ID to account for repeated measures within pharmacies.

Results: This study was approved by the Indiana University institutional review board in 2 phases (August 2, 2021, and April 26, 2022) and was funded by the Indiana University Grand Challenge: Responding to the Addictions Crisis.

Conclusions: If this study produces evidence that the PharmNet intervention results in increased naloxone dispensing relative to control pharmacies, it will be both appropriate and important to study it in a large, full-scale randomized controlled trial.

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KEYWORDS

naloxone; opioid; overdose; pharmacy; randomized controlled trial; RCT; opioid use; digital health intervention; community health; drug use; prevention; PharmNet; health resources; health outcome

Introduction

Overdose Deaths in the United States

The prevalence of overdose deaths in the United States has continued to increase in recent years, eclipsing 100,000 such deaths (year over year) for the first time in June 2021 [1]. The majority of such deaths involve opioids; more specifically, in the current wave of the overdose epidemic, they involve heroin, fentanyl, and its analogues—the latter 2 of which are often introduced as adulterants in other substances (eg, stimulants) [1,2]. Largely related to such deaths, the United States renewed a declaration of an opioid public health emergency in April 2022 [3]. In the state of Indiana, where the proposed study will take place, provisional data indicated 2554 fatal drug overdoses in 2021, of which more than 78% involved opioids [4].

Naloxone, an opioid antagonist, has become a key component of the US response to the crisis [5], as it can reverse the effects of an overdose and prevent death [6,7]. However, the effectiveness of naloxone depends on the time it is administered relative to the time of the overdose. Deaths from heroin overdose can occur relatively quickly [8], and even when they do not, they typically happen within 1 to 3 hours of overdose [9]. Deaths from fentanyl overdose may occur even more rapidly [10], potentially due to differences in pharmacology between fentanyl and other opioids [11,12]. Unfortunately, individuals who witness an overdose may be hesitant to contact first responders [13,14], and even when they do, there is still variable lag time between the call for assistance and the arrival of assistance due to a variety of factors (eg, distance from the dispatch site to the overdose location). In some cases involving fentanyl, death may occur before first responders arrive [10]. Thus, there is an ongoing need to better ensure that naloxone is readily available to prevent overdose deaths.

In 2018, the US Surgeon General recommended that all people in the United States be prepared by having naloxone on hand to help in case of an overdose [15]. That recommendation followed, and has been followed by, evidence that overdose education and layperson and/or bystander administration of naloxone are safe and effective approaches to reducing the likelihood of opioid overdose fatality [16-19]. Similar to many states, Indiana has adopted laws to facilitate community overdose reduction using naloxone [20], including "good Samaritan" laws [21]. Although the means by which people obtain naloxone and other information related to harm reduction remain diverse, our focus in this proposed study is on community pharmacies.

Role of Community Pharmacies in Harm Reduction

Community pharmacies are well positioned to provide harm reduction services to all community members, along with more targeted services to individuals at risk of overdose. Almost 9 in 10 Americans live within 5 miles of a community pharmacy [22], meaning pharmacists are among the most accessible health care professionals [23]. Among some populations (eg, Medicare beneficiaries), it has been shown that pharmacists interact with patients more often than their primary care physicians [24].

In addition to their accessibility, pharmacies increasingly are perceived as effective venues for both clinical and nonclinical harm reduction owing to pharmacists' expertise in fields such as medication management and pharmaceutical education [25,26]. A study of Arizona pharmacists found that even when uncomfortable with most forms of harm reduction, pharmacists were generally comfortable with dispensing naloxone [27]. In Indiana, qualitative data from managing pharmacists found conceptual support for harm reduction but, simultaneously, concerns about systemic barriers to implementation, including a lack of time for interventions as well as concerns about role clarity and patients' expectations of what should happen in a pharmacy [28]. Similar patterns of support and concern were raised in a more recent study of key informants (including pharmacists) in Connecticut, Kentucky, and Wisconsin, reflecting willingness to discuss naloxone with patients but barriers related to role clarity as well as the financial cost of naloxone [29].

Thus, despite comfort and willingness to support harm reduction and treatment, as well as faciliatory state laws (eg, standing orders permitting naloxone dispensing without a patient-specific prescription), a recent systematic review found that naloxone was stocked on average in 62.8% of community pharmacies, with both the likelihood of stocking and willingness to dispense without a prescription significantly lower in independent pharmacies than in chain pharmacies [30]. That finding was echoed by a contemporary analysis of naloxone nasal spray stocking in 11 US states, which reported a similar rate (69.5%) and a significantly lower likelihood of stocking among independent pharmacies [31].

Our Approach to Harm Reduction Intervention in Pharmacy: the Proposed Study

The proposed study will be a pilot randomized controlled assessment of the effectiveness of PharmNet, a harm reduction intervention for community pharmacies focused on naloxone distribution, awareness building, and referral. As described in the write-up of our single-site pilot study, "the intention was to study procedures that have as minimal an impact as possible on pharmacy costs and operational functioning while maximally facilitating harm reduction from opioid overdose—in other words, to find an optimal intersection point of those concerns" [32]. In brief, the intervention includes [32]:

- Building awareness of naloxone availability at the site among patients (eg, the use of yard signs and scrolling messages on television screens);
- Supporting awareness among pharmacists and pharmacy technicians about proactively offering naloxone (eg, customized post-it notes);

- Facilitating service provision by conducting a priori negotiations and establishing written agreements with local nonprofits to facilitate a pipeline of no-cost naloxone for the pharmacy;
- Emphasizing bidirectional naloxone provision (eg, pharmacist- and pharmacy technician–initiated offers in addition to patient-initiated requests); and
- Facilitating referral by providing a physical, durable, and curated list of community resources that can be used by pharmacists, handed to patients, and placed into pharmaceutical bags.

Our previous single-site pilot study found that during the intervention, compared to the mean of the 3 months of practice prior to the intervention, the monthly rate of naloxone sold had a relative increase of 34.4% (+3.33 doses/month), and the overall naloxone dispensing rate through *any* mechanism (eg, including newly added no-cost dispensing) increased 96.48% (+9.33 doses/month) [32].

Although the intervention is conceptually simple, the decisions made in its development involved highly intentional design. Changes to the program were rooted in the Consolidated Framework for Implementation Research because it allows for considerations to be addressed within complex settings, such as pharmacies [33]. The PharmNet team conducted numerous information gathering, feasibility, and methodological studies in preparation for the single-site pilot to obtain increasingly specific information and context, including both quantitative and qualitative work. Much of this work was conducted in conjunction with academic and community-based pharmacists and involved data collection from hundreds of managing pharmacists in 2 states [27,28,34-42]. The single-site pilot itself was informed by independent community pharmacists at a more granular level to maximize likely acceptability and feasibility [32].

Study Objectives and Hypotheses

Our study will be designed to facilitate an improved understanding of whether it is reasonable to believe that the PharmNet intervention causes increased dispensing of naloxone by randomizing independent pharmacies that are part of the same small pharmacy chain to either (1) the PharmNet intervention or (2) operations as usual (control). It will also explore multiple secondary outcomes and questions.

- Hypothesis 1: Monthly naloxone dispensing (combined sales and no-cost distribution) will be significantly increased in the pharmacies implementing PharmNet compared to those in the control arm.
- Other preregistered analyses: This study will observe the volume of PharmNet referral cards distributed by the intervention sites. It will also collect several measures from staff members (pharmacists and technicians) to provide a broader understanding of the intervention, such as staff members' comfort with multiple harm reduction practices, stigmatizing beliefs about people who use drugs, and perceptions of intervention acceptability.

Methods

Ethics Approval

This study will comply with all ethical regulations as outlined and approved by the Indiana University institutional review board (IRB; 12339 and 13956). The pharmacy employee data collection for this study was approved with a designation of "exempt" from the Indiana University IRB (13956).

Consent to Participate

Pharmacy employees who choose to participate in the staff-specific components of the study will complete an electronic consent form prior to providing any data. The completion of the pretest survey will be compensated by a US $5 digital gift card, and the completion of the posttest survey will be remunerated by a US $10 digital gift card. All other components of PharmNet have been deemed an organizational level research project and received a not human subjects research designation from the Indiana University IRB (12339). Participating pharmacy sites will each be paid US $1000 following the successful completion of this pilot study based on estimated cost data provided to author JA by the parent organization following the single-site pilot study.

Confidentiality

Pharmacy employees' responses will be linked to their provided email addresses in a survey platform (QualtricsXM) that is approved by Indiana University for "critical data," the highest security designation. Survey responses will not be shared outside of the research team, and data will only be reported and analyzed in aggregate.

No other identifiable data will be obtained by the research team (eg, naloxone-dispensing data will be obtained only in aggregate for the prespecified time periods).

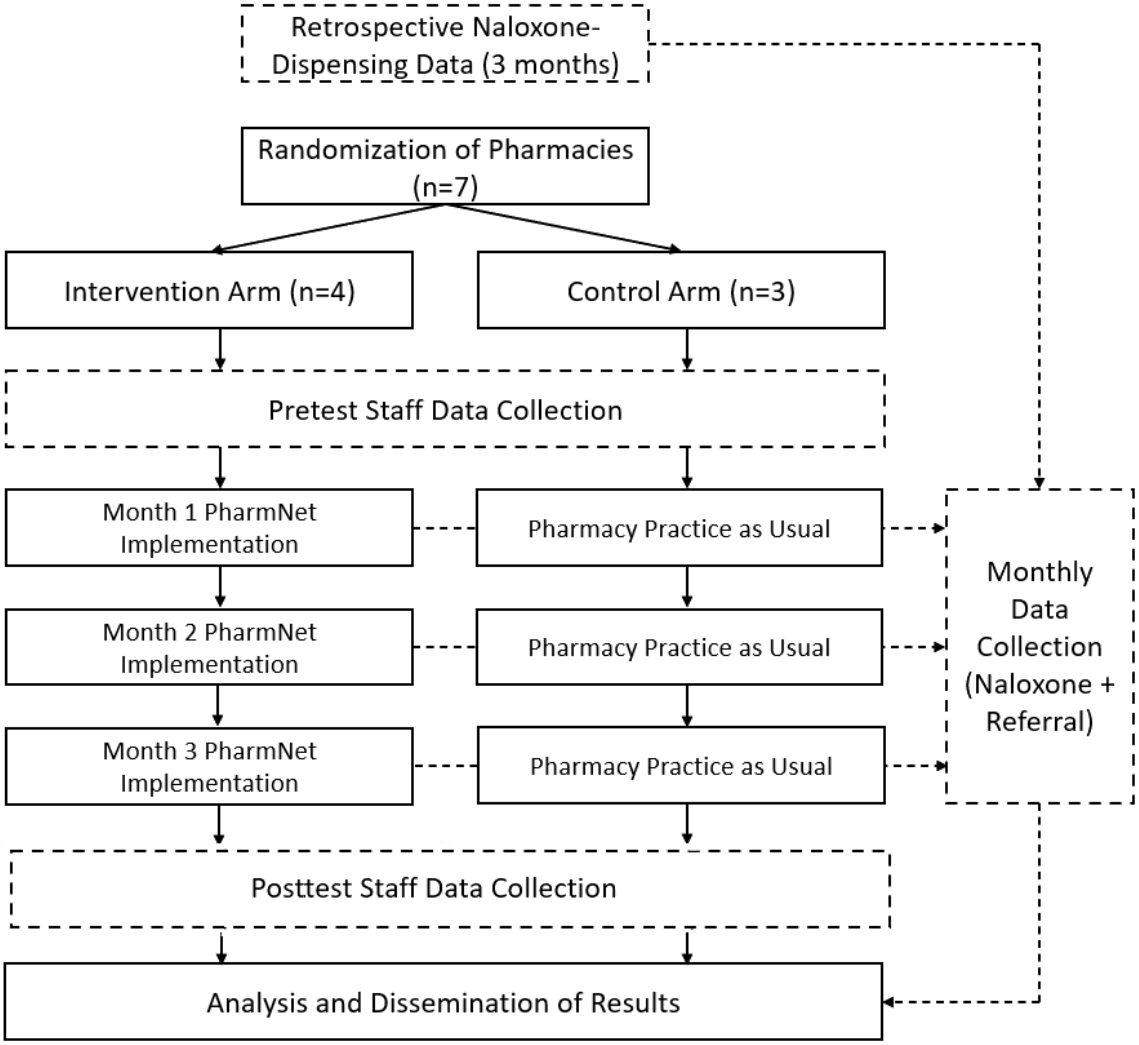
Design

Trial Design

The PharmNet pilot trial will be a cluster randomized trial consisting of 2 parallel groups and a 4:3 allocation ratio of intervention to control. The independent pharmacy organization participating in the project consists of 8 pharmacies, of which 1 was the pilot and feasibility test site [32]. The remaining 7 pharmacies will be allocated using a web-based random sequence generator (conducted by author LAE), such that 4 pharmacies will be selected to implement PharmNet, and 3 pharmacies will serve as controls (pharmacy practice as normal). The workflow for the study is provided in Figure 1.

This study will utilize partial blinding; the research team and the pharmacy manager (who supervises all 7 pharmacies, see description in our prior paper [32]) will not be blinded to assignment because it would not be possible to do so, but individual pharmacists, pharmacy technicians, and others working in the control arms will not be aware that their pharmacies are serving as controls.

Figure 1. Project flow diagram.



Participants and Procedures

This study will be conducted with an Indiana family-owned independent pharmacy system consisting of 8 pharmacies. The organization has been operational for over 120 years and predominantly operates in rural communities. Its pharmacies offer a variety of services including infusions, durable medical equipment, medication delivery, and cost containment. This organization reports continually seeking ways to expand its services to meet community needs.

The pharmacy manager has already agreed in principle that the organization sites will participate in this pilot cluster randomized trial. Data collected at the site level will be obtained from these entities, which are the only eligible pharmacies (n=7). Within each pharmacy, all pharmacists and pharmacy technicians will be asked to complete 2 questionnaires. These individuals will be asked to provide individual-level consent and will not be required to complete the questionnaires.

Data from individual staff members will be collected prior to the intervention (a 2-week window before the start date) and after the intervention (a 2-week window after the end date). Staff members who are hired after the intervention begins will be eligible to take the second survey (posttest) but not the first (pretest). Aggregated data (ie, counts) on naloxone dispensing from the pharmacies will be collected retrospectively (the 3 months prior to the intervention initiation) and then monthly for the 3-month duration of the intervention using the pharmacies' record systems. Data on the distribution of additional items (no-cost naloxone and referral cards) will be obtained through staff member counts of products at predetermined monthly intervals (all items will be numbered to facilitate accuracy).

Intervention Description

The development of this intervention and the decisions made during that process, including the recent changes that were informed by the single-site pilot study, are described in detail in a prior paper [32]. Therefore, we have prepared a structured table (see Table 1) outlining the sequential steps in the intervention and refer readers to our prior paper for additional detail.

Table 1. Intervention components.

Intervention stage	Steps	Other notes
Introduction to study (prior to study start date)	1. Digital video (.mp4) describing the intervention (~5 minutes in length) is distributed to the pharmacy manager. 2. Pharmacy manager disseminates the video. 3. All staff members view the video. 4. Lead pharmacists are asked to include the video in the orientation package for new pharmacists and pharmacy technicians and those who may have missed the initial meeting.	Each pharmacy has a regular, site-specific "all hands" meeting each month. In the pilot and feasibility study, this meeting was identified as the appropriate venue to disseminate intervention information.
Early implementation (prior to study start date)	1. Confirm with the managing pharmacist that all intervention pharmacies have viewed the video at the "all hands" staff meeting. 2. Deliver a set of 30 doses of naloxone (presently, individually packaged Narcan nasal spray) to each pharmacy in numerically marked bags imprinted with "Not for Sale." 3. Deliver a set of 500 consecutively numbered harm reduction referral slips to each pharmacy (customized for each pharmacy location). 4. Deliver sets of reminder post-it notes to pharmacies. 5. Deliver the requested number of yard signs to each pharmacy (based on the number of routes of travel around the pharmacy). 6. Ensure that pharmacy's in-store television has access to the scrolling reminder text.	Digital copies of all of the visual materials described here (3, 4, and 5) are freely available in a prior publication [32].
Launch (on the study start date)	1. Reminder post-its placed in visible areas on the interior of the dispensing location (eg, staff side rather than patient side). 2. Harm reduction referral cards placed at each checkout for easy access. 3. Yard signs placed outside the building in visible locations where traffic (vehicle or foot) is common. 4. Scrolling television banner will be enabled to run continuously through the intervention. "76.7% of overdoses happen at home. Bystanders who witness an overdose can be effective in reducing overdose mortality. Ask us about how you can save a life with naloxone today!"	• Digital copies of all materials for this project are provided as attachments to the single-site pilot study manuscript [32]. • All marketing materials will be standardized, except that the referral and recovery resource information (referral cards) will be specific to each local community.
Implementation (continuous after start)	There are 4 primary procedural events that result in offers of naloxone as well as provision of harm reduction cards. Three are initiated on the pharmacy side and were tailored for this project based on harm reduction management plan recommendations for clinicians from the Centers for Disease Control and Prevention [43]. Those are: 1. Prescription fill for a medication for opioid use disorder; 2. High-dose opioid prescription (50 morphine milligram equivalents or greater); 3. Request for syringes without a prescription, even if syringes are not available at the site. The fourth is initiated on the patient side: 4. Patient request for naloxone. The existence of these guidelines is specifically not intended to preclude offers or dispensing in other situations (eg, pharmacist discretion).	• Naloxone will be dispensed based on the patient's ability to pay, as determined by the pharmacist or pharmacy technician. • Referral cards will be provided at each procedural event regardless of whether naloxone is dispensed. Pharmacy staff may either briefly acknowledge the card ("We wanted to share with you some community resources that may interest you") or not. The cards can be placed inside the prescription bag (they are one-quarter of a standard 8.5 × 11 in page) or handed directly to the patient.
Ongoing supplies (continuous after start)	The pharmacy manager, as well as the lead pharmacist at each site, will be instructed to contact the research team a minimum of 3 business days prior to any intervention component (eg, naloxone, referral cards, and reminder post-its) being exhausted. The research team will then provide additional supplies.	Based on the single-site pilot, the initial materials provided at launch are expected to be sufficient for the project duration.
Fidelity monitoring (~1 month after start)	Approximately 1 month after the intervention's launch, we will conduct a single fidelity site visit to each intervention site. This will include inspection for presence of all materials (eg, yard signs, television messaging, and field observations). Any major concerns will be addressed with the pharmacy manager.	Since our orientation to this project is pragmatic, we do not plan to engage in extensive fidelity monitoring, as this would not be available in a real-world implementation of the program [44].

An essential component of the PharmNet intervention is that pharmacies have naloxone on hand that they can dispense at no cost to patients who cannot afford it. Such dispensing accounted for roughly two-thirds of the overall increase in dispensing in our single-site pilot [32]. However, we had identified that the independent pharmacies in this project did not have direct access to free or reduced cost naloxone and often must order it in response to prescriptions. Thus, as part of the intervention, the study team developed memoranda of understanding (MOUs) with (1) one of the largest nonprofit agencies that provides free naloxone to the state of Indiana, (2) a secondary nonprofit as a "backup," and (3) the pharmacy organization. These MOUs were initially designed to serve for the duration of the project and facilitated the structured transfer of naloxone at the needed volume to participating pharmacies at no cost. The MOUs did not reference a specific limit on available doses but indicated the possibility that the nonprofit may, at times, not have free naloxone available to distribute—leading to our engagement of the "backup" organization. Importantly, now that procedures and agreements are in place, the study team will be able to "withdraw" from the MOUs at the end of the study and facilitate similar MOUs directly between the nonprofits and pharmacy organization to continue the supply of naloxone without an intermediary. Facilitating this supply of naloxone to the pharmacy was perceived as critical to the program's success in the single-site pilot [32] and may be important to supporting the sustainability of ongoing programs of this kind.

Sampling Plan: Sample Size Determination and Power Analysis

As noted above, we will conduct this study among 7 independent community pharmacies, with a 4:3 allocation to intervention and control arms. With 80% power (α=.05, 2-tailed), this sample will allow us to detect large effect sizes (Cohen d=2.68). In our single-site pilot study, we observed a large increase in the average number of monthly naloxone doses dispensed (from 9.67 doses/month prior to the intervention to 19 doses/month during the intervention). We further do not expect that the control pharmacies will substantially vary in the number of naloxone doses dispensed over time.

We made the decision to conduct this smaller, pilot randomized controlled trial, because although our single-site pilot study produced a sizeable effect on naloxone dispensing, we could not be certain that it was not attributable in part to unmeasured confounding (eg, external trends in naloxone dispensing). In addition, recruiting and providing materials (especially naloxone) to a large sample of pharmacies represents a substantial cost, and so, prior to investing in a more conservative, fully powered, and pragmatic study, we wanted to obtain additional data. Thus, we plan to report all P values exactly rather than by threshold and undertake a nuanced interpretation of the findings [45], including a visual inspection and presentation of the trends in intervention and control pharmacies, with the purpose of determining whether a large, randomized study appears to be an appropriate and valuable investment.

Since the pharmacy manager has agreed in principle to participation among all 7 individual pharmacies, we do not intend to apply any inclusion or exclusion criteria but note that individual-level data collection will still be subject to exclusion via declining to participate at the point of informed consent.

Analysis Plan

Primary Outcomes

The number of naloxone doses dispensed will be treated as the overall number of doses, which is the sum of those that are (1) sold, as tracked by the pharmacy's record system; and (2) dispensed free of cost, as tracked by sequentially numbered doses stored separately in the pharmacy. This value will be obtained retrospectively for the 3 months prior to the intervention and then monthly for 3 months (the duration of the intervention).

Secondary Outcomes

As noted previously, this study will collect, describe, and in some cases analyze secondary outcomes to facilitate the interpretation of the study findings. These data and analyses will be treated as exploratory.

We will produce a count of the referral cards distributed by each intervention pharmacy by manual inspection of the individually numbered cards provided to each pharmacy. In addition, using a pretest-posttest methodology, we will collect individual-level data from pharmacy staff members (pharmacists and pharmacy technicians). Measures collected prior to the intervention will include the following (see Multimedia Appendix 1 for a copy of each instrument):

- Sociodemographic information (age, gender, race, ethnicity, and sexual identity);
- Information about current pharmacy practice experience;
- Comfort with multiple harm reduction practices, as used in our prior study to explore harm reduction latent classes [27]; and
- Measures of stigmatizing beliefs about people who use drugs, which combine components of the 2019 Brief Opioid Stigma Scale by Yang et al [46] and work by author BEM's interdisciplinary group of medication for opioid use disorder patients and providers, which is in review.

The postintervention survey will include the comfort and stigma items (above) as well as additional sets of items (see Multimedia Appendices 2-3):

- Intervention acceptability (4 questions adapted from the Consolidated Framework for Implementation Research [33]);
- A set of questions targeted at implementation optimization validated by Livet et al [47]; and
- Four evaluative items developed by our team to potentially inform future work (eg, "If you could wave a magic wand, how would you improve the PharmNet intervention?").

Statistical Analyses

We will analyze the primary outcome using a generalized linear mixed model with a Poisson distribution to compare change over time of the number of naloxone doses dispensed between study arms. We will include fixed effects for group, time, and

their interaction and a random effect for pharmacy ID to account for repeated measures within pharmacy.

We do not anticipate any missingness in the primary outcome because the data are objective measures and can be accessed retrospectively if needed. If missing data are present in the individual-level data (>5%), we will perform multiple imputation by chained equations to assess the degree to which missingness affects the results. If missing data meaningfully affect the findings, we will report the analyses with imputation. If individuals provide a survey at one time point but not another (eg, a pretest without a posttest or vice versa), we will analyze the data as unmatched in our mixed models.

Data Management and Monitoring

As noted earlier in this paper, individual-level data from pharmacy staff members will be collected in QualtricsXM, which is a secure platform. Only the research team will have access to the raw data in QualtricsXM. Any identifying information used to match pretest and posttest data will be removed prior to the distribution of the data set for analysis. Based on the opinion of a professional biostatistician, additional data may be redacted prior to public data set release in the specific case that it might allow the identification of an individual staff member.

Harms

We do not anticipate that any harms would be accrued to participating pharmacies as a result of participating in this study. Based on our single-site pilot study, we strongly suspect that the burden on staff members will be minimal (since this is a pragmatic study, that is by design). However, pharmacies will always have the option to withdraw from the trial. In the unlikely event that such a thing occurs, we will report the data as they exist and describe the impetus behind the withdrawal in our final write-up. Similarly, we do not anticipate any risks to individual pharmacy staff participants related to completing study questionnaires, which are voluntary. However, we will follow all appropriate IRB procedures in the event of a loss of confidentiality.

Data and Code Availability

All data and analytic code associated with this project will be made public alongside the article describing the study results. We will publish an open account of the results regardless of the direction or nature of the findings.

Results

The not human subjects research designation (12339) was applied by the Indiana University IRB on August 2, 2021. The "exempt" declaration (13956) was granted by the same IRB on April 26, 2022.

Discussion

Next Steps

This study is designed to be a pragmatic, pilot randomized controlled trial of the PharmNet intervention. We plan to move forward with preparations for a much larger trial if either 1 of the following 2 cases are true: (1) Hypothesis 1 is upheld and there is evidence of a strong, significant effect of the intervention compared to control; or (2) Hypothesis 1 is not upheld (eg, the primary effect is nonsignificant), but the visual and numeric inspection of differences suggests a reasonable inference that favorable differences might be observed given a fully powered study.

Limitations

The proposed study is a pragmatic pilot trial, which imposes some limitations on the types of data and nature of information that can be collected, as our goal is to demonstrate real-world effectiveness. In addition, we expect that limitations may be identified during the course of study completion, and they will be identified and described in the results-oriented manuscript to follow the experimental intervention.

Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed in preparation of this protocol.

Authors' Contributions

JA, BEM, and LAE contributed to conceptualization. JA and LG contributed to formal analysis. JA and BEM contributed to funding acquisition. JA contributed to projection administration, resources, and supervision. LAE and JA wrote the original draft. All authors contributed to investigation, methodology, validation, and writing—review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PharmNet baseline survey.
[PDF File (Adobe PDF File), 151 KB - resprot_v11i10e42373_app1.pdf]

Multimedia Appendix 2
PharmNet postintervention survey (existing staff only).
[PDF File (Adobe PDF File), 175 KB - resprot_v11i10e42373_app2.pdf]

Multimedia Appendix 3
PharmNet postintervention survey (new hires only).
[PDF File (Adobe PDF File), 197 KB - resprot_v11i10e42373_app3.pdf]

References

1. 12 month-ending provisional number and percent change of drug overdose deaths. Centers for Disease Control and Prevention. 2022. URL: https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm [accessed 2022-04-21]
2. Issue brief: nation's drug-related overdose and death epidemic continues to worsen. American Medical Association. 2022 Sep 07. URL: https://www.ama-assn.org/system/files/issue-brief-increases-in-opioid-related-overdose.pdf [accessed 2022-06-24]
3. Renewal of determination that a public health emergency exists. Administration for Strategic Preparedness & Response. 2022 Apr 04. URL: https://aspr.hhs.gov/legal/PHE/Pages/Opioid-4Apr22.aspx [accessed 2022-05-02]
4. Indiana drug overdose dashboard. Indiana Department of Health. 2022 Feb 24. URL: https://www.in.gov/health/overdose-prevention/data/indiana/ [accessed 2022-10-06]
5. Williams AR, Nunes EV, Bisaga A, Levin FR, Olfson M. Development of a cascade of care for responding to the opioid epidemic. Am J Drug Alcohol Abuse 2019 Jan 24;45(1):1-10 [FREE Full text] [doi: 10.1080/00952990.2018.1546862] [Medline: 30675818]
6. Naloxone for opioid overdose: life-saving science. National Institute on Drug Abuse. 2017 Mar 30. URL: https://www.drugabuse.gov/publications/naloxone-opioid-overdose-life-saving-science [accessed 2021-12-15]
7. Naloxone DrugFacts. National Institute on Drug Abuse. 2022 Jan 11. URL: https://nida.nih.gov/publications/drugfacts/naloxone [accessed 2022-05-03]
8. Baca CT, Grant KJ. Take-home naloxone to reduce heroin death. Addiction 2005 Dec;100(12):1823-1831. [doi: 10.1111/j.1360-0443.2005.01259.x] [Medline: 16367983]
9. Opioid poisoning, overdose and prevention: 2015 report to the Governor and NYS Legislature. New York State Department of Health. 2015. URL: https://www.health.ny.gov/diseases/aids/general/opioid_overdose_prevention/docs/annual_report2015.pdf [accessed 2022-10-19]
10. Britch SC, Walsh SL. Treatment of opioid overdose: current approaches and recent advances. Psychopharmacology (Berl) 2022 Jul;239(7):2063-2081 [FREE Full text] [doi: 10.1007/s00213-022-06125-5] [Medline: 35385972]
11. Pergolizzi JVJ, Webster LR, Vortsman E, LeQuang JA, Raffa RB. Wooden chest syndrome: the atypical pharmacology of fentanyl overdose. J Clin Pharm Ther 2021 Dec;46(6):1505-1508. [doi: 10.1111/jcpt.13484] [Medline: 34240442]
12. Kelly E, Sutcliffe K, Cavallo D, Ramos-Gonzalez N, Alhosan N, Henderson G. The anomalous pharmacology of fentanyl. Br J Pharmacol 2021 May 24 [FREE Full text] [doi: 10.1111/bph.15573] [Medline: 34030211]
13. Koester S, Mueller SR, Raville L, Langegger S, Binswanger IA. Why are some people who have received overdose education and naloxone reticent to call emergency medical services in the event of overdose? Int J Drug Policy 2017 Oct;48:115-124 [FREE Full text] [doi: 10.1016/j.drugpo.2017.06.008] [Medline: 28734745]
14. Beletsky L. America's favorite antidote: drug-induced homicide in the age of the overdose crisis. Utah Law Rev 2019 Sep;2019(4, Article 4):833-890 [FREE Full text]
15. Adams J. U.S. Surgeon General's advisory on naloxone and opioid overdose. U.S. Department of Health and Human Services. 2018. URL: https://www.hhs.gov/surgeongeneral/priorities/opioids-and-addiction/naloxone-advisory/index.html [accessed 2021-07-03]
16. Giglio RE, Li G, DiMaggio CJ. Effectiveness of bystander naloxone administration and overdose education programs: a meta-analysis. Inj Epidemiol 2015 Dec;2(1):10 [FREE Full text] [doi: 10.1186/s40621-015-0041-8] [Medline: 27747742]
17. Clark AK, Wilder CM, Winstanley EL. A systematic review of community opioid overdose prevention and naloxone distribution programs. J Addict Med 2014 May;8(3):153-163. [doi: 10.1097/ADM.0000000000000034] [Medline: 24874759]
18. Razaghizad A, Windle SB, Filion KB, Gore G, Kudrina I, Paraskevopoulos E, et al. The effect of overdose education and naloxone distribution: an umbrella review of systematic reviews. Am J Public Health 2021 Aug;111(8):e1-e12. [doi: 10.2105/AJPH.2021.306306] [Medline: 34214412]
19. Chimbar L, Moleta Y. Naloxone effectiveness: a systematic review. J Addict Nurs 2018 Jul;29(3):167-171. [doi: 10.1097/JAN.0000000000000230] [Medline: 30180002]
20. Naloxone: summary of state laws. Legislative Analysis and Public Policy Association. 2022 Jul. URL: https://legislativeanalysis.org/wp-content/uploads/2022/09/Naloxone-Access-Summary-of-State-Laws.pdf [accessed 2022-10-06]
21. Aaron's Law and Overdose Good Samaratin Law. Indiana State Government. URL: https://www.in.gov/health/overdose-prevention/files/Aarons-Law-Primer.pdf [accessed 2022-10-06]

22. Berenbrok LA, Tang S, Gabriel N, Guo J, Sharareh N, Patel N, et al. Access to community pharmacies: a nationwide geographic information systems cross-sectional analysis. J Am Pharm Assoc (2003) 2022 Jul 15 [FREE Full text] [doi: 10.1016/j.japh.2022.07.003] [Medline: 35965233]
23. Pharmacies - the face of neighborhood healthcare since well before the pandemic. National Association of Community Drug Stores. 2021 Feb 07. URL: https://www.nacds.org/pdfs/about/rximpact-leavebehind.pdf [accessed 2022-08-18]
24. Berenbrok LA, Gabriel N, Coley KC, Hernandez I. Evaluation of frequency of encounters with primary care physicians vs visits to community pharmacies among Medicare beneficiaries. JAMA Netw Open 2020 Jul 01;3(7):e209132 [FREE Full text] [doi: 10.1001/jamanetworkopen.2020.9132] [Medline: 32667653]
25. Kelling SE, Rondon-Begazo A, DiPietro Mager NA, Murphy BL, Bright DR. Provision of clinical preventive services by community pharmacists. Prev Chronic Dis 2016 Oct 27;13:E149 [FREE Full text] [doi: 10.5888/pcd13.160232] [Medline: 27788064]
26. Cochran G, Gordon AJ, Field C, Bacci J, Dhital R, Ylioja T, et al. Developing a framework of care for opioid medication misuse in community pharmacy. Res Social Adm Pharm 2016 Mar;12(2):293-301 [FREE Full text] [doi: 10.1016/j.sapharm.2015.05.001] [Medline: 26048710]
27. Agley J, Meyerson BE, Eldridge LA, Crosby RA, Bentele KG, Jun M, et al. Exploration of pharmacist comfort with harm reduction behaviors: cross-sectional latent class analysis. J Am Pharm Assoc (2003) 2022 Mar;62(2):432-440. [doi: 10.1016/j.japh.2021.10.015] [Medline: 34742654]
28. Vadiei N, Eldridge LA, Meyerson BE, Agley J. "The gatekeepers in prevention": community pharmacist perceptions of their role in the opioid epidemic. Subst Abus 2022 Jul 02;43(1):319-327. [doi: 10.1080/08897077.2021.1941516] [Medline: 34214407]
29. Spector AL, Galletly CL, Christenson EA, Montaque HDG, Dickson-Gomez J. A qualitative examination of naloxone access in three states: Connecticut, Kentucky, and Wisconsin. BMC Public Health 2022 Jul 19;22(1):1387 [FREE Full text] [doi: 10.1186/s12889-022-13741-5] [Medline: 35854278]
30. Lai RK, Friedson KE, Reveles KR, Bhakta K, Gonzales G, Hill LG, et al. Naloxone accessibility without an outside prescription from U.S. community pharmacies: a systematic review. J Am Pharm Assoc (2003) 2022 Jul 31 [FREE Full text] [doi: 10.1016/j.japh.2022.07.008] [Medline: 35989151]
31. Hill LG, Loera LJ, Torrez SB, Puzantian T, Evoy KE, Ventricelli DJ, et al. Availability of buprenorphine/naloxone films and naloxone nasal spray in community pharmacies in 11 U.S. states. Drug Alcohol Depend 2022 Aug 01;237:109518. [doi: 10.1016/j.drugalcdep.2022.109518] [Medline: 35691255]
32. Eldridge LA, Meyerson BE, Agley J. Pilot implementation of the PharmNet naloxone program in an independent pharmacy. J Am Pharm Assoc (2003) 2022 Sep 09:1-9 [FREE Full text] [doi: 10.1016/j.japh.2022.09.004] [Medline: 36209035]
33. CFIR Research Team - Center for Clinical Management Research. Constructs. Consolidated Framework for Implementation Research. 2022. URL: https://cfirguide.org/constructs/ [accessed 2022-06-24]
34. Agley J, Meyerson BE, Eldridge LA, Smith C, Arora P, Richardson C, et al. Just the fax, please: updating electronic/hybrid methods for surveying pharmacists. Res Social Adm Pharm 2019 Feb;15(2):226-227. [doi: 10.1016/j.sapharm.2018.10.028] [Medline: 30416040]
35. Agley J, Meyerson BE, Shannon D, Ryder PT, Ritchie K, Gassman RA. Using the hybrid method to survey U.S. pharmacists: applying lessons learned to leverage technology. Res Social Adm Pharm 2017 Jan;13(1):250-252. [doi: 10.1016/j.sapharm.2016.09.007] [Medline: 27743847]
36. Eldridge LA, Agley J, Meyerson BE. Naloxone availability and dispensing in Indiana pharmacies 2 years after the implementation of a statewide standing order. J Am Pharm Assoc (2003) 2020 May;60(3):470-474. [doi: 10.1016/j.japh.2019.11.024] [Medline: 31917248]
37. Meyerson B, Agley J, Davis A, Jayawardene W, Hoss A, Shannon D, et al. Predicting pharmacy naloxone stocking and dispensing following a statewide standing order, Indiana 2016. Drug Alcohol Depend 2018 Jul 01;188:187-192 [FREE Full text] [doi: 10.1016/j.drugalcdep.2018.03.032] [Medline: 29778772]
38. Meyerson B, Agley J, Jayawardene W, Eldridge LA, Arora P, Smith C, PharmNet Research Team. Feasibility and acceptability of a proposed pharmacy-based harm reduction intervention to reduce opioid overdose, HIV and hepatitis C. Res Social Adm Pharm 2020 May;16(5):699-709 [FREE Full text] [doi: 10.1016/j.sapharm.2019.08.026] [Medline: 31611071]
39. Meyerson BE, Davis A, Agley JD, Shannon DJ, Lawrence CA, Ryder PT, et al. Predicting pharmacy syringe sales to people who inject drugs: policy, practice and perceptions. Int J Drug Policy 2018 Jun;56:46-53 [FREE Full text] [doi: 10.1016/j.drugpo.2018.02.024] [Medline: 29558701]
40. Meyerson BE, Dinh PC, Agley JD, Hill BJ, Motley DN, Carter GA, et al. Predicting pharmacist dispensing practices and comfort related to pre-exposure prophylaxis for HIV prevention (PrEP). AIDS Behav 2019 Jul 3;23(7):1925-1938 [FREE Full text] [doi: 10.1007/s10461-018-02383-7] [Medline: 30607758]
41. Meyerson BE, Lawrence CA, Cope SD, Levin S, Thomas C, Eldridge LA, et al. I could take the judgment if you could just provide the service: non-prescription syringe purchase experience at Arizona pharmacies, 2018. Harm Reduct J 2019 Sep 18;16(1):57 [FREE Full text] [doi: 10.1186/s12954-019-0327-1] [Medline: 31533730]

42. Meyerson BE, Moehling TJ, Agley JD, Coles HB, Phillips J. Insufficient access: naloxone availability to laypeople in Arizona and Indiana, 2018. J Health Care Poor Underserved 2021 Jun 09;32(2):819-829. [doi: 10.1353/hpu.2021.0107] [Medline: 34120979]
43. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing oopioids for chronic pain--United States, 2016. JAMA 2016 Apr 19;315(15):1624-1645 [FREE Full text] [doi: 10.1001/jama.2016.1464] [Medline: 26977696]
44. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. BMJ 2015 May 08;350(may08 1):h2147-h2147. [doi: 10.1136/bmj.h2147] [Medline: 25956159]
45. Wasserstein RL, Lazar NA. The ASA statement on p-values: context, process, and purpose. Am Stat 2016 Jun 09;70(2):129-133. [doi: 10.1080/00031305.2016.1154108]
46. Yang LH, Grivel MM, Anderson B, Bailey GL, Opler M, Wong LY, et al. A new brief opioid stigma scale to assess perceived public attitudes and internalized stigma: evidence for construct validity. J Subst Abuse Treat 2019 Apr;99:44-51 [FREE Full text] [doi: 10.1016/j.jsat.2019.01.005] [Medline: 30797393]
47. Livet M, Blanchard C, Richard C, Sheppard K, Yannayon M, Sorensen T, et al. Measuring implementation of medication optimization services: development and validation of an implementation outcomes questionnaire. Res Social Adm Pharm 2021 Sep;17(9):1623-1630. [doi: 10.1016/j.sapharm.2021.01.001] [Medline: 33526353]

Abbreviations

IRB: institutional review board
MOU: memorandum of understanding

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Protocol

A Rehabilitation Program for Individuals With Chronic Low Back Pain: Protocol for a Randomized Clinical Trial

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This is a corrected version. See correction statement: https://www.researchprotocols.org/2022/11/e44067

Abstract

Background: Low back pain (LBP) is the leading cause of disability worldwide. Physical exercise, as a treatment, is beneficial for the improvement of quality of life in patients with LBP, and it is widely accepted.

Objective: We aimed to develop a protocol for a feasibility study that is designed to compare the effectiveness of different interventions in reducing pain, functional, and psychosocial factors among patients with chronic LBP after 8 weeks of randomization.

Methods: This is a study protocol for a randomized controlled trial that will consist of individuals with chronic LBP who are aged between 18 and 65 years. Participants will be allocated, through block randomization, to one of the following groups: the motor control exercises (MCEs), pain education, MCEs+pain education, and usual care groups. The primary outcome will be pain intensity, and the secondary outcomes will be the pressure pain threshold, which will be measured with a digital algometer; LBP-related disability; fears and beliefs; the fear of movement; quality of life; mood states; and levels of depression and anxiety. The trial was approved by the ethics committee for research involving human beings of the Federal University of Pelotas (reference number: 5.717.390) in September 2022, and it will be conducted until August 2023.

Results: The researchers are being trained to apply the questionnaires and carry out the interventions. Patient recruitment will begin at the end of 2022 and results are expected to be achieved by August 2023.

Conclusions: Our trial will provide preliminary data regarding the feasibility and safety of MCEs and pain education for patients with LBP. It will also provide preliminary outcome data that can be used to identify the most efficient intervention and the level of health care that should be implemented in public health services.

Trial Registration: Brazilian Registry of Clinical Trials U1111-1221-4106; https://ensaiosclinicos.gov.br/rg/RBR-2xx2r2/

International Registered Report Identifier (IRRID): PRR1-10.2196/31345

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KEYWORDS

low back pain; chronic pain; therapeutic exercise; pain education

Introduction

Background

Low back pain (LBP) is the leading cause of disability worldwide [1], resulting in significant economic burden for individuals, families, communities, industries, and governments [2]. LBP is deemed a chronic condition when the duration of continuous pain in the sacral, lumbar, or lumbosacral region exceeds 3 months. This may or may not be accompanied by irradiation to the lower limbs, which is called *lumbosciatalgia* [3].

Despite the high prevalence of LBP, many individuals prefer to modify their tasks at work rather than seek help due to the fear of losing their job [4]. However, these modifications may worsen the pain, as they can trigger other symptoms. Studies have shown that biopsychosocial factors, such as catastrophization, kinesiophobia, anxiety, depression, stress, job dissatisfaction, and financial concerns, may be associated with LBP [5-7].

Chronic pain treatment through physical exercise is beneficial for the improvement of patients' quality of life, and it is widely accepted. Studies have demonstrated positive results with strength training, walking, and stretching practices, such as pain reduction and improvements in depression and sleep quality [8]. In addition, there is evidence indicating that a multidisciplinary, biopsychosocial rehabilitation approach is more effective than an isolated approach for the treatment and management of chronic LBP [9].

Among the recommended exercise practices, it has been noted that motor control exercises (MCEs) are widely used for the reduction of recurrent LBP [10]. These exercises involve the voluntary contraction of deep muscles, especially the transverse abdominis and multifidus muscles, and aim to promote the activation of trunk stabilizing muscles to reduce symptoms and improve mobility [11,12]. The prescription and development of these exercises should be gradual and individualized, respecting the pain threshold of each patient in order to reduce the functional disability and catastrophization of the individual [13].

Despite research advances in LBP treatment, further studies that compare the effects of different treatment approaches are warranted to gain better understanding and develop intervention strategies that may be applicable to individuals with chronic LBP. There is currently no consensus about the effectiveness of treatments that account for the pain, functionality, and psychological factors in these individuals. Furthermore, few studies present their intervention protocols in detail, making it difficult to apply their obtained results in clinical practice. Therefore, we aim to provide detailed intervention protocols for MCEs and health that are reproducible and serve as a reference for interested professionals.

Goal of the Study

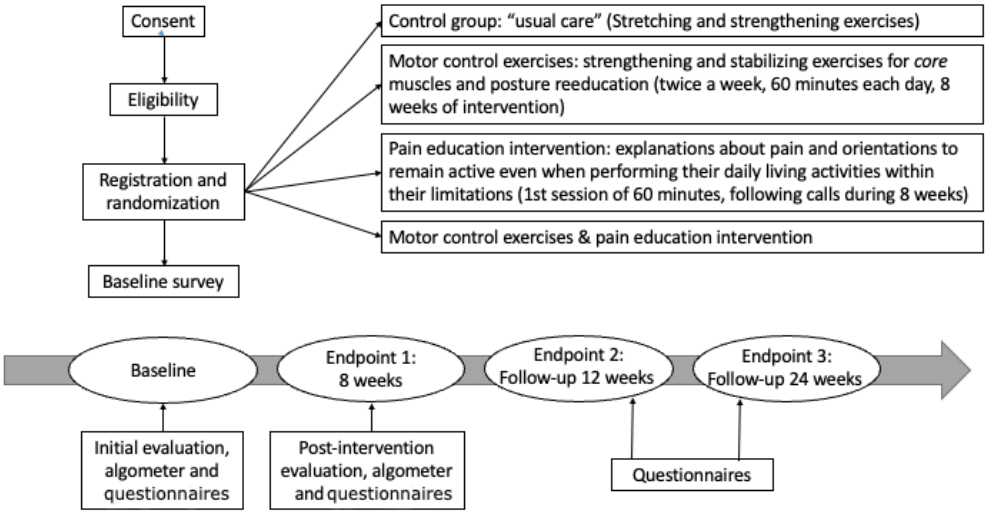
The primary aim of our study is to analyze the effectiveness of a program that includes MCEs and pain education. The secondary aims are (1) to clarify the effects of the program on pain outcomes, including the subjective intensity of pain and the pressure pain threshold, and compare the MCEs group (M-group) and MCEs+pain education group (MP-group) to the pain education group (P-group) and usual care group (U-group), the P-group and MP-group to the M-group and U-group, and all 4 groups; (2) to clarify the effects of MCEs on physiologic and psychologic stress measurements and compare the U-group to the M-group, the U-group and P-group to the M-group and MP-group, and all 4 groups; and (3) to clarify the effects of the pain education intervention on physiologic and psychologic stress measurements and compare the U-group to the P-group and U-group and the M-group to the P-group and MP-group.

Methods

Study Design

Our study will be a parallel-group randomized controlled superiority trial with 4 arms, as shown in Figure 1. The target sample size is 900 individuals with LBP, who will be randomized (1:1:1:1 allocation) via computer-generated randomization. The groups will receive their assigned intervention according to the following allocations: (1) M-group, (2) P-group, and (3) MP-group; the U-group will receive the usual care intervention. Individuals will be instructed to not perform any form of physical exercise during the intervention period. We will compare the three types of interventions to determine their relative superiority to usual care.

Figure 1. Flowchart of the study design.



Ethics Approval

The study protocol was registered in the Brazilian Registry of Clinical Trials (registration code: RBR-2xx2r2; universal trial number: U1111-1221-4106). This protocol was created according to the SPIRIT (Standard Protocol Items: Recommendations for Randomized Trials) 2013 guidelines checklist [14].

Our research was approved by the ethics committee for research involving human beings of the Federal University of Pelotas (reference number: 5.717.390) in September 2022, and it will be conducted until August 2023.

Recruitment

We will recruit individuals with LBP at outpatient clinics of basic health units in Pelotas, Brazil, while they wait for an evaluation. During recruitment, we will determine their study eligibility based on the inclusion and exclusion criteria in Textbox 1.

Individuals will be randomly allocated to intervention groups, having the same probability of being allocated to a group that will be exposed to the test interventions or the control group.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- History of low back pain in the last 6 months
- Pain intensity of ≥3 (Numeric Pain Rating Scale) during movement in at least one direction (flexion, extension, or rotation)
- Aged between 18 and 65 years

Exclusion criteria

- Previous history of rheumatic disease, lumbar myelopathy, tumors, or central or peripheral neurological disorders
- History of major trauma, fractures, or surgery in the lumbar region or signs of nerve root compression (major muscle weakness affecting the lower limbs, reduction or abolition of patellar and calcaneal reflexes, and decreased sensitivity in lower limb dermatomes)

Intervention Program

The physiotherapists who will participate in the clinical trial will undergo prior training to standardize the interventions.

The interventions will be divided into the following groups:

- Group 1 (MCEs): individuals will perform a strengthening and stabilization exercise program for core muscles (stabilizers of the lumbar, pelvic, and abdominal muscles and the diaphragm muscle) and postural correction.
- Group 2 (pain education): individuals will receive a postural care guide and will be encouraged to remain active, performing their daily living activities within their limitations.
- Group 3 (MCEs+pain education): individuals will receive intervention through physical exercises and pain education.
- Group 4 (usual care intervention): individuals will undergo the usual treatment through the use of resources and the application of conventional techniques.

The MCE Program

The purpose of the MCE program is to normalize the difficulty in the motion domain for each participant. The exercises will be divided into 3 stages of training. A progressive increase in the level of difficulty will occur as the patients correctly perform the exercises with ideal movement patterns (Table 1). A detailed anamnesis and physical examination will be performed to account for the condition of each individual participant. Additionally, these will allow us to determine the levels and

goals for each stage of exercise and the progression time for each difficulty level.

In the first stage, individuals will start to learn how to perform isometric contractions of the transverse abdominis and multifidus muscles in the prone, supine, and quadrupedal positions. To ensure the correct activation of the transverse abdominis, it will be emphasized to participants that the lower part of the anterior abdominal wall (ie, below the level of the umbilical scar) should be pushed toward the spine to activate the muscle. Participants will be instructed to progressively increase the waiting time and number of contractions to up to 10 contraction repetitions×10 seconds of sustainment. At the first appointment, patients will receive awareness-raising advice for performing the deep muscle contractions and instructions on how to activate the aforementioned muscles, so that they can sustain the contractions during the exercises for about 30 to 45 minutes throughout the appointments. The patients will advance to the next stage when they show the ability to perform the exercise and control pelvic and lumbar movements with minimal effort while moving their upper and lower extremities.

In the second stage, the complexity of the exercises will be increased by progressing to functional exercises that involve performing trunk and upper limb coordination while maintaining trunk stability [15]. Patients will be taught to perform abdominal cocontraction in different postures and control movements of the lumbopelvic region with minimal effort while performing functional activities.

After learning all of the exercises in stages 1 and 2, participants will be instructed to perform trunk coordination exercises and weight loading for the upper limbs (ie, while maintaining the stability of the trunk) and consider the activities that presented difficulty or the activities for which they reported pain during implementation in the initial evaluation.

The last 10 minutes of appointments will be reserved for returning to baseline through free walking and stretching exercises.

Table 1. Progression of the exercises in the different stages of the motor control exercises.

	Phase 1	Phase 2	Phase 3
Progression 1	• Prone position (10 repetitions×10 seconds of sustainment)	• Supine position with alternating hip flexion • Bridge exercise (isometric hip lift; 10 repetitions×20 seconds of sustainment)	• Gym ball and dumbbell lifting in supine positiona
Progression 2	• Supine position (10 repetitions×10 seconds of sustainment)	• Quadrupedal position with alternating shoulder flexion and hip extension	• Gym ball or dumbbell lifting in sitting and standing positionsa
Progression 3	• Quadrupedal position (10 repetitions×10 seconds of sustainment)	• Squats (20 repetitions) • Elevation of upper limbs in sitting and standing positions (20 repetitions)	• Hold weight in hands while simultaneously performing activities (sitting, standing, walking, and climbing stairs)[a]

[a]Progression will be determined according to the patient's functional condition.

Pain Education

The educational program will be based on the protocol described by Traeger et al [16] and will consist of a biopsychosocial approach to dealing with fears and clarifying behavioral beliefs about pain and movement. Additionally, the program will explain the influence of emotional symptoms (stress, anxiety, kinesiophobia, etc) on chronic pain; the influence of lack of sleep and physical activity on LBP, gradual exposure to physical activity, and daily movements; and the neurophysiology of pain. The program will include the following three major components: (1) clarifying any useless beliefs about the nature of LBP, (2) presenting key concepts of the biology of pain, and (3) evaluating patients' understanding and discussing recovery. Participants who are randomized to the pain education intervention will participate in two 1-hour sessions of pain education that will be conducted by a physiotherapist. The physiotherapist will be appropriately trained for the study and will be contacted weekly for clarifications on doubts and possible further guidance. Multimedia Appendix 1 shows the 3 steps of the Pain Education Program.

MCEs and Pain Education

Individuals who are allocated to both interventions will receive guidance regarding the educational program for 1 hour during the first appointment, before participating in the MCE program for 8 weeks. The topics that will be covered throughout the treatment will be reinforced, emphasizing the factors for which individuals have more difficulty with changing their behavior.

Usual Care Intervention

Conventional intervention will be based on exercises that are usually performed in clinical practice. It will involve the active stretching of the posterior thigh muscles (hamstrings) by using a resistance band. The therapeutic exercises will include (1) isometric exercises that activate the muscles of the core region and stabilizers of the loin-pelvic region and hips (the transverse abdominis and multifidus muscles, oblique and rectus abdominal muscles, gluteus minimus, and gluteus maximus); (2) isotonic exercises for the lower limbs (hip abduction and adduction and hip flexion and extension); (3) exercises that focus on movement functionality, which will be augmented by breathing and body perception techniques, body realignment, and muscular and joint imbalance correction; (4) resistance exercises that involve using an elastic band to strengthen lower limb musculature; and

(5) guidance for performing daily life activities and explaining the importance of staying active to prevent recurrence or increases in pain, which will be given spontaneously as an initiative of the responsible physiotherapist.

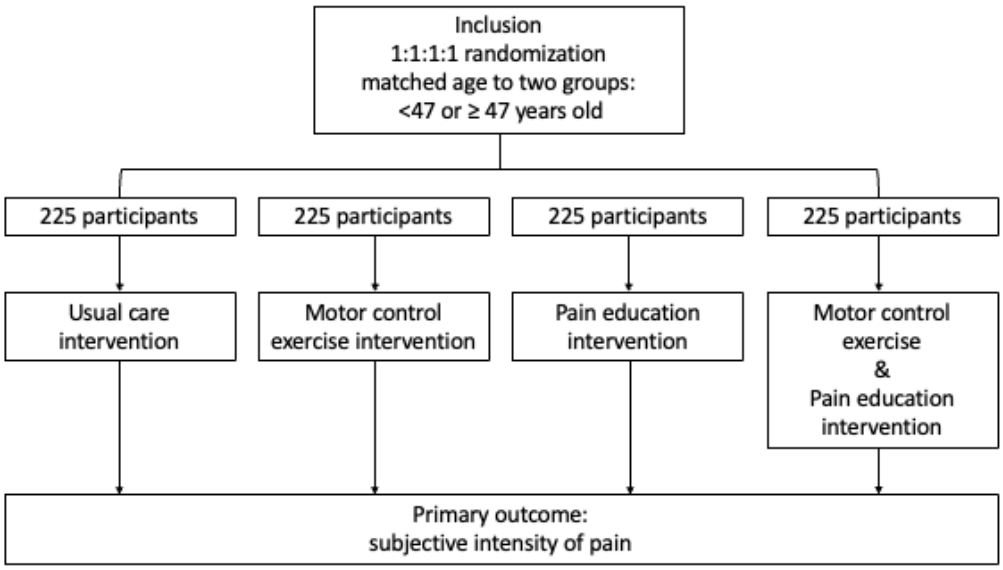
The exercise interventions will be conducted with groups of 3 patients, and the program will last for 8 weeks. Patients will receive care twice per week, totaling 16 visits. The patients cannot perform any other types of exercises during the study period. To maintain patients' compliance with the program, researchers will contact them each week to inquire about the progress of the interventions.

Data Collection

The professionals (physicians, nurses, physiotherapists, psychologists, and physical education professionals) from the health network of Pelotas City, Rio Grande do Sul, Brazil, will refer patients to the program after assessing their eligibility. Patients who show an interest in participating in the program will be marked for an initial evaluation, during which the patients will be informed about the research procedures, evaluations, interventions, and duration. After obtaining all of the necessary information, patients who wish to participate must sign the informed consent form. Only researchers will have access to the database. To maintain data confidentiality, patients will be identified by numbers.

The study protocol is shown in Figure 2. A baseline survey will be conducted after the allocation. Participants will receive questionnaires, including questions on demographic data and baseline data for outcomes.

Figure 2. Study protocol.



Outcome Measures and Assessment Points

Evaluations will be carried out before and after 8 weeks of intervention and the 12- and 24-week follow-ups. Individuals will be monitored weekly during the study period, and messages will be sent through WhatsApp (Meta Platforms) to collect information about pain intensity.

Primary Outcome Measure

The primary outcome measure will be a report of pain intensity on the Numerical Pain Rating Scale [17].

Secondary Outcome Measures

The secondary outcome measures will be as follows:

1. Comparison of disability outcomes
   - Scores measured by using the Roland Morris Disability Questionnaire [18]
2. Comparison of physiologic and psychologic stress
   - Score for the Fear Avoidance Belief Questionnaire [19]
   - Score for the Tampa Scale of Kinesiophobia [20]
   - Score for health-related quality of life from the Short Form-12 Health Survey Version 2 [21,22]
   - Score for the Brunel Humor Scale [23]
   - Scores measured by using the Beck Depression Inventory [24] and Beck Anxiety Inventory [25]
   - Scores measured by using the Pittsburg Sleep Quality Index [26] for evaluating sleep quality and behavior

Any adverse effects that are observed or reported by the patients will be recorded and considered for the final study outcomes. Furthermore, patients who experience adverse effects will be sent to a physician for adequate treatment.

Study Procedures

Sample Size Calculation

Sampling will be probabilistic, and patients will be extracted from the LBP waiting list. The required sample size was calculated by assuming a mean difference of 1.5 and an SD of 2.4 [27]; the study requires a sample size of 225 per group, that is, 900 individuals in total.

Random Allocation and Blinding

After the initial evaluation, the participants will be allocated, through block randomization, to receive different interventions, which will be conducted by physiotherapists. Individuals who fulfill the inclusion criteria will receive clarification about the

objectives and the procedures that will performed in the research, and their consent will be requested by asking them to sign the informed consent form, of which the terms were approved by the ethics committees of the Federal University of Pelotas and the Health Department of Pelotas City.

The participants will then be referred to the physiotherapist who will be selecting the interventions according to the groups to which the participants will be allocated. The individuals who are allocated to the M-group, MP-group, and U-group will participate in 16 treatment sessions (2 sessions per week, totaling 8 weeks of treatment) with an average duration of 40 minutes.

It will not be possible to blind the physiotherapists who are responsible for the interventions due to the type of research that will be conducted. However, evaluators and patients will be blinded to the treatment groups. Nonblinding conditions will only occur in cases of health emergencies.

Statistical Analysis

The data will be analyzed by using SPSS version 20.0 (IBM Corporation). Descriptive statistics (means, SDs, and frequencies) will be used to present the characteristics of the participants, and inferential tests will be used to analyze the differences among the groups. Analyses will be performed based on intent-to-treat principles. The outcomes (Numeric Pain Rating Scale, Roland Morris Disability Questionnaire, Fear Avoidance Belief Questionnaire, Tampa Scale of Kinesiophobia, Short Form-36 Health Survey, Brunel Humor Scale, Beck Depression Inventory, Beck Anxiety Inventory, and Pittsburg Sleep Quality Index scores and the pressure threshold for pain) will be analyzed by using generalized estimation equations to compare the M-group, P-group, MP-group, and U-group at baseline, after 8 weeks, and at the 12- and 24-week follow-ups. The effects of groups, time, and group interactions with time (group×time) will be analyzed. The Bonferroni post hoc test will be used to identify the differences among the means of all variables. Missing data will be handled via multiple imputation [28]. The α established as the level of significance will be $P<.05$ (95%) for all hypothesis tests. The effect sizes will be checked by using the Hedges g test. The magnitudes of effect sizes will be interpreted as *trivial* (<0.2), *small* (0.2-0.6), *moderate* (0.6-1.2), *large* (1.2-2.0), *very large* (2.0-4.0), and *perfect* (>4.0) [29]. To represent the effect of the intervention, the delta (Δ) of the analyzed variables (Δ = x postintervention − x preintervention) will be calculated.

Results

The trial was presented to the municipal authorities and its practical applications were discussed in August 2022. The researchers are being trained to apply the questionnaires and carry out the interventions. Patient recruitment will begin at the end of 2022 and results are expected to be achieved by August 2023.

Discussion

Study Overview

Some studies have identified the positive effects of using a biopsychosocial approach in interventions for patients with chronic pain [9]. There is evidence that motor exercises reduce LBP through the activation of the deep lumbopelvic musculature [10].

In contrast to other randomized controlled trials, our study will investigate the effects of the association between motor exercises and pain education and compare them to the effects of an exclusively biopsychosocial approach.

The structure of our study reflects a scenario of actual clinical practice, and it will investigate the effects of the interventions on pain reduction after 8 weeks of intervention. A follow-up at 3 months after randomization will be performed to obtain information on pain and other clinical factors from the patients.

The results of our clinical trial study will give us information on the most efficient intervention strategies that will be implemented in a public health service within Brazil, which may be expanded to other physiotherapy centers and serve as a basis for planning health actions with the greatest impact on the population of people with LBP.

Future studies could explore the use of complementary modalities, such as mindful movements, among patients with chronic pain to identify the promotion of well-being.

Study Implications

The structure of our study reflects a real scenario of actual clinical practice in a public health service. Its application may benefit many patients who have never been treated. The study proposal also offers a detailed exercise protocol and pain education approach that can serve as a reference for many professionals. Further, the identification of more appropriate intervention strategies for individuals with chronic LBP may result in changes in professional conduct and more treatment tools with a greater clinical impact.

Conclusions

Our trial will provide preliminary data regarding the feasibility and safety of MCEs and pain education for patients with LBP. It will also provide preliminary outcome data that can be used to identify the most efficient intervention and the level of health care that should be implemented in public health services.

Authors' Contributions

MJ-C and AA conceived the study and defined the original study protocol. MJ-C and SMS developed the intervention parameters. MJ-C is responsible for the ethics applications and the ethical reporting of the study. GTV, GB, and MJ-C are responsible for recruitment, data collection, and the implementation of the study. All authors have read and approved the final manuscript. MJ-C and GTV drafted the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Pain Education Program.
[DOCX File , 14 KB - resprot_v11i10e31345_app1.docx]

References

1. Hoy D, March L, Brooks P, Blyth F, Woolf A, Bain C, et al. The global burden of low back pain: estimates from the Global Burden of Disease 2010 study. Ann Rheum Dis 2014 Jun;73(6):968-974. [doi: 10.1136/annrheumdis-2013-204428] [Medline: 24665116]
2. Olafsson G, Jonsson E, Fritzell P, Hägg O, Borgström F. Cost of low back pain: results from a national register study in Sweden. Eur Spine J 2018 Nov;27(11):2875-2881. [doi: 10.1007/s00586-018-5742-6] [Medline: 30155730]
3. Ferreira ML, Machado G, Latimer J, Maher C, Ferreira PH, Smeets RJ. Factors defining care-seeking in low back pain--a meta-analysis of population based surveys. Eur J Pain 2010 Aug;14(7):747.e1-747.e7. [doi: 10.1016/j.ejpain.2009.11.005] [Medline: 20036168]
4. Froud R, Patterson S, Eldridge S, Seale C, Pincus T, Rajendran D, et al. A systematic review and meta-synthesis of the impact of low back pain on people's lives. BMC Musculoskelet Disord 2014 Feb 21;15:50 [FREE Full text] [doi: 10.1186/1471-2474-15-50] [Medline: 24559519]
5. Andersson GB. Epidemiological features of chronic low-back pain. Lancet 1999 Aug 14;354(9178):581-585. [doi: 10.1016/S0140-6736(99)01312-4] [Medline: 10470716]
6. Moseley GL, Nicholas MK, Hodges PW. A randomized controlled trial of intensive neurophysiology education in chronic low back pain. Clin J Pain 2004;20(5):324-330. [doi: 10.1097/00002508-200409000-00007] [Medline: 15322439]
7. Uluğ N, Yakut Y, Alemdaroğlu İ, Yılmaz Ö. Comparison of pain, kinesiophobia and quality of life in patients with low back and neck pain. J Phys Ther Sci 2016 Jan;28(2):665-670 [FREE Full text] [doi: 10.1589/jpts.28.665] [Medline: 27064399]
8. Andrade A, Vilarino GT, Bevilacqua GG. What is the effect of strength training on pain and sleep in patients with fibromyalgia? Am J Phys Med Rehabil 2017 Dec;96(12):889-893. [doi: 10.1097/PHM.0000000000000782] [Medline: 28650860]
9. Kamper SJ, Apeldoorn AT, Chiarotto A, Smeets RJEM, Ostelo RWJG, Guzman J, et al. Multidisciplinary biopsychosocial rehabilitation for chronic low back pain. Cochrane Database Syst Rev 2014 Sep 02(9):CD000963. [doi: 10.1002/14651858.CD000963.pub3] [Medline: 25180773]
10. Byström MG, Rasmussen-Barr E, Grooten WJA. Motor control exercises reduces pain and disability in chronic and recurrent low back pain: a meta-analysis. Spine (Phila Pa 1976) 2013 Mar 15;38(6):E350-E358. [doi: 10.1097/BRS.0b013e31828435fb] [Medline: 23492976]
11. Freeman MD, Woodham MA, Woodham AW. The role of the lumbar multifidus in chronic low back pain: a review. PM R 2010 Feb;2(2):142-146; quiz 1 p following 167. [doi: 10.1016/j.pmrj.2009.11.006] [Medline: 20193941]
12. Hodges PW, Richardson CA. Inefficient muscular stabilization of the lumbar spine associated with low back pain. A motor control evaluation of transversus abdominis. Spine (Phila Pa 1976) 1996 Nov 15;21(22):2640-2650. [doi: 10.1097/00007632-199611150-00014] [Medline: 8961451]
13. López-de-Uralde-Villanueva I, Muñoz-García D, Gil-Martínez A, Pardo-Montero J, Muñoz-Plata R, Angulo-Díaz-Parreño S, et al. A systematic review and meta-analysis on the effectiveness of graded activity and graded exposure for chronic nonspecific low back pain. Pain Med 2016 Jan;17(1):172-188. [doi: 10.1111/pme.12882] [Medline: 26235368]
14. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013 Feb 05;158(3):200-207 [FREE Full text] [doi: 10.7326/0003-4819-158-3-201302050-00583] [Medline: 23295957]
15. Costa LOP, Maher CG, Latimer J, Hodges PW, Herbert RD, Refshauge KM, et al. Motor control exercise for chronic low back pain: a randomized placebo-controlled trial. Phys Ther 2009 Dec;89(12):1275-1286. [doi: 10.2522/ptj.20090218] [Medline: 19892856]
16. Traeger AC, Moseley GL, Hübscher M, Lee H, Skinner IW, Nicholas MK, et al. Pain education to prevent chronic low back pain: a study protocol for a randomised controlled trial. BMJ Open 2014 Jun 02;4(6):e005505 [FREE Full text] [doi: 10.1136/bmjopen-2014-005505] [Medline: 24889854]
17. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken) 2011 Nov;63 Suppl 11:S240-S252 [FREE Full text] [doi: 10.1002/acr.20543] [Medline: 22588748]

18. Nusbaum L, Natour J, Ferraz MB, Goldenberg J. Translation, adaptation and validation of the Roland-Morris questionnaire--Brazil Roland-Morris. Braz J Med Biol Res 2001 Feb;34(2):203-210 [FREE Full text] [doi: 10.1590/s0100-879x2001000200007] [Medline: 11175495]
19. Waddell G, Newton M, Henderson I, Somerville D, Main CJ. A Fear-Avoidance Beliefs Questionnaire (FABQ) and the role of fear-avoidance beliefs in chronic low back pain and disability. Pain 1993 Feb;52(2):157-168. [doi: 10.1016/0304-3959(93)90127-B] [Medline: 8455963]
20. Siqueira FB, Teixeira-Salmela LF, de Castro Magalhães L. Análise das propriedades psicométricas da versão brasileira da escala tampa de cinesiofobia. Acta Ortop Bras 2007;15(1):19-24 [FREE Full text] [doi: 10.1590/S1413-78522007000100004]
21. Castillo II. [A comparative analysis of SF-12 with the SF-36 among patients in methadone treatment]. Adicciones 2007;19(1):59-67 [FREE Full text] [Medline: 17687883]
22. Damásio BF, Andrade TF, Koller SH. Psychometric properties of the Brazilian 12-Item Short-Form Health Survey Version 2 (SF-12v2). Paidéia (Ribeirão Preto) 2015;25(60):29-37 [FREE Full text] [doi: 10.1590/1982-43272560201505]
23. de Miranda Rohlfs ICP, Rotta TM, Di Bernardi Luft C, Andrade A, Krebs RJ, de Carvalho T. A Escala de Humor de Brunel (Brums): instrumento para detecção precoce da síndrome do excesso de treinamento. Revista Brasileira de Medicina do Esporte 2008 Jun;14(3):176-181 [FREE Full text] [doi: 10.1590/s1517-86922008000300003]
24. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961 Jun;4:561-571. [doi: 10.1001/archpsyc.1961.01710120031004] [Medline: 13688369]
25. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 1988 Dec;56(6):893-897. [doi: 10.1037//0022-006x.56.6.893] [Medline: 3204199]
26. Buysse D, Reynolds CF3, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989 May;28(2):193-213. [doi: 10.1016/0165-1781(89)90047-4] [Medline: 2748771]
27. Childs JD, Piva SR, Fritz JM. Responsiveness of the numeric pain rating scale in patients with low back pain. Spine (Phila Pa 1976) 2005 Jun 01;30(11):1331-1334. [doi: 10.1097/01.brs.0000164099.92112.29] [Medline: 15928561]
28. Carpenter J, Kenward M. Multiple Imputation and its Application. New York, NY: John Wiley & Sons, Inc; Feb 2013.
29. Hopkins WG, Marshall SW, Batterham AM, Hanin J. Progressive statistics for studies in sports medicine and exercise science. Med Sci Sports Exerc 2009 Jan;41(1):3-13. [doi: 10.1249/MSS.0b013e31818cb278] [Medline: 19092709]

Abbreviations

LBP: low back pain
M-group: motor control exercises group
MCE: motor control exercise
MP-group: motor control exercises+pain education group
P-group: pain education group
SPIRIT: Standard Protocol Items: Recommendations for Randomized Trials
U-group: usual care group

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Protocol

Training Intervention and Program of Support for Fostering the Adoption of Family-Centered Telehealth in Pediatric Rehabilitation: Protocol for a Multimethod, Prospective, Hybrid Type 3 Implementation-Effectiveness Study

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Abstract

Background: Children with disability face long wait times for rehabilitation services. Before the COVID-19 pandemic, telehealth adoption was low across pediatric rehabilitation. Owing to the COVID-19 pandemic restrictions, pediatric therapists were asked to rapidly shift to telehealth, often with minimal training. To facilitate the behavior changes necessary for telehealth adoption, provision of appropriate evidence-based training and support is required. However, evidence to support the effective implementation of such training is lacking. The successful real-world implementation of a training intervention and program of support (TIPS) targeting pediatric therapists to enhance the adoption of family-centered telerehabilitation (FCT) requires the evaluation of both implementation and effectiveness.

Objective: This study aimed to evaluate TIPS implementation in different pediatric rehabilitation settings and assess TIPS effectiveness, as it relates to therapists' adoption, service wait times, families' perception of service quality, and costs.

Methods: This 4-year, pan-Canadian study involves managers, pediatric occupational therapists, physiotherapists, speech-language pathologists, and families from 20 sites in 8 provincial jurisdictions. It will use a multimethod, prospective, hybrid type 3 implementation-effectiveness design. An interrupted time series will assess TIPS implementation. TIPS will comprise a 1-month training intervention with self-paced learning modules and a webinar, followed by an 11-month support program, including monthly site meetings and access to a virtual community of practice. Longitudinal mixed modeling will be used to analyze indicators of therapists' adoption of and fidelity to FCT collected at 10 time points. To identify barriers and facilitators to adoption and fidelity, qualitative data will be collected during implementation and analyzed using a deductive-inductive thematic approach. To evaluate effectiveness, a quasi-experimental pretest-posttest design will use questionnaires to evaluate TIPS effectiveness at service, therapist, and family levels. Generalized linear mixed effects models will be used in data analysis. Manager, therapist, and family interviews will be conducted after implementation and analyzed using reflective thematic analysis. Finally, cost data will be gathered to calculate public system and societal costs.

Results: Ethics approval has been obtained from 2 jurisdictions (February 2022 and July 2022); approval is pending in the others. In total, 20 sites have been recruited, and data collection is anticipated to start in September 2022 and is projected to be completed by September 2024. Data analysis will occur concurrently with data collection, with results disseminated throughout the study period.

Conclusions: This study will generate knowledge about the effectiveness of TIPS targeting pediatric therapists to enhance FCT adoption in pediatric rehabilitation settings, identify facilitators for and barriers to adoption, and document the impact of telehealth adoption on therapists, services, and families. The study knowledge gained will refine the training intervention, enhance intervention uptake, and support the integration of telehealth as a consistent pediatric rehabilitation service option for families of children with disabilities.

Trial Registration: ClinicalTrials.gov NCT05312827; https://clinicaltrials.gov/ct2/show/NCT05312827

International Registered Report Identifier (IRRID): PRR1-10.2196/40218

(JMIR Res Protoc 2022;11(10):e40218) doi:10.2196/40218

KEYWORDS

telehealth; pediatric rehabilitation; training; therapists; pediatrics; physical therapy; health care; family-centered care

Introduction

Background

Timely access to family-centered services for children with disabilities and their families is crucial for supporting their development and well-being [1-3]. Currently, many children face long wait times (ie, up to 2 years) as well as organizational, geographic, or cultural barriers to services [4-6]. Lack of service access can lead to negative developmental, health, and social consequences for children and their families [7-10]. The COVID-19 pandemic further exacerbated these issues, as rehabilitation support for children was significantly reduced [11], increasing parental mental health burden (eg, stress and depression) [7-10]. To minimize the negative impacts of these service disruptions, therapists shifted to telehealth service delivery [7,9,12,13].

Telehealth is defined as any asynchronous or real-time clinical intervention provided remotely by clinicians (in this case, therapists) to patients or caregivers [14-16]. Telehealth is an important alternative for families living in underserved or remote areas [14,17-21]. However, some families in well-served urban locations also prefer the convenience of telehealth over in-person visits for reasons such as decreased travel time and schedule flexibility [15,16]. Before the COVID-19 pandemic, a systematic review of randomized controlled trials of pediatric rehabilitation delivered via telehealth supported the efficacy of rehabilitation provided via telehealth for diverse populations and a wide range of effects, including improved service access, child outcomes (eg, behavior), and family satisfaction [22]. Telehealth interventions have yielded promising results [23,24], and the acceptability [17,25-28] of telehealth has been previously established, further supporting its integration into comprehensive family-centered services [17,27,29,30].

Despite its established efficacy, the adoption of telehealth is low across rehabilitation, including in pediatric patients. An international survey conducted in August 2019 involving 1133 pediatric therapists from 76 countries reported that 3.9% of the pediatric therapists were using telehealth. However, in a follow-up survey completed in May 2020 (ie, during the public health restrictions imposed by the COVID-19 pandemic) with a subsample, 70.1% of the pediatric therapists had adopted telehealth. Many reported doing so without prior experience and lacked confidence, knowledge, and training in effective intervention strategies [12]. When asked about the support required to implement telehealth, training was by far the most frequently cited, and elements of training considered important included communication skills with families over the telephone and internet, safe and effective use of platforms, reliable assessment tools and processes, and intervention strategies for children of various ages and health conditions [12]. Although therapists' knowledge, skills, and attitudes toward telehealth can improve with time and experience [31], training and support are required for behavioral changes to occur [32-34]. Unfortunately, there is a paucity of evidence on how personal and contextual factors may influence telehealth training and support [35]. Targeting therapists' knowledge, skills, and attitudes associated with their intention to adopt telehealth and their role within family-centered services appears vital to the effective implementation of telehealth [35-43].

Family-centered telerehabilitation (FCT) is defined as pediatric rehabilitation that uses family-centered care practices while working with families remotely. Family-centered care is recognized as the best practice approach in pediatric rehabilitation [44]. Described as a partnership approach, family-centered care is based on the belief that the child's well-being and care needs are best supported within the family context through effective family-provider collaborations [45]. A central family-centered care tenet is the assumption that the processes of care delivery are as important to child and family outcomes as the specific characteristics of the clinical intervention delivered [45]. Family-centered care is characterized by practices that promote clinical flexibility; respect and dignity for families' perspectives, knowledge, strengths, and characteristics; effective information sharing (general and specific), partnership, and collaboration among parties to support decision-making; and coordinated and comprehensive care delivery [30]. Furthermore, family-centered care occurs in therapeutic environments that optimize the development of family-provider partnerships [46-49], in which parents are active participants in collaborative goal-setting therapy [50,51], planning, implementation, and evaluation [44,46,52,53] and where activities are integrated within daily routines and contexts such as home and community [54].

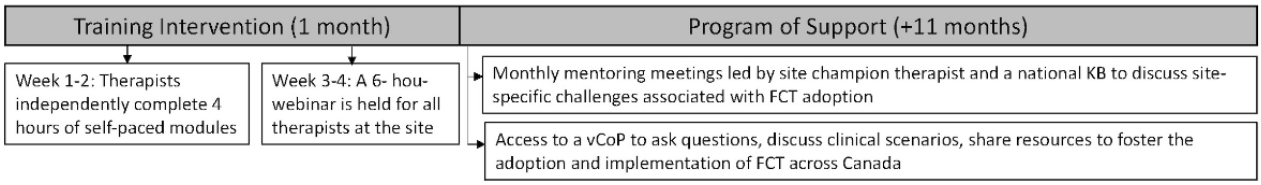
Telehealth offers additional opportunities to enhance family-centered care practices [30,55] as it provides convenient and flexible ways to partner with families, respecting individual family composition, characteristics, and constraints (eg, geographical, temporal, and financial) [21]. Furthermore, it allows real-time knowledge acquisition and information sharing about the child within their contexts and supports family decision-making and parents' psychosocial well-being such as decreased anxiety, stress, and depression [21]. Finally, telehealth has been recognized as an important addition to comprehensive care coordination and service delivery [56].

As a result of the pandemic, considerable momentum exists to support the uptake of FCT and foster its ongoing sustainable use within accessible and supportive services for the families of children with disabilities. Pediatric rehabilitation therapists, service managers, professional associations, policy makers, and patients are calling for resistance to *returning to normal* and instead are requesting help to sustain telehealth as part of the FCT continuum of care [28,29,56,57]. For this shift to occur, therapists require tools, training, and support. The proposed study aims to evaluate the implementation of a training intervention and program of support (TIPS) to enhance the adoption of FCT in pediatric rehabilitation centers across Canada and to assess its impact on wait times, families' perception of service quality, and costs.

Intervention

TIPS is an evidence-informed, multifaceted intervention, informed by empirical evidence in the field of pediatric rehabilitation and effective implementation strategies [16,58-62]. TIPS consists of the following components: (1) a 10-hour intensive training program offered to participating therapists at each site over a 1-month period, which includes 4 hours of self-paced learning modules and a 6-hour mandatory webinar and (2) an 11-month program of support composed of monthly mentoring meetings at each site led by the local therapist champion and a national, virtual community of practice. The virtual community of practice will be offered simultaneously to all participating therapists across Canada and facilitated by 3 national knowledge brokers—an occupational therapist, a physiotherapist, and a speech and language pathologist—experienced in FCT in pediatric rehabilitation. Figure 1 illustrates components and time frame of TIPS.

Figure 1. Training intervention and program of support description. FCT: family-centered telerehabilitation; KB: knowledge broker; vCoP: virtual community of practice.



The TIPS self-paced learning modules are informed by contemporary family-centered care frameworks and the family-oriented service continuum [30]. More specifically, they will address FCT core components and provide practice examples. Modules will address the following topics, as they apply to telehealth: (1) overview of family-centered care premises and principles (eg, information provision; respectful, supportive, and comprehensive care; and enabling partnerships) [63,64], (2) parent-professional collaborative partnerships (eg, goal cocreation, parent and child engagement, and role negotiation) and helpful FCT instruments and strategies [65], (3) coaching in the FCT context (eg, various approaches and strategies) [52,66], and (4) factors influencing service delivery model choice (ie, face-to-face or telehealth) [12]. As per best practice [16] and using education course creation software, several members of the study team will codevelop multimedia content (eg, videos and presentations) for the asynchronous training in consultation with pediatric clinicians and other experts (eg, parent partners, national organizational partners, inclusion and diversity experts, and knowledge keepers). We will upload the curriculum to a password-protected web-based platform for which a unique username and password will be required. Knowledge acquisition, based on specified learning objectives and key messages targeted in each training module, will be assessed through short quizzes. Completion of the asynchronous modular training and knowledge assessment will be recommended before undertaking the synchronous webinar.

A 6-hour synchronous webinar component will also be delivered to participants by members of the research team and 3 knowledge brokers. The webinars will engage therapists in discussions using case studies and interactive activities (eg, role play, vignettes, and simulations) to build their critical thinking on how to implement these practices in their context and with the families they serve. The webinar content will be adapted for each site in consultation with the local leadership team (ie, a site manager, a therapist champion, and a parent or patient partner). This coadaptation phase will ensure that activities and practice examples are tailored to individual site contexts and processes (eg, engagement practices, site clinical goal-setting processes, and service coordination as per team procedures) and that webinars are learner-centered and clinically relevant. Therapists will be encouraged to consider various asynchronous and real-time technologies, including email, telephone, web-based platforms, and videoconferencing systems that best respond to families' needs and preferences and are approved by their organizations. The research team will refrain from recommending specific technologies. There will be no prescribed frequency or duration for the FCT interventions; rather, therapist participants will work with families according to their goals and preferences, and site-specific organizational policies.

Finally, a program of support will be offered for the remaining year via monthly videoconference mentoring meetings and access to the virtual community of practice, which will be housed on the password-protected web-based platform. Monthly meetings will focus on sharing site-specific successes and challenges, proposing solutions and reporting results, as well as sharing practical evidence-informed resources. The evidence-informed virtual community of practice, facilitated by the 3 national knowledge brokers, will be used to canvas for solutions to address challenges at a national level; share successes; discuss specific cases for guidance, feedback, and input; and share useful tips, tricks, and resources [43,59,67-71].

Research Question and Study Objectives

Our hybrid implementation-effectiveness study examining the implementation of TIPS aims to answer the following research question: *Can TIPS enhance the adoption of FCT interventions by therapists working in different contexts?*

Specific objectives of the study include the following:

1. Implementation evaluation primary objectives: to assess therapists' intention to adopt FCT practices and evaluate therapists' fidelity to FCT practices
2. Implementation evaluation secondary objectives: to document the contextual variations required to coadapt TIPS to meet each site's needs and identify factors influencing FCT adoption and fidelity

For the implementation evaluation, we hypothesize that, in the short term (ie, 1 month after TIPS), therapists' intention to adopt FCT will increase minimally and their fidelity to FCT practices will improve minimally. After the implementation of TIPS (ie, >1 month), we expect that FCT adoption will increase and the fidelity of FCT practices will improve modestly. We also expect that engagement will fluctuate over time, across sites and therapists and will depend on therapist, client, organizational, and system factors.

1. Effectiveness evaluation: to compare service wait times, families' perceptions of service quality, and changes in service delivery before and after the implementation of TIPS and explore the costs (and cost savings) related to increased use of FCT

For the effectiveness evaluation, we hypothesize that for sites with the largest effect change in intention to adopt FCT and the fidelity of FCT practices, (1) wait times will significantly decrease and (2) families' perceptions of service quality will significantly improve after the implementation of TIPS. In relation to cost, we also expect families to experience cost savings after the implementation of TIPS and managers to report no additional costs incurred because of TIPS.

Methods

Study Design

The TIPS study is a 4-year, multimethod, hybrid type 3 implementation-effectiveness trial, registered with ClinicalTrials.gov (NCT05312827). Hybrid implementation-effectiveness trial designs are recommended when the traditional research pipeline of efficacy-effectiveness-implementation is too time-consuming and considered unethical, failing to adequately respond to the urgency of the expressed need [72]. TIPS is well suited to this type of hybrid implementation-effectiveness design because (1) there is momentum for its implementation within the health care system, (2) minimal risk is associated with the clinical intervention and the implementation strategy to support

generalizability, (3) there is strong face validity and indirect evidence for the clinical intervention and implementation strategy to support generalizability, and (4) there is evidence of feasibility for the implementation strategy and support in the clinical and organizational context under study [72]. A prospective, hybrid type 3 design reflects a collaborative ethos because it allows end users to inform the refinement and improvement of clinical interventions and their implementation processes [72,73]. Implementation strategies will be adjusted during the intervention refinement process in consultation with parents of children with a disability, clinicians supporting these families, individuals with experience implementing digital health, including health services managers, as well as the pediatric rehabilitation implementation sciences literature. Potential additional user-identified strategies will be integrated as part of the consultation process and according to the collaborative approach adopted. These strategies may allow previously unrecognized FCT implementation barriers to be acknowledged and addressed.

Study Settings

Participating sites are publicly funded organizations providing outpatient pediatric rehabilitation or child development services to children aged 0 to 12 years with, or at risk of, disability. *Disability* is used inclusively to recognize all medical diagnoses associated with limitations in functioning, such as cerebral palsy and autism spectrum disorder. The term *at risk* includes children presenting with delayed development who may not yet have a diagnosis but who experience functional limitations and qualify for rehabilitation services. The upper age limit of 12 years was chosen, as best practices regarding transition of care suggest that different relationships should be fostered with adolescents aged >12 years [74].

The 20 participating sites were selected to be representative based on various characteristics (eg, population, size, services provided, catchment area, and geography) posited to influence outcomes, the effects of which will be explored. These sites are clustered into 6 regions (one of which includes 3 provinces with a single participating site). To limit the risk of contamination, and as per the interrupted time series design, TIPS will be implemented in all sites in the same region during the same month and sequentially introduced across all regions, 2 months apart. Training will be conducted on a site-by-site basis to create team cohesion. The 2-month implementation interval between regions provides flexibility for organizing implementation and data collection activities.

Participants

Participants will be recruited from study sites according to the following eligibility criteria:

1. Managers (n=20; one per site): managers, or their delegates, responsible for rehabilitation services at the site and members of the local leadership team, will participate in the coadaptation of TIPS to their site. Managers may contribute to their site's monthly mentoring meetings; aid in the recruitment of therapists, parents, a therapist champion, and a parent-partner for their site; and complete site- or service-specific data collection instruments before and after the implementation of TIPS.
2. Therapists (n=600 with 50% anticipated response; n=300): physiotherapists, occupational therapists, or speech-language pathologists providing outpatient pediatric rehabilitation services to children aged 0 to 12 years at each site are recruited via the managers and are interested in using FCT. Therapists will participate in the TIPS program, complete data collection instruments as prescribed, and aid in parent recruitment.
3. Parents (n=20 per therapist with an anticipated response rate of 33%; n=2000 families per assessment time point): 1-time data collection will be undertaken with 2 samples (preimplementation and postimplementation samples) of parents or caregivers who received services (either in-person, virtually, or both) from at least one participating therapist in the previous 3 months.
4. Therapist champion (n=20; one per site): a therapist selected based on their telehealth experience and on peer recognition within their organization. Therapist champions are members of the local leadership team participating in the coadaptation of TIPS to their site and will oversee the monthly mentoring meetings and agree to report on the implementation process after the implementation of TIPS.
5. Parent or patient partner (n=20; one per site): parent or patient partners will primarily be recruited from family, parent, or patient advisory committees at the participating sites or, in the absence of such initiatives, from regional, provincial, or national patient engagement programs. As members of the local leadership team, parent or patient partners will participate in the coadaptation of TIPS to their site and could be called upon to contribute to their site's monthly mentoring meetings.

Recruitment procedures will be flexible and will be adapted to the preferences, policies, and procedures at each site. The recruitment of participants may be undertaken by email and sent directly to the potential participant by the research team (eg, therapists) or by the manager or therapist on behalf of the research team (eg, parents).

Sample Size

Number of Sites

A total of 20 sites across 8 Canadian provinces (grouped into 6 regions for the intervention rollout) are included in the study. Whenever possible, at least 3 sites per province were included to ensure sample diversity, enable the exploration of the provincial health systems' effects on the outcomes, and estimate site-related variations in outcomes. A total of 5 regions will include sites in the same province, whereas 1 region will consist of sites from 3 different provinces where only 1 rehabilitation program is available.

Number of Therapists

At the therapist level, implementation outcomes will be assessed 3 times during each period (before, during, and after the implementation of TIPS) for a total of 10 data collection time points. Assuming an autocorrelation of repeated measures of $r<0.3$, data collected from 300 therapists will provide >80%

power to detect moderate effect sizes (Cohen $d \geq 0.5$), using a first-order autoregressive segmented regression model [75] and a global type I error level of 5%, accounting for multiplicity of outcome assessments (Šidák correction) [76].

Number of Families

With a minimum expected sample size of 20 families per therapist being assessed before and after the implementation of TIPS, statistical power will be >90% to detect even small effect sizes ($0.1 < \text{Cohen } d < 0.3$) for the effectiveness outcomes (ie, change in wait times and change in families' perceptions of service quality).

Conceptual Framework

The structure of this study (Figure 2) builds on implementation science frameworks that aim to accelerate the translational research pipeline [72], bridging the current knowledge-to-practice gap. Specifically, the Consolidated Framework for Implementation Research [77] will guide the identification of factors influencing the adoption of FCT and will help engage leaders in participating sites in adapting the TIPS to their own contextual drivers, while maintaining the FCT key ingredients. A type 3 hybrid design will be used, primarily focusing on implementation indicators (bold text in Figure 2), while also collecting some effectiveness outcomes, with comparative assessments occurring at the therapist, service, or family level. This design is recommended when there is (1) momentum for implementation within the health care system, (2) strong face validity and indirect evidence for the clinical intervention and implementation strategy to support generalizability, (3) minimal risk associated with the clinical intervention and the implementation strategy, and (4) evidence of feasibility for the implementation strategy and support in the clinical and organizational context under study [72].

Data collection procedures are presented in Figure 2, and Table 1 presents an overview of the tools used and the participant groups involved. Details are provided in the next sections.

Figure 2. Conceptual framework and key concepts as per implementation-effectiveness design. FCT: family-centered telerehabilitation; TIPS: training intervention and program of support.

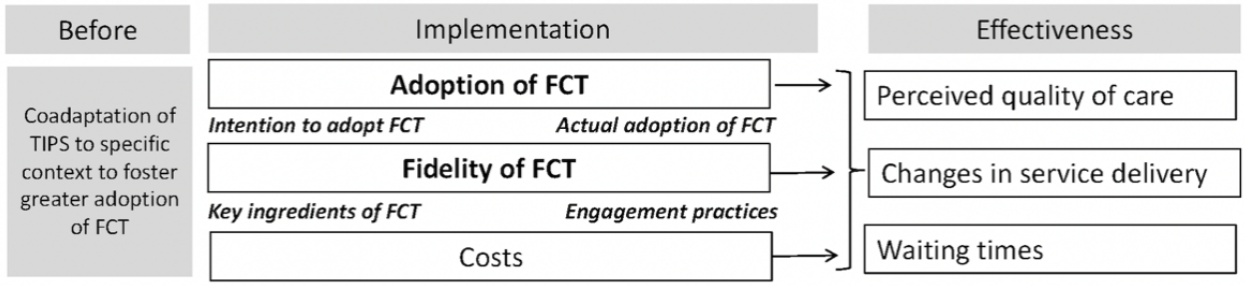


Table 1. Data collection measures, targeted participants, and time points.

Objective and measures	Participants	Time points									
		Before TIPS[a]			During TIPS				After TIPS		
		T–3[b]	T–2[c]	T–1[d]	T0[e]	T1[f]	T2[g]	T3[h]	T4[i]	T5[j]	T6[k]
Implementation evaluation											
Intention to adopt: ACCEPT-VFCC[l]	Therapists	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Fidelity to FCT[m] practices											
FCT fidelity checklist	Therapists	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
PRIME-SP[n]	Therapists	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Documentation of TIPS coadaptation											
Organizational readiness for eHealth questionnaire	Managers	✓									
Group discussion recordings	Leadership team		✓								
Influencing factors											
Monthly therapists' meetings recordings	Therapists					✓	✓	✓	✓		
Virtual community of practice discussion threads	Therapists					✓	✓	✓	✓		
Effectiveness evaluation											
Service wait times: time from service eligibility to first scheduled appointment	Managers	✓								✓	
Perceptions of service quality: MPOC-20[o]	Parents	✓								✓	
Changes in service delivery: semistructured interviews	Managers, therapist champions, therapists, and parents									✓	
Costs											
Organizational costs	Managers									✓	
Family costs	Parents	✓								✓	
Implementation cost (cost journal)	Research team		✓	✓	✓	✓	✓	✓	✓		

[a]TIPS: training intervention and program of support.

[b]T–3: 3 months before implementation.

[c]T–2: 2 months before implementation.

[d]T–1: 1 month before implementation.

[e]T0: implementation initiation.

[f]T1: 1 month after implementation + end of training intervention.

[g]T2: 4 months after implementation.

[h]T3: 8 months after implementation.

[i]T4: 12 months after implementation + end of support program.

[j]T5: 15 months after implementation.

[k]T6: 18 months after implementation+6 months after end of implementation.

[l]ACCEPT-VFCC: Assessment of Competencies and Contributors to Enhance Practice Transition to Virtual Family Centered Care Survey.

[m]FCT: family-centered telehealth.

[n]PRIME-SP: Pediatric Rehabilitation Intervention Measure of Engagement-Service Provider version.

[o]MPOC-20: Measure of Processes of Care-20.

Implementation Evaluation

Overview

The implementation evaluation will primarily seek *to assess therapists' intention to, and adoption of FCT, and their fidelity to FCT practices* (ie, objective 1). An interrupted time series was selected to assess primary implementation outcomes as recommended for research in real-world settings [78,79]. Unlike other design types that rely on randomization (eg, stepped wedge), this design allows for site leadership teams to be included in the discussion about the timing of the initiation of the intervention [80]. An interrupted time series consists of observing the same dependent variables over time with a break in the series of observations corresponding to the introduction of an intervention. If the intervention is effective, a change in the series' pre- and postintervention averages will be observed [79]. TIPS will be implemented in all sites in a specified jurisdiction during the same month and sequentially introduced across all jurisdictions, 2 months apart. Implementation data will be collected at least 3 times during each study period [81]: before (T–3 to T–1), during (T0 to T3), and after the implementation of TIPS (T4 to T6). The additional data collection time point at 1 month following the TIPS implementation will allow documentation of the short-term impact of the *training intervention* portion of TIPS (ie, the self-paced modules and webinar). Statistical analysis models will account for the inequivalent time intervals across study periods [75].

Data Collection

The *therapist's implementation questionnaire*, completed electronically by therapists at multiple time points (ie, T–3 to T6), will include questionnaires addressing the *primary objectives* and will comprise the measures discussed next.

To compare changes in therapists' intention to, and adoption of, FCT (ie, objective 1), the *Assessment of Competencies and Contributors to Enhance Practice Transition to Virtual Family Centered Care survey* will be used. This measure, based on the validated Theoretical Domain Framework Questionnaire template [81-83], examines 8 constructs across 41 items and considers factors, including knowledge and skills, social or professional role identity, beliefs in capacity-building attitudes, therapists' intention to adopt a virtual practice based on FCT, and environmental, patient-targeted, and other factors perceived to affect FCT implementation. Therapist participants will be asked to rate their responses to 36 specific statements associated with each theoretical domain framework domain using a 7-point Likert scale (1=strongly disagree to 7=strongly agree). A total of 4 open-ended or multiple-choice questions related to identification of facilitators and barriers and training preferences round out the instrument. Furthermore, the number of FCT sessions conducted in the proceeding months will document the actual adoption of FCT by therapists. Upon the initial completion (ie, at T–3), participants will be asked to respond to questions associated with sociodemographic characteristics (eg, professional education and work experience) and their previous telehealth experience, including prior training and use. This section will not be repeated at subsequent data collection time points (ie, T–2 to T6).

To monitor therapist fidelity to FCT practices (ie, objective 1b), the *FCT fidelity self-perceived checklist* and *Pediatric Rehabilitation Intervention Measure of Engagement-Service Provider version (PRIME-SP)* will be used. The *FCT fidelity self-perceived checklist*, a 4-item instrument, developed and pilot tested in a previous study [84], will measure therapists' perceptions of the perceived quality of 3 interventional behaviors associated with the FCT clinical intervention (ie, goal focused, active parent partnerships, and evidence of supportive and trusting parent-professional relationships) based on their last telehealth session. Each behavior, comprising 4 criteria, is scored on a 5-point Likert scale (0=behavior not implemented when it should have been to 4=all the identified behaviors were implemented when appropriate and within context). The fourth item assesses the representability of the chosen session to a typical parent-therapist interaction. The *PRIME-SP* will be used to measure therapists' views on how engagement practices were implemented with clients during their last telehealth session and the clients' responses [85]. It consists of an overall rating, as well as separate ratings of affective, cognitive, and behavioral aspects of a client's engagement state, based on a 4-point descriptive scale (disengaged to extremely engaged). Face, content, and construct validity of the PRIME-SP have been established [85].

Data Analysis

To evaluate implementation (ie, objective 1), longitudinal mixed modeling accounting for and considering potential methodological issues associated with an interrupted time series analysis (eg, autocorrelation and time-varying confounders) will be used to analyze implementation indicators (ie, Assessment of Competencies and Contributors to Enhance Practice Transition to Virtual Family Centered Care survey, therapists' self-reported FCT frequency, FCT fidelity self-perceived checklist, and PRIME-SP). Changes will be documented in the short term (ie, 1 month after TIPS introduction) and in the long term (ie, at the end of TIPS, 12 months after its introduction). Models will be covariate-adjusted to reduce potential confounding bias, including the therapists' characteristics (eg, gender and years of experience) and site characteristics (eg, service provided, geography, and general patient characteristics), to estimate associations of key explanatory variables alongside TIPS. Secondary analyses will explore the heterogeneity in changes of outcome measures across genders, sites, therapists, and health jurisdiction levels.

Secondary implementation objectives will be evaluated using a multimethod approach.

Data Collection and Analysis

The local leadership team, involved in *documenting the coadaptation of TIPS* (ie, objective 2), will be asked to complete a sociodemographic questionnaire to record their characteristics such as years of experience, level of expertise, and previous experience with telehealth services and technologies. An initial draft logic model will be developed by the research team based on the best evidence related to knowledge translation strategies to best address the FCT needs identified by therapists in a national survey and in recent publications. This draft will subsequently be presented to the local site team members for

feedback. A *discussion group format* [86] will be used to gather the local leadership team members' input, which will then be used to coadapt TIPS (ie, logic model, training curriculum, and materials) to site-specific needs. Throughout the coadaptation process, discussions will be audio recorded, meeting documents will be collected, and proposed adaptations and decisions made by local leadership team committee members, and their reasoning for these modifications will be recorded during the discussion group in real-time and in the TIPS logic model, training curriculum, and materials.

To *identify the factors influencing therapists' intention to adopt and use FCT* (ie, objective 3), *monthly mentoring meeting, audio recordings* and *materials* (eg, meeting agendas and suggested resources), *virtual community of practice discussion thread content*, and *semistructured interview audio recordings* with participating managers, therapist champions, therapists, and families after the implementation of TIPS will be collected. Data will be analyzed thematically using a deductive-inductive approach guided by the Consolidated Framework for Implementation Research domains [77].

Effectiveness Evaluation

Overview

To *evaluate TIPS effectiveness* (objective 4) and *costs* (objective 5), a mixed methods pre-post design has been chosen to measure the intervention effectiveness outcomes and costs using easily accessible service indicators and questionnaires administered to parents. To capture additional effects, semistructured interviews will also be conducted after the implementation of TIPS, with all participant groups. Instruments and processes are described in detail in further sections.

Data Collection

At the service level, the *site profile questionnaire*, completed by managers before and after the implementation, includes questions related to organizational readiness for eHealth [87] as well as clinically relevant *wait time indicators* (eg, the average service wait time for service) [88,89]. To estimate changes in wait times (before vs after), a confounder-adjusted analysis using generalized linear mixed effects models will use a log-link function to account for the typically right-skewed nature of time data. Estimated fixed (intervention) effects for the effectiveness outcomes will be reported with Šidák-corrected 95% CIs [76].

To evaluate changes in perceived service quality, the *family questionnaire* will be electronically distributed by managers or therapists to eligible families. It includes a sociodemographic questionnaire (eg, remoteness of location), and *Measurement of Processes of Care-20* (MPOC-20), a valid and reliable 20-item self-reported measure of parents' perceptions of the extent to which rehabilitation services are family-centered [90]. It contains five scales: (1) enabling and partnership, (2) providing general information, (3) providing specific information about the child, (4) coordinated and comprehensive care for the child and family, and (5) respectful and supportive care; it is scored on a 7-point Likert response scale, which indicates the extent to which the service provider engaged in the behavior (1=not at all to 7=to a very great extent). Each scale yields its own score, and no total score is calculated. Data will be analyzed using generalized linear mixed effects models with nested random effects (families within therapists within sites) to control for the correlated nature of the data (ie, the possibility that families have responded once or twice to the MPOC-20) and to account for therapist and site cluster effects. Analyses will be conducted for each of the 5 MPOC-20 domains and controlled for the same confounding variables described in the analysis for objective 1, as well as for family-level variables (eg, sociocultural background, child's age, and gender).

To explore all changes in service delivery (both negative and positive), participants will be invited to participate in audio-recorded *semistructured interviews* after the implementation of TIPS. The sample will include all managers, some therapists (all local site champions and a subsample of therapists showing high or low adoption in different sites), and parents with diverse sociocultural characteristics, levels of perception of quality of care, and experience with FCT. Interview data will be analyzed thematically using an inductive approach to better understand the breadth and depth of changes to pediatric rehabilitation service delivery according to various stakeholder perspectives. Integration of quantitative and qualitative data using the aforementioned explanatory approach [91] will allow us to uncover the anticipated and unanticipated effects of FCT on pediatric rehabilitation service delivery.

To *explore costs*, an economic evaluation following a health care perspective as recommended by the Canadian Agency for Drugs and Technologies in Health [92,93] will be used primarily. The research team will maintain a *costs journal* related to TIPS implementation (eg, knowledge brokers' salary). Costs relating to therapist participation in TIPS (time × average salary) and those resulting from changes in the organizational setting (eg, telehealth equipment) will be documented in the managers' *site profile questionnaire*. *Families' costs and savings*, including impact on travel time, parking costs, missed work, and costs related to equipment or internet, will be included in the *family questionnaire*. The total costs related to the implementation of the TIPS will be calculated (ie, additional therapists and knowledge brokers' time and salary), as well as costs per participating therapist and costs per site accounting for different organizational characteristics. Relative cost, an estimation of costs per session, cost per client seen by the therapist, and incremental ratios (ie, change in costs to use the TIPS divided by change in the primary implementation outcomes measures and secondary effectiveness measures) will also be computed. Finally, societal costs (ie, savings for families in decreased travel time, parking, missed work, and costs related to equipment or internet) will be explored for robustness analysis.

Ethics Approval

The research ethics committees overseeing the 20 participating sites will approve this research project. At the time of manuscript submission, the Research Ethics Board of the *Centre intégré de santé et des services sociaux de l'Estrie—Centre hospitalier universitaire de Sherbrooke* approved this project (ID MP-31-2022-4546) along with the Health Research Ethics Board-Health Panel at the University of Alberta (ID

Pro00119976). Ethics approvals have also been submitted to the Hamilton Integrated Research Ethics Board and the Human Ethics Board at the University of British Columbia. Finally, ethics submissions are in preparation for the Interdisciplinary Committee on Ethics in Human Research at the Memorial University of Newfoundland, the Izaak Walton Killam Research Ethics Board, the University of Manitoba Ethics Board, and the University of Saskatchewan Human Ethics Board. Informed consent will be obtained before data collection from the participating managers, therapists, and parents. Participants will be informed that the study data will not constitute an evaluation of their professional performance. Data collection will occur entirely on the web using secure data collection and management solutions.

Results

Funding was provided by the Canadian Institutes for Health Research on July 22, 2021. All 20 sites were recruited for the funding application. Ethics approval for the first participating site (ID MP-31-2022-4546) was received in February 2022 and for the second site (ID Pro00119976) in July 2022; submissions are either in preparation or pending in the other jurisdictions. To prepare sites, manager meetings were conducted between October 2021 and November 2021 to review responsibilities (eg, identification of site leadership members) and discuss timing for study initiation. As a result, data collection is anticipated to start in September 2022 and conclude by September 2024. Data analysis will occur concurrently with data collection until late 2024. Study- and site-specific results will be available for dissemination from early- to mid-2025, with publications available throughout the same year.

Discussion

Overview

Telehealth is a feasible, acceptable, and cost-effective service delivery option for pediatric rehabilitation for children experiencing, or at risk for, disability, and has established effectiveness in improving service access, child outcomes, and family satisfaction with pediatric rehabilitation [12,15,16,19,28,29]. However, before the pandemic, adoption in pediatric rehabilitation was low [12,35]. Despite the recent rapid uptake and dramatic increase in the use of telehealth owing to the public health restrictions imposed by the pandemic, many pediatric therapists provided telehealth without appropriate training and support [12].

To fill this gap, this hybrid implementation-effectiveness study aims to (1) evaluate whether the implementation of TIPS will enhance the adoption of FCT interventions by therapists working in different contexts and the contextual factors that may influence their adoption, (2) assess TIPS effectiveness on wait times and families' perceptions of service quality, and (3) explore costs from a health care perspective. Therapists' intention to adopt FCT is expected to increase minimally in the short term (ie, 1 month after the implementation of TIPS), as is their fidelity to FCT practices. Modest increases in adoption and in fidelity in the longer term (ie, >1 month after TIPS), with fluctuating engagement over time dependent on therapist, family, organizational, and system factors are anticipated. For sites with the largest effect change in intention to adopt FCT and fidelity of FCT practices, it is hypothesized that wait times will significantly decrease, whereas families' perceptions of service quality will significantly improve after TIPS implementation. Finally, families' cost savings after TIPS are anticipated, with managers reporting no additional cost incurred because of TIPS.

Moreover, we hope that this study will generate the knowledge required on how to support therapists in implementing FCT practices within pediatric rehabilitation services. We will also identify the contextual factors that may influence therapists' adoption of telehealth and affect telehealth effectiveness at therapist, service, and family levels. As a prospective study, this knowledge will be contextualized to support therapists working in varied settings, building local capacity, and ensuring pediatric therapists have the established skills needed to deliver FCT interventions effectively. Study- and site-specific findings will be disseminated to organizational partners via webinar presentations. All training materials will be made readily available across Canada and internationally to facilitate the development of telehealth knowledge and skills more broadly in the current and upcoming national and international pediatric rehabilitation workforce. Training materials, implementation strategies, and study findings may also assist pediatric rehabilitation organizations and their leaders in generating appropriate policies, ongoing training opportunities, and procedures to ensure sustained delivery of comprehensive, high-quality rehabilitation service models, which include telehealth as an option. Finally, the study findings may also be the catalyst for the development of a set of required competencies for physiotherapists, occupational therapists, and speech-language pathologists who use telehealth to deliver rehabilitation services. To ensure wide dissemination to a variety of interested audiences, the study results will be shared as publications, conference presentations, on social media, and via newsletters.

Strengths and Limitations

The strengths of the TIPS study lie in its implementation in various real-world contexts and its use of a hybrid implementation-effectiveness approach. The multimethod design will allow for the inclusion of multiple implementation measures and an in-depth exploration of the contextual factors affecting the implementation and adoption of FCT. Finally, the multilevel (ie, service, organizational, and consumer) assessment of effectiveness will create a comprehensive overview of its impact. In addition to leveraging implementation science theory and evidence, the research processes are carefully designed to ensure the inclusion and integration of key stakeholder implementation knowledge at strategic moments (eg, before implementation and following the training) throughout the study, keeping the focus on the end users, to ensure implementation success. The participation of multiple and varied pediatric rehabilitation services allows for the examination of TIPS implementation and its impacts across various diverse real-world contexts that exist in Canada. It is hoped that the triangulation of a comprehensive range of both qualitative and quantitative data will provide useful insights into the wide range of factors affecting FCT implementation and adoption and the plethora

of potential resulting effects. However, this study has some limitations. First, as recruitment is being facilitated through the site managers, the possibility of a considerable selection bias in participant recruitment (ie, therapists and parents) exists. The individuals approached may share similar characteristics, views, and perspectives on this service option, which could limit the variability in our sample. Second, this study relies on self-reported outcome measures, some of which have been developed specifically for this study, and for which psychometric properties are being assessed. Third, multiple data collection time points increase the risk for missing data. Some strategies have been planned to mitigate these constraints; those that persist will be acknowledged in the reporting of the results to assist in appropriate interpretation of the findings.

Conclusions

The TIPS study will inform the contextual implementation of a training and support program to enhance the adoption of FCT. This study will assess the effectiveness of a training and support program in changing pediatric therapists' FCT adoption, parents' perceptions of service quality, service access wait times, and the cost associated with this service option. The study outcomes will increase pediatric rehabilitation service delivery options for families, improve access to services, and foster greater well-being for families of children with, or at risk of, disability.

Acknowledgments

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Data Availability

The data sets generated or analyzed during this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

This study was conceived and designed by CC and KH, with methodological expertise provided by IG, MCB, TP, and TS. KH and JB prepared the manuscript and IG, MCB, and MP critically revised it. All authors reviewed and approved the final draft of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
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[PDF File (Adobe PDF File), 90 KB - resprot_v11i10e40218_app1.pdf]

References

1. Feldman DE, Swaine B, Gosselin J, Meshefedjian G, Grilli L. Is waiting for rehabilitation services associated with changes in function and quality of life in children with physical disabilities? Phys Occup Ther Pediatr 2008;28(4):291-304; discussion 305. [doi: 10.1080/01942630802224868] [Medline: 19042472]
2. Grilli L, Feldman D, Swaine B, Gosselin J, Champagne F, Pineault R. Wait times for paediatric rehabilitation. Healthc Policy 2007 Feb 15;2(3). [doi: 10.12927/hcpol.2007.18681]
3. Miller A, Armstrong R, Mâsse LC, Klassen A, Shen J, O'Donnell ME. Waiting for child developmental and rehabilitation services: an overview of issues and needs. Dev Med Child Neurol 2008 Nov;50(11):815-821 [FREE Full text] [doi: 10.1111/j.1469-8749.2008.03113.x] [Medline: 18811706]
4. Camden C, Swaine B, Levasseur M. Did waiting times really decrease following a service reorganization? Results from a retrospective study in a pediatric rehabilitation program in Québec. Disabil Rehabil 2013 May 16;35(9):719-724. [doi: 10.3109/09638288.2012.705948] [Medline: 22897135]
5. Phoenix M, Jack SM, Rosenbaum PL, Missiuna C. Parents' attendance, participation and engagement in children's developmental rehabilitation services: part 1. Contextualizing the journey to child health and happiness. Disabil Rehabil 2020 Jul;42(15):2141-2150. [doi: 10.1080/09638288.2018.1555617] [Medline: 30669893]
6. Porterfield SL, McBride TD. The effect of poverty and caregiver education on perceived need and access to health services among children with special health care needs. Am J Public Health 2007 Feb;97(2):323-329. [doi: 10.2105/ajph.2004.055921]
7. Bentenuto A, Mazzoni N, Giannotti M, Venuti P, de Falco S. Psychological impact of Covid-19 pandemic in Italian families of children with neurodevelopmental disorders. Res Dev Disabil 2021 Feb;109:103840 [FREE Full text] [doi: 10.1016/j.ridd.2020.103840] [Medline: 33383468]

8. Cacioppo M, Bouvier S, Bailly R, Houx L, Lempereur M, Mensah-Gourmel J, ECHO Group. Emerging health challenges for children with physical disabilities and their parents during the COVID-19 pandemic: the ECHO French survey. Ann Phys Rehabil Med 2021 May;64(3):101429 [FREE Full text] [doi: 10.1016/j.rehab.2020.08.001] [Medline: 32818674]
9. Dhiman S, Sahu P, Reed W, Ganesh G, Goyal R, Jain S. Impact of COVID-19 outbreak on mental health and perceived strain among caregivers tending children with special needs. Res Dev Disabil 2020 Dec;107:103790 [FREE Full text] [doi: 10.1016/j.ridd.2020.103790] [Medline: 33091712]
10. Grumi S, Provenzi L, Gardani A, Aramini V, Dargenio E, Naboni C, Engaging with Families through On-line Rehabilitation for Children during the Emergency (EnFORCE) Group. Rehabilitation services lockdown during the COVID-19 emergency: the mental health response of caregivers of children with neurodevelopmental disabilities. Disabil Rehabil 2021 Jan 10;43(1):27-32. [doi: 10.1080/09638288.2020.1842520] [Medline: 33167738]
11. Arim R, Findlay L, Kohen D. The impact of the COVID-19 pandemic on Canadian families of children with disabilities. Statistics Canada. 2020 Aug 27. URL: https://www150.statcan.gc.ca/n1/pub/45-28-0001/2020001/article/00066-eng.htm [accessed 2021-03-29]
12. Camden C, Silva M. Pediatric teleheath: opportunities created by the COVID-19 and suggestions to sustain its use to support families of children with disabilities. Phys Occup Ther Pediatr 2021;41(1):1-17. [doi: 10.1080/01942638.2020.1825032] [Medline: 33023352]
13. Murphy A, Pinkerton L, Bruckner E, Risser H. The impact of the novel coronavirus disease 2019 on therapy service delivery for children with disabilities. J Pediatr 2021 Apr;231:168-77.e1 [FREE Full text] [doi: 10.1016/j.jpeds.2020.12.060] [Medline: 33359629]
14. Cason J, Behl D, Ringwalt S. Overview of states' use of telehealth for the delivery of early intervention (IDEA part C) services. Int J Telerehab 2012 Dec 14;4(2). [doi: 10.5195/ijt.2012.6105]
15. Edelstein H, Schippke J, Sheffe S, Kingsnorth S. Children with medical complexity: a scoping review of interventions to support caregiver stress. Child Care Health Dev 2017 May;43(3):323-333. [doi: 10.1111/cch.12430] [Medline: 27896838]
16. Levac D, Glegg SM, Camden C, Rivard LM, Missiuna C. Best practice recommendations for the development, implementation, and evaluation of online knowledge translation resources in rehabilitation. Phys Ther 2015 Apr;95(4):648-662. [doi: 10.2522/ptj.20130500] [Medline: 25301966]
17. Little L, Pope E, Wallisch A, Dunn W. Occupation-based coaching by means of telehealth for families of young children with autism spectrum disorder. Am J Occup Ther 2018;72(2):7202205020p1-7202205020p7. [doi: 10.5014/ajot.2018.024786] [Medline: 29426380]
18. Bradford N, Caffery L, Smith A. Telehealth services in rural and remote Australia: a systematic review of models of care and factors influencing success and sustainability. Rural Remote Health 2016;16(4):3808 [FREE Full text] [Medline: 27744708]
19. Edirippulige S, Reyno J, Armfield NR, Bambling M, Lloyd O, McNevin E. Availability, spatial accessibility, utilisation and the role of telehealth for multi-disciplinary paediatric cerebral palsy services in Queensland. J Telemed Telecare 2016 Oct;22(7):391-396. [doi: 10.1177/1357633X15610720] [Medline: 26519377]
20. Heitzman-Powell L, Buzhardt J, Rusinko L, Miller T. Formative evaluation of an ABA outreach training program for parents of children with autism in remote areas. Focus Autism Other Dev Disabl 2013 Oct 14;29(1):23-38. [doi: 10.1177/1088357613504992]
21. Ingersoll B, Berger NI. Parent engagement with a telehealth-based parent-mediated intervention program for children with autism spectrum disorders: predictors of program use and parent outcomes. J Med Internet Res 2015 Oct 06;17(10):e227 [FREE Full text] [doi: 10.2196/jmir.4913] [Medline: 26443557]
22. Camden C, Pratte G, Fallon F, Couture M, Berbari J, Tousignant M. Diversity of practices in telerehabilitation for children with disabilities and effective intervention characteristics: results from a systematic review. Disabil Rehabil 2020 Dec;42(24):3424-3436. [doi: 10.1080/09638288.2019.1595750] [Medline: 30978110]
23. Alonazi A. Effectiveness and acceptability of telerehabilitation in physical therapy during COVID-19 in children: findings of a systematic review. Children (Basel) 2021 Nov 29;8(12):1101 [FREE Full text] [doi: 10.3390/children8121101] [Medline: 34943295]
24. Tamboosi M, Al-Khathami S, El-Shamy S. The effectiveness of tele-rehabilitation on improvement of daily living activities in children with cerebral palsy: narrative review. Bull Fac Phys Ther 2021 Dec 24;26(1):1-12. [doi: 10.1186/s43161-021-00055-7]
25. Camden C, Couture M, Pratte G, Morin M, Roberge P, Poder T, et al. Recruitment, use, and satisfaction with a web platform supporting families of children with suspected or diagnosed developmental coordination disorder: a randomized feasibility trial. Dev Neurorehabil 2019 Oct 01;22(7):470-478. [doi: 10.1080/17518423.2018.1523243] [Medline: 30273508]
26. Dostie R, Gaboury I, Cinar E, Camden C. Acceptability of pediatric telerehabilitation interventions provided by physical therapists and occupational therapists-a scoping review. Phys Occup Ther Pediatr 2022 Apr 19:1-20. [doi: 10.1080/01942638.2022.2064203] [Medline: 35440285]
27. Little L, Wallisch A, Pope E, Dunn W. Acceptability and cost comparison of a telehealth intervention for families of children with autism. Infants Young Children 2018;31(4):275-286. [doi: 10.1097/IYC.0000000000000126]

28. Tanner K, Bican R, Boster J, Christensen C, Coffman C, Fallieras K, et al. Feasibility and acceptability of clinical pediatric telerehabilitation services. Int J Telerehabil 2020 Dec 08;12(2):43-52 [FREE Full text] [doi: 10.5195/ijt.2020.6336] [Medline: 33520094]
29. Valentine A, Hall S, Young E, Brown BJ, Groom MJ, Hollis C, et al. Implementation of telehealth services to assess, monitor, and treat neurodevelopmental disorders: systematic review. J Med Internet Res 2021 Jan 20;23(1):e22619 [FREE Full text] [doi: 10.2196/22619] [Medline: 33326409]
30. King G, Williams L, Hahn Goldberg S. Family-oriented services in pediatric rehabilitation: a scoping review and framework to promote parent and family wellness. Child Care Health Dev 2017 May;43(3):334-347. [doi: 10.1111/cch.12435] [Medline: 28083952]
31. Bierbooms J, van HM, IJsselsteijn W, De Kort Y, Feijt M, Bongers I. The 'new normal' in mental healthcare: will the COVID-19 pandemic be the catalyst for online mental healthcare? Serious Games Professional Skills 2020 Jun (forthcoming).
32. Barnett JE, Kolmes K. The practice of tele-mental health: ethical, legal, and clinical issues for practitioners. Pract Innov 2016 Mar;1(1):53-66. [doi: 10.1037/pri0000014]
33. Goldstein F, Glueck D. Developing rapport and therapeutic alliance during telemental health sessions with children and adolescents. J Child Adolesc Psychopharmacol 2016 Apr;26(3):204-211. [doi: 10.1089/cap.2015.0022] [Medline: 26491890]
34. Malliaras P, Merolli M, Williams C, Caneiro J, Haines T, Barton C. 'It's not hands-on therapy, so it's very limited': telehealth use and views among allied health clinicians during the coronavirus pandemic. Musculoskelet Sci Pract 2021 Apr;52:102340 [FREE Full text] [doi: 10.1016/j.msksp.2021.102340] [Medline: 33571900]
35. Edirippulige S, Armfield N. Education and training to support the use of clinical telehealth: a review of the literature. J Telemed Telecare 2016 Jul 08;23(2):273-282. [doi: 10.1177/1357633x16632968]
36. Faija C, Connell J, Welsh C, Ardern K, Hopkin E, Gellatly J, et al. What influences practitioners' readiness to deliver psychological interventions by telephone? A qualitative study of behaviour change using the theoretical domains framework. BMC Psychiatry 2020 Jul 16;20(1):371 [FREE Full text] [doi: 10.1186/s12888-020-02761-3] [Medline: 32677917]
37. Glegg S, Holsti L, Stanton S, Hanna S, Velikonja D, Ansley B, et al. Evaluating change in virtual reality adoption for brain injury rehabilitation following knowledge translation. Disabil Rehabil Assist Technol 2017 Apr;12(3):217-226. [doi: 10.3109/17483107.2015.1111944] [Medline: 28508725]
38. Glegg S, Levac D. Barriers, facilitators and interventions to support virtual reality implementation in rehabilitation: a scoping review. PM R 2018 Nov;10(11):1237-51.e1 [FREE Full text] [doi: 10.1016/j.pmrj.2018.07.004] [Medline: 30503231]
39. Glegg SM, Livingstone R, Montgomery I. Facilitating interprofessional evidence-based practice in paediatric rehabilitation: development, implementation and evaluation of an online toolkit for health professionals. Disabil Rehabil 2016;38(4):391-399. [doi: 10.3109/09638288.2015.1041616] [Medline: 25924019]
40. Levac D, Glegg S, Colquhoun H, Miller P, Noubary F. Virtual reality and active videogame-based practice, learning needs, and preferences: a cross-Canada survey of physical therapists and occupational therapists. Games Health J 2017 Aug;6(4):217-228. [doi: 10.1089/g4h.2016.0089] [Medline: 28816511]
41. Levac D, Glegg S, Miller P, Colquhoun H, Wright V, Young R. A survey of Canadian physiotherapists' and occupational therapists' use of virtual reality and active video games in pediatric rehabilitation. In: Proceedings of the American Academy of Cerebral Palsy and Developmental Medicine (AACPDM) 70th Annual Meeting. 2016 Presented at: American Academy of Cerebral Palsy and Developmental Medicine (AACPDM) 70th Annual Meeting; Sep, 2016; Hollywood, FL.
42. Levac D, Glegg S, Sveistrup H, Colquhoun H, Miller PA, Finestone H, et al. A knowledge translation intervention to enhance clinical application of a virtual reality system in stroke rehabilitation. BMC Health Serv Res 2016 Oct 06;16(1):557 [FREE Full text] [doi: 10.1186/s12913-016-1807-6] [Medline: 27716179]
43. Ross J, Stevenson F, Lau R, Murray E. Factors that influence the implementation of e-health: a systematic review of systematic reviews (an update). Implement Sci 2016 Oct 26;11(1):146 [FREE Full text] [doi: 10.1186/s13012-016-0510-7] [Medline: 27782832]
44. Law M, Hanna S, King G, Hurley P, King S, Kertoy M, et al. Factors affecting family-centred service delivery for children with disabilities. Child Care Health Dev 2003 Sep;29(5):357-366. [doi: 10.1046/j.1365-2214.2003.00351.x] [Medline: 12904243]
45. McCarthy E, Guerin S. Family-centred care in early intervention: a systematic review of the processes and outcomes of family-centred care and impacting factors. Child Care Health Dev 2022 Jan;48(1):1-32. [doi: 10.1111/cch.12901] [Medline: 34324725]
46. Dunst CJ, Trivette CM, Hamby DW. Meta-analysis of family-centered helpgiving practices research. Ment Retard Dev Disabil Res Rev 2007;13(4):370-378. [doi: 10.1002/mrdd.20176] [Medline: 17979208]
47. Espe-Sherwindt M. Family-centred practice: collaboration, competency and evidence. Support Learn 2008 Aug;23(3):136-143. [doi: 10.1111/j.1467-9604.2008.00384.x]
48. King G, Chiarello L. Family-centered care for children with cerebral palsy: conceptual and practical considerations to advance care and practice. J Child Neurol 2014 Aug;29(8):1046-1054. [doi: 10.1177/0883073814533009] [Medline: 24810084]

49. Kuo DZ, Houtrow AJ, Arango P, Kuhlthau KA, Simmons JM, Neff JM. Family-centered care: current applications and future directions in pediatric health care. Matern Child Health J 2012 Feb 12;16(2):297-305 [FREE Full text] [doi: 10.1007/s10995-011-0751-7] [Medline: 21318293]
50. Pritchard-Wiart L, Phelan SK. Goal setting in paediatric rehabilitation for children with motor disabilities: a scoping review. Clin Rehabil 2018 Jul 23;32(7):954-966. [doi: 10.1177/0269215518758484] [Medline: 29473440]
51. Wiart L. Goal setting in paediatric rehabilitation. In: Siegert R, Levack W, editors. Rehabilitation Goal Setting: Theory, Practice and Evidence. Boca Raton: CRC Press; 2014:291-304.
52. Akhbari Ziegler S, Hadders-Algra M. Coaching approaches in early intervention and paediatric rehabilitation. Dev Med Child Neurol 2020 May;62(5):569-574 [FREE Full text] [doi: 10.1111/dmcn.14493] [Medline: 32065385]
53. Moreau K, Cousins J. Program evaluation in family-centred pediatric rehabilitation settings. Eval J Australasia 2011 Sep 01;11(2):3-13. [doi: 10.1177/1035719X1101100202]
54. Ward R, Reynolds J, Pieterse B, Elliott C, Boyd R, Miller L. Utilisation of coaching practices in early interventions in children at risk of developmental disability/delay: a systematic review. Disabil Rehabil 2020 Oct;42(20):2846-2867. [doi: 10.1080/09638288.2019.1581846] [Medline: 31021669]
55. Jeglinsky I, Autti-Rämö I, Brogren Carlberg E. Two sides of the mirror: parents' and service providers' view on the family-centredness of care for children with cerebral palsy. Child Care Health Dev 2012 Jan;38(1):79-86. [doi: 10.1111/j.1365-2214.2011.01305.x] [Medline: 21902711]
56. Rosenbaum PL, Silva M, Camden C. Let's not go back to 'normal'! lessons from COVID-19 for professionals working in childhood disability. Disabil Rehabil 2021 Apr 23;43(7):1022-1028. [doi: 10.1080/09638288.2020.1862925] [Medline: 33355010]
57. Graham ID, Kothari A, McCutcheon C, Integrated Knowledge Translation Research Network Project Leads. Moving knowledge into action for more effective practice, programmes and policy: protocol for a research programme on integrated knowledge translation. Implement Sci 2018 Feb 02;13(1):22 [FREE Full text] [doi: 10.1186/s13012-017-0700-y] [Medline: 29394932]
58. Camden C, Shikako-Thomas K, Nguyen T, Graham E, Thomas A, Sprung J, et al. Engaging stakeholders in rehabilitation research: a scoping review of strategies used in partnerships and evaluation of impacts. Disabil Rehabil 2015 Sep 22;37(15):1390-1400. [doi: 10.3109/09638288.2014.963705] [Medline: 25243763]
59. Camden C, Rivard L, Hurtubise K, Héguy L, Berbari J. Can a community of practice improve physical therapists' self-perceived practice in developmental coordination disorder? Phys Ther 2017 Jul 01;97(7):746-755. [doi: 10.1093/ptj/pzx041] [Medline: 28444245]
60. Gaid D, Ahmed S, Alhasani R, Thomas A, Bussières A. Determinants that influence knowledge brokers' and opinion leaders' role to close knowledge practice gaps in rehabilitation: a realist review. J Eval Clin Pract 2021 Aug 25;27(4):836-846. [doi: 10.1111/jep.13482] [Medline: 32975895]
61. Quinn ED, Cook A, Rowland C. An online community of practice to improve intervention for individuals with complex communication needs. Augment Altern Commun 2019 Jun;35(2):142-147. [doi: 10.1080/07434618.2019.1566400] [Medline: 30900476]
62. Schleifer Taylor J, Verrier MC, Landry MD. What do we know about knowledge brokers in paediatric rehabilitation? A systematic search and narrative summary. Physiother Can 2014;66(2):143-152 [FREE Full text] [doi: 10.3138/ptc.2012-71] [Medline: 24799751]
63. Almasri NA, An M, Palisano RJ. Parents' perception of receiving family-centered care for their children with physical disabilities: a meta-analysis. Phys Occup Ther Pediatr 2018 Nov 28;38(4):427-443. [doi: 10.1080/01942638.2017.1337664] [Medline: 28753054]
64. Bamm EL, Rosenbaum P. Family-centered theory: origins, development, barriers, and supports to implementation in rehabilitation medicine. Arch Phys Med Rehabil 2008 Aug;89(8):1618-1624. [doi: 10.1016/j.apmr.2007.12.034] [Medline: 18586223]
65. An M, Palisano R. Family-professional collaboration in pediatric rehabilitation: a practice model. Disabil Rehabil 2014;36(5):434-440. [doi: 10.3109/09638288.2013.797510] [Medline: 23713990]
66. Schwellnus H, King G, Thompson L. Client-centred coaching in the paediatric health professions: a critical scoping review. Disabil Rehabil 2015;37(15):1305-1315. [doi: 10.3109/09638288.2014.962105] [Medline: 25289943]
67. Pratte G, Hurtubise K, Rivard L, Berbari J, Camden C. Developing a web platform to support a community of practice: a mixed methods study in pediatric physiotherapy. J Contin Educ Health Prof 2018;38(1):19-24. [doi: 10.1097/CEH.0000000000000185] [Medline: 29369269]
68. Cameron D, Russell D, Rivard L, Darrah J, Palisano R. Knowledge brokering in children's rehabilitation organizations: perspectives from administrators. J Contin Educ Health Prof 2011;31(1):28-33. [doi: 10.1002/chp.20098] [Medline: 21425357]
69. Hurtubise K, Rivard L, Héguy L, Berbari J, Camden C. Virtual knowledge brokering: describing the roles and strategies used by knowledge brokers in a pediatric physiotherapy virtual community of practice. J Contin Educ Health Prof 2016;36(3):186-194. [doi: 10.1097/ceh.0000000000000101]

70. Rivard L, Russell D, Roxborough L, Ketelaar M, Bartlett D, Rosenbaum P. Promoting the use of measurement tools in practice: a mixed-methods study of the activities and experiences of physical therapist knowledge brokers. Phys Ther 2010 Nov;90(11):1580-1590. [doi: 10.2522/ptj.20090408] [Medline: 20813819]
71. Russell DJ, Rivard LM, Walter SD, Rosenbaum PL, Roxborough L, Cameron D, et al. Using knowledge brokers to facilitate the uptake of pediatric measurement tools into clinical practice: a before-after intervention study. Implement Sci 2010 Nov 23;5(1):92 [FREE Full text] [doi: 10.1186/1748-5908-5-92] [Medline: 21092283]
72. Curran G, Bauer M, Mittman B, Pyne J, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. Med Care 2012 Mar;50(3):217-226 [FREE Full text] [doi: 10.1097/MLR.0b013e3182408812] [Medline: 22310560]
73. Bernet AC, Willens DE, Bauer MS. Effectiveness-implementation hybrid designs: implications for quality improvement science. Implementation Sci 2013;8(Suppl 1):S2-S7. [doi: 10.1186/1748-5908-8-S1-S2]
74. Naylor MD, Shaid EC, Carpenter D, Gass B, Levine C, Li J, et al. Components of comprehensive and effective transitional care. J Am Geriatr Soc 2017 Jun 03;65(6):1119-1125 [FREE Full text] [doi: 10.1111/jgs.14782] [Medline: 28369722]
75. Zhang F, Wagner AK, Ross-Degnan D. Simulation-based power calculation for designing interrupted time series analyses of health policy interventions. J Clin Epidemiol 2011 Nov;64(11):1252-1261. [doi: 10.1016/j.jclinepi.2011.02.007] [Medline: 21640554]
76. Vickerstaff V, Omar RZ, Ambler G. Methods to adjust for multiple comparisons in the analysis and sample size calculation of randomised controlled trials with multiple primary outcomes. BMC Med Res Methodol 2019 Jun 21;19(1):129 [FREE Full text] [doi: 10.1186/s12874-019-0754-4] [Medline: 31226934]
77. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. Implement Sci 2009 Aug 07;4(1):50 [FREE Full text] [doi: 10.1186/1748-5908-4-50] [Medline: 19664226]
78. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. Int J Epidemiol 2017 Feb 01;46(1):348-355 [FREE Full text] [doi: 10.1093/ije/dyw098] [Medline: 27283160]
79. Lopez Bernal J, Soumerai S, Gasparrini A. A methodological framework for model selection in interrupted time series studies. J Clin Epidemiol 2018 Nov;103:82-91. [doi: 10.1016/j.jclinepi.2018.05.026] [Medline: 29885427]
80. Handley MA, Lyles CR, McCulloch C, Cattamanchi A. Selecting and improving quasi-experimental designs in effectiveness and implementation research. Annu Rev Public Health 2018 Apr 01;39:5-25 [FREE Full text] [doi: 10.1146/annurev-publhealth-040617-014128] [Medline: 29328873]
81. Cox N, Alison J, Holland A. Interventions for promoting physical activity in people with cystic fibrosis. Cochrane Database Syst Rev 2013 Dec 13(12):CD009448 [FREE Full text] [doi: 10.1002/14651858.CD009448.pub2] [Medline: 24338214]
82. Huijg JM, Gebhardt WA, Dusseldorp E, Verheijden MW, van der Zouwe N, Middelkoop BJ, et al. Measuring determinants of implementation behavior: psychometric properties of a questionnaire based on the theoretical domains framework. Implement Sci 2014 Mar 19;9(1):33 [FREE Full text] [doi: 10.1186/1748-5908-9-33] [Medline: 24641907]
83. Huijg JM, Gebhardt WA, Crone MR, Dusseldorp E, Presseau J. Discriminant content validity of a theoretical domains framework questionnaire for use in implementation research. Implement Sci 2014 Jan 15;9(1):11 [FREE Full text] [doi: 10.1186/1748-5908-9-11] [Medline: 24423394]
84. Camden C, Zwicker JG, Morin M, Schuster T, Couture M, Poder TG, et al. Web-based early intervention for children with motor difficulties aged 3–8 years old using multimodal rehabilitation (WECARE): protocol of a patient-centred pragmatic randomised trial of paediatric telerehabilitation to support families. BMJ Open 2021 Apr 08;11(4):e046561. [doi: 10.1136/bmjopen-2020-046561]
85. King G, Schwellnus H, Keenan S, Chiarello LA. Youth engagement in pediatric rehabilitation: service providers' perceptions in a real-time study of solution-focused coaching for participation goals. Phys Occup Ther Pediatr 2018 Jan 05;38(5):527-547. [doi: 10.1080/01942638.2017.1405864] [Medline: 29303397]
86. Doria N, Condran B, Boulos L, Curtis Maillet DG, Dowling L, Levy A. Sharpening the focus: differentiating between focus groups for patient engagement vs. qualitative research. Res Involv Engagem 2018 Jun 25;4(1):19 [FREE Full text] [doi: 10.1186/s40900-018-0102-6] [Medline: 29983994]
87. Touré M, Poissant L, Swaine BR. Assessment of organizational readiness for e-health in a rehabilitation centre. Disabil Rehabil 2012 Sep 22;34(2):167-173. [doi: 10.3109/09638288.2011.591885] [Medline: 21936712]
88. Camden C, Swaine B, Tétreault S, Bergeron S. SWOT analysis of a pediatric rehabilitation programme: a participatory evaluation fostering quality improvement. Disabil Rehabil 2009;31(16):1373-1381. [doi: 10.1080/09638280802532696] [Medline: 19294544]
89. Camden C, Swaine B, Tétreault S, Carrière M. Going beyond the identification of change facilitators to effectively implement a new model of services: lessons learned from a case example in paediatric rehabilitation. Dev Neurorehabil 2011;14(4):247-260. [doi: 10.3109/17518423.2011.577049] [Medline: 21732809]
90. King S, King G, Rosenbaum P. Evaluating health service delivery to children with chronic conditions and their families: development of a refined measure of processes of care (MPOC−20). Children's Health Care 2004 Mar;33(1):35-57. [doi: 10.1207/s15326888chc3301_3]
91. Creswell J. A Concise Introduction to Mixed Methods Research. London: SAGE publications; 2014.

92. Canadian Agency for Drugs and Technologies in Health (CADTH). Guidelines for Canadian agency for drugs and technologies in health (4th Edition). CADTH Ottawa. 2017 Dec 04. URL: https://www.cadth.ca/guidelines-economic-evaluation-health-technologies-canada-4th-edition [accessed 2021-03-29]
93. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. Oxfordshire United Kingdom: OUP Oxford; 2015.

Abbreviations

FCT: family-centered telerehabilitation
MPOC-20: Measure of Processes of Care-20
PRIME-SP: Pediatric Rehabilitation Intervention Measure of Engagement-Service Provider version
TIPS: training intervention and program of support

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Protocol

A Multilevel Integrated Intervention to Reduce the Impact of HIV Stigma on HIV Treatment Outcomes Among Adolescents Living With HIV in Uganda: Protocol for a Randomized Controlled Trial

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Abstract

Background: HIV stigma remains a formidable barrier to HIV treatment adherence among school-attending adolescents living with HIV, owing to high levels of HIV stigma within schools, rigid school structures and routines, lack of adherence support, and food insecurity. Thus, this protocol paper presents an evidence-informed multilevel intervention that will simultaneously address family- and school-related barriers to HIV treatment adherence and care engagement among adolescents living with HIV attending boarding schools in Uganda.

Objective: The proposed intervention—Multilevel Suubi (MSuubi)—has the following objectives: examine the impact of M-Suubi on HIV viral suppression (primary outcome) and adherence to HIV treatment, including keeping appointments, pharmacy refills, pill counts, and retention in care; examine the effect of M-Suubi on HIV stigma (internalized, anticipated, and enacted), with secondary analyses to explore hypothesized mechanisms of change (eg, depression) and intervention mediation; assess the cost and cost-effectiveness of each intervention condition; and qualitatively examine participants' experiences with HIV stigma, HIV treatment adherence, and intervention and educators' attitudes toward adolescents living with HIV and experiences with group-based HIV stigma reduction for educators, and program or policy implementation after training.

Methods: MSuubi is a 5-year multilevel mixed methods randomized controlled trial targeting adolescents living with HIV aged 10 to 17 years enrolled in a primary or secondary school with a boarding section. This longitudinal study will use a 3-arm cluster randomized design across 42 HIV clinics in southwestern Uganda. Participants will be randomized at the clinic level to 1 of the 3 study conditions (n=14 schools; n=280 students per study arm). These include the bolstered usual care (consisting of the literature on antiretroviral therapy adherence promotion and stigma reduction), multiple family groups for HIV stigma reduction plus family economic empowerment (MFG-HIVSR plus FEE), and Group-based HIV stigma reduction for educators (GED-HIVSR). Adolescents randomized to the GED-HIVSR treatment arm will also receive the MFG-HIVSR plus FEE treatment. MSuubi will be provided for 20 months, with assessments at baseline and 12, 24, and 36 months.

Results: This study was funded in September 2021. Participant screening and recruitment began in April 2022, with 158 dyads enrolled as of May 2022. Dissemination of the main study findings is anticipated in 2025.

Conclusions: MSuubi will assess the effects of a combined intervention (family-based economic empowerment, financial literacy education, and school-based HIV stigma) on HIV stigma among adolescents living with HIV in Uganda. The results will expand our understanding of effective intervention strategies for reducing stigma among HIV-infected and noninfected populations in Uganda and improving HIV treatment outcomes among adolescents living with HIV in sub-Saharan Africa.

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KEYWORDS

HIV/AIDS; stigma; adolescents; school

Introduction

Background

HIV/AIDS among adolescents remains a public health concern worldwide. Over 1.7 million children aged<15 years live with HIV [1], and almost half of all new HIV infections worldwide occurs in youth aged 15 to 24 years [2]. Sub-Saharan Africa (SSA) bears the brunt of the HIV epidemic in children and adolescents, accounting for more than 88% of the global population of adolescents living with HIV and 80% of the 460,000 new infections worldwide among adolescents [1]. Uganda is home to more than 170,000 adolescents living with HIV. This figure is expected to increase as adolescents remain highly vulnerable to HIV infection [3], perinatal transmission of HIV continues to occur [4], and expanded access to antiretroviral therapy (ART) increases the longevity of persons infected with HIV [5-7]. However, similar to other countries [8-11], adolescents living with HIV in Uganda have lower levels of ART adherence (<50%) [12,13], low rates of viral suppression [14], and high attrition from HIV care than children and adults living with HIV [15-18]. Nonadherence to HIV care potentiates secondary transmission of drug-resistant HIV among nonvirally suppressed adolescents living with HIV engaging in unprotected sex [19-21], and undermines global efforts to eradicate AIDS [22]. Without improvements in HIV prevention, testing, and treatment, a staggering 360,000 adolescents may die of AIDS-related diseases by 2030 [4].

Adolescents living with HIV in boarding schools are more disadvantaged and have lower levels of HIV treatment adherence. HIV stigma [23-25], poverty (including food insecurity) [26,27], and poor mental health [13,28-31] are increasingly being listed as the most potent barriers to ART adherence in Uganda and SSA. The school social context is very disadvantageous for adolescents living with HIV. First, adolescents living with HIV lack the family support that typically facilitates treatment adherence [13,32]. Second, the lack of privacy (given the living arrangements) coupled with high levels of HIV stigma (internalized, anticipated, and enacted) heightens adolescents living with HIV's concerns about unintentional disclosure of HIV status. In our preliminary studies, adolescents living with HIV reported shaming, peer rejection, and exclusion from school activities after disclosure of their HIV status, resulting in suicidal thoughts and thoughts of school dropout [33,34]. Third, poverty-related food insecurity, manifesting as lack of food to accompany medications, is another barrier [35-38]. Adolescents living with HIV are often advised to take their drugs at bedtime to reduce medication side effects (eg, drowsiness or nausea) that may interfere with school activities. However, taking drugs on an empty stomach usually amplifies side effects. Poor parents are often unable to supplement their children's school meals to support treatment adherence. The aim of this study is to examine the effects of an evidence-informed multilevel intervention—Multilevel Suubi (M-Suubi)—that seeks to simultaneously address multiple barriers to HIV treatment adherence and care engagement among school-attending adolescents living with HIV in Uganda.

High levels of HIV stigma persist in SSA, including Uganda [39,40], creating a formidable barrier to HIV treatment adherence among adolescents living with HIV [23-25]. Stigma is a societal process that manifests at multiple socioecological levels [41,42]. HIV stigma can manifest internally (ie, internalized and anticipated stigma) based on the perceived negative public attitude and encompassing feelings of one as reprehensible, damaged, and ineffective. These feelings may lead to mental health problems such as depression, posttraumatic stress disorder, suicidal ideation [33,43-45], feelings of loneliness and social isolation [23,46,47], diminished physical health [48-51], sexual risk behavior [52,53] and poor treatment adherence [20,25,54-57]. Adolescents living with HIV experience internal and external HIV stigma (ie, anticipated and enacted stigma, respectively) within homes and schools [58]—the most important adolescent development contexts. Many adolescents living with HIV live in extended family settings (owing to orphanhood), where enacted stigma is perpetrated through rejection, verbal insults, and ostracism [23,59-63]. Family members are often condemned and stigmatized in similar ways because of their association with adolescents living with HIV (ie, associative stigma) [64], which can negatively affect family functioning. Within schools, HIV stigma is rampant among peers and educators (eg, teachers, administrators, and nurses), manifesting as gossip, rejection, harassment, social isolation, and loss of friendship and social support [23,58,60,65]. Educators are often indiscreet, ignorant about HIV/AIDS, and uncaring and unresponsive to enacted stigma within schools [65]. These experiences can diminish adolescents living with HIV's ability to develop a positive self-concept and form strong bonds with family members and

peers and increase their risk of mental health problems. HIV stigma and social exclusion lead to, or exacerbate mental health symptoms (eg, depression and suicidal ideation) and contribute to school dropout [23,33,34,58,60,66]. HIV stigma also undermines HIV treatment adherence and impedes adolescents living with HIV's access to social support in school settings [65,67]. These adverse effects of HIV underscore the urgent need for interventions to reduce HIV stigma within schools and families.

HIV stigma exists at the intersection between HIV and poverty and perpetuates disparities among people living with HIV by concentrating the adverse impacts of HIV stigma on the poor [68,69]. Poverty is rampant among HIV-affected households [70-72] and is a significant risk factor for HIV acquisition [73] and poor HIV treatment outcomes [26,27]. People living with HIV from poverty-stricken households face greater challenges in accessing and sustaining HIV treatment owing to economic challenges, such as lack of transport to clinics [74,75] and inadequate meals to support medication adherence [36,38,76]. Numerous studies conducted in SSA [35-38], have identified food insecurity as a formidable barrier to ART adherence. Within boarding schools, inadequate nutrition or lack of foods or snacks may dissuade adolescents living with HIV from taking their medications because of concerns that taking drugs on an empty stomach can intensify side effects. Poverty can adversely affect the quality of family relationships, including parent-child communication, involvement [77-79] and parenting skills [80,81], which increases adolescents' susceptibility to poor outcomes such as emotional and behavioral adjustment [78,82-86].

In SSA, where HIV has disrupted the social function of the family, schools are potential substitutes for providing supportive developmental contexts that can mitigate the risks for poor outcomes in vulnerable children, including adolescents living with HIV [87,88]. For adolescents living with HIV, the typical developmental challenges of adolescence are compounded by HIV-related challenges such as managing complex drug regimens, coping with multiple bereavements, comorbidities, and social challenges (eg, HIV disclosure) [89-91]. As such, adolescents living with HIV need additional support to successfully negotiate adolescence. However, poverty and food insecurity undermine their ability to fully participate in school, and HIV stigma in schools undermines their potential to support adolescents living with HIV. School-attending adolescents spend a large part of the day away from home, and for adolescents living with HIV, this means that they must take their daily medication while at school. Treatment is even more challenging for more than 60% of adolescents living with HIV who spend 9 to 10 months a year away from home in boarding sections—a form of parental opt-in institutional care with limited family visitation (typically monthly). Adolescents living with HIV in boarding schools are vulnerable to HIV stigma, abuse, poor nutrition, mental and physical difficulties, and poverty [23,58-60,67] and have significantly lower levels of ART adherence compared with adolescents living with HIV in day schools [92]. The lack of attention to addressing the school-related needs of the large population of in-school adolescents living with HIV in Uganda and other high HIV burden countries in SSA has adverse consequences for ongoing efforts to end the AIDS epidemic [22]. Targeting HIV stigma within schools is necessary to enhance HIV treatment outcomes and the educational achievement for adolescents living with HIV in SSA.

Recent systematic reviews indicate that interventions to reduce HIV stigma among adolescents living with HIV in resource-limited settings are almost nonexistent [93-98]. For example, of the 48 stigma reduction interventions [97], only 3 studies were aimed at people living with HIV in SSA, and none of these interventions targeted adolescents living with HIV or assessed the impact of stigma reduction on HIV treatment outcomes among adolescents living with HIV. Moreover, these interventions tend to be single-level focused (eg, focus exclusively on family) and use a limited range of intervention strategies [97]. Although several interventions have shown promise in improving HIV treatment adherence among adolescents living with HIV [99-102], they mostly focus on adolescents living with HIV commuting daily from home. However, the majority (>60%) of school-going children in Uganda (and in many sub-Saharan African countries heavily impacted by HIV) spend their time in boarding sections. The lack of attention to this group undermines the efforts to achieve the 95-95-95 targets in SSA. Building on our experience using multiple family groups (MFGs) and family economic empowerment (FEE) interventions to improve health outcomes among adolescents recruited from schools and clinics [26,78,103-106] and supported by the literature on the impact of HIV stigma within families and schools [23,33,34,58,60,65-67] and the impact of FEE on HIV treatment outcomes [107-111], we propose testing a culturally acceptable asset-based multilevel intervention (M-Suubi) that targets HIV stigma within schools and families to improve HIV treatment outcomes among adolescents living with HIV.

Objectives

Although several interventions have shown promise in improving HIV treatment adherence among adolescents living with HIV [99-102], they mostly focus on adolescents living with HIV commuting daily from home. However, most school-going children in Uganda and many sub-Saharan African countries heavily impacted by HIV spend their time in boarding sections. The lack of attention to this group undermines the efforts to achieve the 95-95-95 targets in SSA. Our research finds that MFG and FEE [27,100] can improve HIV care outcomes among adolescents living with HIV. Moreover, consistent with the existing literature in SSA [33], our recent combination intervention study, Bridges, situated within Ugandan schools, points to the importance of building supportive familial and school environments for adolescents affected by HIV/AIDS, including adolescents living with HIV [112-115]. Building on prior experience and evidence of effective HIV stigma reduction strategies [40,95,98,116], we propose to examine an evidence-informed multilevel intervention called M-Suubi (the word *suubi* means hope) intervention that seeks to simultaneously address multiple barriers to HIV treatment adherence and care engagement among adolescents living with HIV attending boarding schools in Uganda. M-Suubi comprises of three study conditions: (1)

Bolstered usual care consisting of literature on ART adherence promotion and stigma reduction, (2) MFG for HIV stigma reduction plus FEE (MFG-HIVSR plus FEE), and (3) group-based HIV stigma reduction for educators (GED-HIVSR). The study is guided by the HIV stigma framework [64], asset theory [117,118], and family system theory [119,120] and has the following goals:

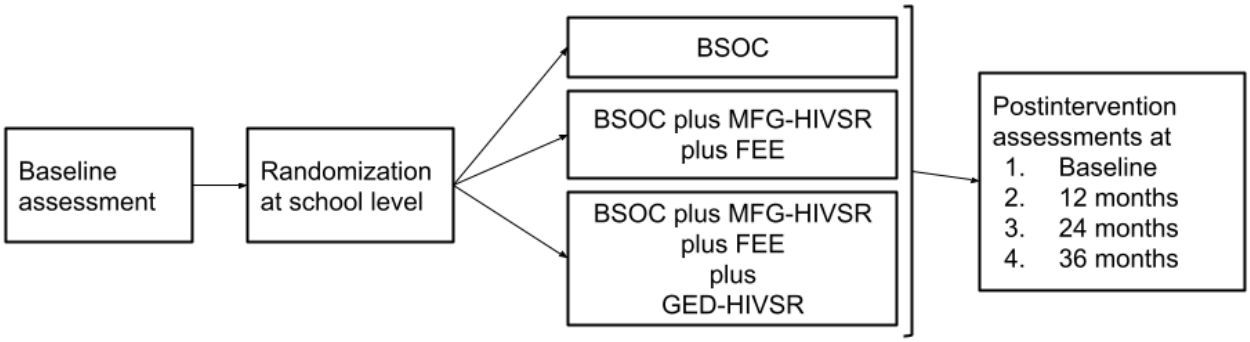
- Aim 1: examine the impact of M-Suubi on HIV viral suppression (primary outcome) and adherence to HIV treatment, including keeping appointments, pharmacy refills, pill counts, and retention in care.
- Aim 2: examine the effect of M-Suubi on HIV stigma (internalized, anticipated, and enacted), with secondary analyses to explore hypothesized mechanisms of change (eg, depression) and intervention mediation.
- Aim 3: assess the cost and cost-effectiveness of each intervention condition.
- Aim 4: qualitatively examine participants' experiences with HIV stigma, HIV treatment adherence, and intervention and educators' attitudes toward adolescents living with HIV and experiences with GED-HIVSR and program/policy implementation after training.

Methods

Study Overview

M-Suubi is a 5-year multilevel mixed methods randomized controlled trial. As shown in Figure 1, the M-Suubi intervention will be evaluated using a 3-arm cluster randomized trial implemented across 42 community health centers (with HIV clinics), targeting adolescents living with HIV aged 10 to 17 years and attending primary and secondary schools with a boarding section (n=14 clinics per arm; n=280 students per study arm). Adolescents living with HIV will be randomized at the clinic level to one of the three study conditions: (1) bolstered usual care, (2) MFG-HIVSR plus FEE, and (3) MFG-HIVSR plus FEE plus GED-HIVSR (Figure 1). M-Suubi will be provided for 20 months, with assessments at baseline and 12, 24, and 36 months.

Figure 1. Study conditions and assessments. BSOC: bolstered standard of care; FEE: family economic empowerment; GED-HIVSR: group-based HIV stigma reduction for educators; MFG-HIVSR: multiple family groups HIV stigma reduction for educators.



Theoretical Framework

This proposal is guided by the HIV stigma framework [64], asset theory [117,118], and family systems theory [119,120]. The HIV stigma framework [64] suggests that HIV stigma affects people living with HIV via three distinct mechanisms: stereotyping (cognitive), prejudice (affective), and discrimination (behavioral). M-Suubi focuses on all forms of HIV stigma (internalized, anticipated, and enacted) and uses a range of strategies (eg, education, skill building, empowerment, and empathy) to address HIV stigma at the individual, interpersonal, and institutional levels [95-98]. Consistent with a multilevel approach to HIV stigma reduction, M-Suubi targets following three ecological levels: (1) school using GED-HIVSR, (2) family using MFG-HIVSR plus FEE, and (3) individual (adolescents living with HIV) using locally adapted Suubi-MAKA [105,121,122] and Suubi+Adherence [26,123,124] curricula. All intervention arms use a variety of strategies (eg, education, cognitive restructuring, empowerment, and skill building) to address HIV stigma.

Our rationale for pairing MFG-HIVSR with FEE comes from mounting evidence that cognitive and behavioral changes in adolescents are influenced by economic stability, whereas family support and protective processes are needed to reinforce and maintain engagement in protective health behaviors. MFG-HIVSR will provide a safe setting for parents and their children to address HIV stigma, foster family communication, facilitate optimism and morale by normalizing shared experiences with other families, and enhance interpersonal and coping skills. FEE will alleviate the impact of family economic insecurity; hence, mitigating the potential impact of food insecurity on ART adherence and caregiver engagement among the study participants. More specifically, financial security will enable parents to support their children in schools through visitations and supplemental nutrition. For adolescents living with HIV, internalized stigma is targeted in the MFG-HIVSR using the locally adapted Suubi+Adherence curriculum [123] that discusses several adherence barriers including HIV stigma. These strategies will impact a range of psychological, behavioral, and health outcomes among adolescents living with HIV, caregivers, and educators. Guided by the HIV stigma framework, the GED-HIVSR targets educators (ie, teachers, school nurses, matrons, and administrators) to build HIV knowledge, foster empathy, and build support for adolescents living with HIV in boarding schools, whereas the MFG-HIVSR targets HIV stigma within families. Asset-based and family systems theory guides the MFG-HIVSR and FEE to alleviate poverty within families. Asset theory also guides our approach to GED-HIVSR, where we draw on skills and values of

educators, emphasize the identification of resources within schools and the local community, and encourage educators to develop their own plans to support the needs of adolescents living with HIV, potentially promoting the ownership of intervention activities.

Setting and Study Population

The target populations for this study are adolescents living with HIV, their caregivers, and educators within the Greater Masaka region in southwestern Uganda, a region heavily affected by HIV [125]. We plan to recruit 840 adolescents living with HIV and their caregivers from 42 community health centers (with HIV clinics) and their primary and secondary schools. We will work with clinics affiliated with Reach The Youth, our local implementing partner. For adolescents living with HIV randomized to treatment arm 2 (ie, MFG-HIVSR plus FEE and GED-HIVSR), we will include all the schools in the GED-HIVSR component, irrespective of the number of participants attending the school. From each of the selected schools, we will recruit up to five educators, including school nurses, head administrators, and teachers.

Inclusion and Exclusion Criteria

The following are the inclusion criteria for participants: (1) the individual is HIV positive, defined as an adolescent who has tested positive with confirmation by medical report and has been disclosed to; (2) the individual is prescribed ART; (3) the individual is living within a family (defined broadly, not necessarily with biological parents); and (4) the individual is aged 10 to 17 years and enrolled in a primary or secondary school with a boarding section within the Greater Masaka region. At the clinic level, all eligible adolescents living with HIV from a particular household will be enrolled in the study and assigned to the same study condition.

The family inclusion criterion is that the participants must be caregivers of adolescents living with HIV who agree to participate in the study.

The educator inclusion criterion is that the participants must be teachers, school nurses, and administrators in the target schools who agree to participate in the study. For adolescents living with HIV randomized to treatment arm 2 (ie, MFG-HIVSR plus FEE and GED-HIVSR), we will include all the schools in the GED-HIVSR component, irrespective of the number of participants attending the school. All educators will be required to consent to participate in the study individually.

The following are the exclusion criteria: (1) significant cognitive impairment that interferes with the participants' understanding of the informed consent process or (2) inability/unwillingness to commit to completing the study.

Enrollment

After identifying potential study participants, we will compile a list of secondary schools attended, including the number of potential participants in each school, associated school features (ie, location and size), and willingness of these schools to participate in the study. Clinics will be randomized to 1 of 3 study arms, and all adolescents living with HIV and their caregivers will be enrolled in the study arm associated with their clinic. Only adolescents and their caregivers who meet inclusion criteria will be recruited. To characterize any potential bias in enrollment, we will collect information about the clinics (eg, location, clinic size, and reasons for nonparticipation) and use HIV clinic information (eg, sociodemographics and viral suppression rates) to characterize the potential bias from adolescents living with HIV and clinics that decline to participate in the study. For participants randomized to the GED-HIVSR intervention arm, we will collect information on the school location, type (eg, private or government-supported), size, and reasons for nonparticipation.

Intervention Conditions

Control Arm: Bolstered Usual Care

All participants (in the control and treatment arms) will receive medical and psychosocial support as part of the bolstered usual care. All public clinics, including our study sites, follow procedures for pediatric ART initiation and monitoring as outlined in the National Guidelines for pediatric HIV care in Uganda [126]. As part of medical care, ART is prescribed by physicians and dispensed monthly by a pharmacist at the clinic. Specifically, immediately after initiation, or if clinically unstable, adolescents living with HIV are seen more frequently (weekly to monthly). Laboratory data—viral load (VL) and CD4 counts—are collected every 6 months until the patient is stabilized and then checked annually. For M-Suubi, data regarding HIV viral load, pharmacy refills, and pill counts will be collected from the charts. Psychosocial care is primarily provided by lay counselors trained in standardized ART adherence counseling. Typically, each patient receives 2 to 4 sessions of adherence counseling at initiation and when nonadherence is identified. Lay counselors also assist families with other psychosocial needs that may arise. However, adherence to counseling can vary substantially. Therefore, the usual care will be bolstered with enhanced adherence sessions to ensure more standardized and sufficient adherence counseling. All study participants will undergo 6 sessions to review HIV, ART, and ART adherence. We will bolster family communication around these topics using materials adapted from the cartoon-based curriculum used in the Suubi+Adherence study with adolescents living with HIV and their families [127]. This curriculum describes the lead characters (Mabebeere and Kamperempe), testing interactions with a nurse in which she describes the working of the HIV, ART, and adherence (including potential barriers such as HIV stigma). These materials will be discussed with the participating adolescents living with HIV to identify questions and barriers. Lay counselors in clinics have been trained to use these materials, and HIV clinics have incorporated this curriculum into their practice. Previous studies have shown that the Suubi+Adherence curriculum promotes adherence among adolescents living with HIV [127-130].

Treatment Arm 1: MFG-HIVSR Plus FEE

In addition to the bolstered usual care described earlier, adolescents living with HIV and their caregivers will participate in a family strengthening intervention delivered via MFG along with an FEE component. MFG is a family-centered, group-delivered, evidence-informed, strength-based 10-session

(weekly) intervention for children whose families struggle with poverty and associated stressors. It integrates components of existing evidence-based practices that successfully improve parental management, mental health–promoting family processes, and family strengthening [77,104,105,121,131-134]. For the purpose of M-Suubi, MFG-HIVSR has 6 additional sessions to cover HIV stigma–related issues. The specific MFG-HIVSR session content will be based on our previous interventions [79,103-105,121,132,133,135-145]. Sessions will focus on the core MFG components, also known as 4 Rs and 2 Ss (rules, responsibility, relationships, respectful communication, stress, and social support). Sessions focused on HIV stigma will be adapted from the existing Suubi curriculum and resources from the Ministry of Health. Each session provides opportunities to contextualize the content to the realities of family life and emergent cultural and values perspectives and tailor messages to the child's age. These will include group activities, role-plays, sharing experiences, and family take-home activities. Families (adolescents living with HIV and their caregivers) will be combined into groups of up to 10 families to promote communication and support within and among families. MFG-HIVSR sessions will last approximately 1 hour and will be delivered twice weekly during school holidays when adolescents living with HIV are more readily available. Parent peer and community health workers already trained in MFG delivery will be recruited and will receive refresher training on M-Suubi's content on HIV stigma. During MFG-HIVSR implementation, facilitators will receive 2 hours of monthly group supervision across sites. Given the significant and protective role families play in the health and well-being of adolescents living with HIV, we expect that strengthening family functioning and dialogue by involving caregivers through MFG-HIVSR will lead to better child outcomes, including reduced HIV stigma. These services will be bolstered with an FEE component provided via a youth development account described next.

In the FEE component, adolescents living with HIV will receive a youth development account with a 1:1 matched savings program at a financial institution accredited by the Bank of Uganda. Each youth development account will be opened in the adolescent's name, with their primary caregiver as a cosigner, until the adolescent turns 18 years, at which time a cosigner will no longer be required. This is consistent with Ugandan banking law, which prohibits children aged <18 years from independently entering into a binding contract/operating a bank account. Family members and friends of adolescents living with HIV will be allowed and encouraged to contribute to this youth development account. It will be matched at a rate of 1:1 using money from the program. The match cap (maximum amount of youth contribution to be matched by the program) will be equivalent to US $20 per month or US $480 for the 24-month intervention period. During the intervention, adolescents will have direct access to both their personal savings deposited in the youth development account and the match provided by the study to pay for food, transportation to health clinics, and other necessities that may affect adherence. Matching will not be conditioned on the usual expenditure and/or savings goals dictated by programs [133,137,146]. The unconditional design recognizes that adolescents living with HIV and attending schools face competing demands (school fees, food for medication adherence, transport to clinics, etc) and that a conditional transfer may prohibit these vital expenditures, which may have implications for antiretroviral treatment adherence. In collaboration with participating financial institutions, the youth development account will be augmented with 4 sessions of financial literacy training, covering the basic principles of financial management, saving, and asset building.

Treatment Arm 2: MFG-HIVSR Plus FEE Plus GED-HIVSR

In addition to the bolstered usual care and MFG plus FEE described earlier, adolescents living with HIV in this arm will receive school-level HIV stigma reduction interventions targeting teachers, school nurses, matrons, and administrators (head teachers and director of studies) in their schools. The GED-HIVSR seeks to empower educators to reduce enacted HIV stigma and build supportive structures for adolescents living with HIV within their schools. Our rationale for adding this component to our intervention package is to test the added benefit of addressing school-level HIV stigma–related challenges on HIV treatment outcomes among adolescents living with HIV. Guided by an asset-based approach and drawing on evidence-based strategies for reducing HIV stigma in non–HIV-infected populations [63,97,98,147,148] and building support for adolescents living with HIV in school settings [149-151], GED-HIVSR seeks to impart educators in the intervention schools with HIV-related knowledge, provide a safe space for educators to explore their personal values and biases that may promote or hinder their role of supportive individuals and systems for adolescents living with HIV, and empower them with knowledge and skills to act as change agents within their schools.

The GED-HIVSR will be delivered as a 2-day workshop with a booster session in years 3 to 4. The details of each topic along with the targeted domain and delivery strategies are presented in Table 1. From each intervention school, we will recruit up to five educators including the school head teacher, director of studies, and school nurse. To standardize training and provide opportunities for peer-to-peer learning through group discussions, all educators will be convened at a central location for training. Workshop content will be delivered using a range of strategies including didactic lectures, role-play, testimonials from adolescents living with HIV, digital media (ie, documentaries), and discussions/brainstorming to promote participant engagement and active learning. Workshops will establish foundational knowledge on HIV transmission and treatment and cover content on HIV stigma and its impact on adolescents living with HIV and their families. Along with testimonials from adolescents living with HIV, we will use educational documentaries that portray the marginalization of people living with HIV to highlight the perpetuation of HIV stigma and its impact on these people, including adolescents living with HIV.

Table 1. Topics, delivery strategies, and targeted domains of group-based HIV stigma reduction for educators.

Intervention topic	Intervention strategy	Targeted domain	Conceptual framework
HIV transmission, treatment, and prevention; misconceptions and misbeliefs about HIV; stereotypes about people living with HIV	Didactic lectures; role-play; discussions	HIV knowledge; feelings toward people living with HIV	Cognitive factors: knowledge and beliefs
HIV and AIDS stigma: understanding and defining manifestations of stigma; intersecting stigmas; consequences for adolescents living with HIV, their families and communities; awareness of HIV stigma in schools and communities; strategies for combating stigma	Educational; documentary; testimony from adolescents living with HIV	Stigma manifestations; intersecting stigma (eg, stigma and poverty); gender	Cognitive factors: knowledge and beliefs
Educators' understanding of the needs and challenges of adolescents living with HIV in school settings, including barriers to HIV treatment adherence; mapping barriers to addressing HIV stigma within schools	Contact with adolescents living with HIV (presentations and testimonials from adolescents living with HIV)	Drivers and facilitators of stigma	Cognitive empathy; parasocial learning; skill building
Evaluating options for action planning for change; task analysis and developing an action plan; identification of stakeholders and resources to support initiatives to reduce stigma and support adolescents living with HIV in schools	Participatory learning through breakout sessions to brainstorm and develop actions plans for their schools	Future actions to support adolescents living with HIV; sustainable programs and policies to support adolescents living with HIV	Social learning theory: modeling; efficacy; empowerment through skill building
Booster sessions			
Review of ongoing programs to support adolescents living with HIV in school setting (successes, challenges, and alternative strategies)	Empowerment; peer-to-peer learning	Institutionalizing change; knowledge generation and transfer	Social learning theory: modeling; efficacy; empowerment through skill building

Previous studies have shown that direct or indirect contact (eg, digital film presentations) with stigmatized groups results in broader and more enduring reductions in stigma [152-154]. Thus, we will use expert testimonials from adolescents living with HIV as direct contact opportunities for the educators to hear their personal experiences in dealing with stigma and to *normalize* adolescents living with HIV as human beings; hence, fostering acceptance and empathy for adolescents living with HIV. Open discussions will provide a safe place for educators to express their views and opinions of adolescents living with HIV, as well as explore strategies, resources, and barriers to support adolescents living with HIV within schools. This strategy of actively engaging educators in examining their biases and developing supportive strategies for adolescents living with HIV within their settings is consistent with the principles of empowerment that build a sense of ownership. Participants will then act as change agents within their schools by implementing activities that address the needs of adolescents living with HIV. To facilitate context-specific discussions, we will conduct quarterly visits (at least one visit per academic term) to individual intervention schools in between the workshops to establish how educators are supporting adolescents living with HIV within their schools and offer additional services (eg, training) based on the requests from the schools.

Ethics Approval and Consent

The research staff will obtain written informed consent and assent from the adult caregivers and children, respectively, before study enrollment. The consenting process for adults and children will be performed separately to avoid coercion. During face-to-face meetings, the adolescent's primary caregiver will read and sign a standard consent form. In doing so, caregivers will be consenting to participation for themselves and assenting to the participation of their adolescents. Adolescents will sign an assent form that will be read aloud verbatim. If either the adolescent or caregiver refuses to participate, they will not be enrolled. According to the Uganda Law, emancipated minors, defined as persons aged ≤18 years who are pregnant, married, have a child, or are self-sufficient, will be allowed to consent on their own. Both consent and assent forms will be translated into Luganda (the most widely spoken local language in the study region) and back translated to English to ensure consistency. Both the assent and consent processes will be conducted verbally in Luganda, given that some caregivers and adolescents were illiterate. The study team will receive training on Good Clinical Practices so that sensitive research activities can be handled appropriately. In addition, all interviewers have completed the Collaborative Institutional Training Initiative certificate and National Institutes of Health certificate to safeguard the research participants.

We have obtained approval for the study procedures from the institutional review boards (IRBs) at the University of Washington in St. Louis, Missouri (IRB ID 202201128) and University of Michigan (HUM00211945) and from the in-country local IRBs in Uganda: Uganda Virus Research Institute (GC/127/867) and Uganda National Council of Science and Technology (SS1166ES).

The study has been registered with ClinicalTrials.gov (NCT05307250), as of April 1, 2022. The dissemination of the main study findings is targeted for 2025.

Measures

As shown in Figure 1, assessment will be conducted at baseline and at 12-, 24-, and 36-month follow-ups. All assessments, each lasting approximately 60 minutes, will take place at the clinic during school breaks. Although all the adolescents living with HIV will be attending school and expect to be English-speaking (the instructional language in all Ugandan schools), assessments will be conducted in English or Luganda (the local language)

depending on the English proficiency of the participants. All the interviewers will be fluent in English and Luganda. The questions will be translated from English to Luganda and back translated by a certified translator from a local university (Department of Languages) following standard procedures. The research team members who are fluent in Luganda and English will crosscheck all translated assessments. All the interviewers will receive highly structured and intensive training. Assessments will be conducted using standardized measures adapted from previous studies conducted in Uganda [104,133,141]. Any measures that have not been used will be pretested and made culturally appropriate to the Ugandan context. For questions measuring sensitive behaviors (eg, adherence), we will use audio computer-assisted self-interviews, where the participant takes the survey herself on a mini laptop. Nonsensitive questions will be administered by the interviewer. For the biological assay, blood specimens for HIV VL testing will be collected at baseline and 12, 24, and 36 months after the intervention. In accordance with the Abbott platform, VL will be dichotomized into undetectable (<40 copies/ml) and detectable (≥40 copies/ml) levels.

Qualitative Component

Semistructured in-depth interviews will be conducted at baseline and at 12-, 24-, and 36-month follow-ups with adolescents living with HIV and their caregivers (n=40 dyads) in the 2 intervention arms. Baseline interviews will focus on the following aspects: (1) participants' experience of decision-making (eg, costs, benefits, barriers, and facilitators) associated with HIV treatment adherence and (2) HIV stigma and its perceived impact on their lives. Follow-up interviews will unpack the longer-term impact, including experiences of stigma and key multilevel factors affecting HIV treatment–related behaviors of the participants after the intervention. Specifically, in addition to the baseline interview topics, 12-month interviews will examine the following: (1) experiences of the participants with their respective intervention components (ie, MFG-HIVSR, FEE, and GED-HIVSR), including perceived benefits and key multilevel (individual, family, school, contextual, and programmatic) influences that affect their participation and (2) intervention sustainability. In addition to topics explored at baseline (HIV stigma and decision-making on HIV treatment), the follow-up interviews will explore the sustained impact of the intervention to examine changes over time in HIV stigma and decision-making associated with treatment adherence and the sustained impact of the intervention over time.

In addition, educators (n=20) will be interviewed at baseline and at follow-up (12, 24, and 36 months). Baseline interviews will focus on their attitudes toward adolescents living with HIV and how HIV stigma manifests within their school context. Follow-up interviews, in addition to topics covered during baseline, will explore educators' experiences with the training and resulting programs implemented within their school, facilitators and barriers to program implementation, recommendations, and sustainability. A purposive criterion sampling strategy [155] will be used to select adolescents living with HIV and their caregivers. adolescents living with HIV who score in the highest and lowest quartiles of internalized stigma at baseline (to be identified using the HIV stigma mechanism scale), and 20 participants (10 from each quartile) and their caregivers from each treatment condition will be randomly selected (n=40 dyads; these numbers will be sufficient for theoretical saturation) [156-158] and interviewed. This sampling method will ensure that participants with varying experiences are represented and will allow us to identify common patterns and variations across participants' experiences. In addition, 20 educators across the 2 treatment arms will be randomly selected for interviews. Interviews will be conducted in English or Luganda, based on the participants' preferences. The questions will be translated (English to Luganda) and back translated by research assistants, and then reviewed by 2 proficient team members (MM and PN). Each interview will last approximately 60 minutes and will be audiotaped. The same participants will be interviewed at each time point.

Data Analysis

Primary Analyses for Aim 1

To examine the effect of M-Suubi on HIV viral suppression, we hypothesize the following:

- H1a: MFG-HIVSR plus FEE will have higher odds of viral suppression than control participants (bolstered usual care).
- H1b: MFG-HIVSR plus FEE plus GED-HIVSR will have higher odds of viral suppression than control participants.
- H1c: MFG-HIVSR plus FEE plus GED-HIVSR will have higher odds of viral suppression than MFG-HIVSR plus FEE.

To test these 3 hypotheses, we will fit a 3-level generalized linear mixed model (LMM) with fixed effects for the study arm, time, and their interaction. Our analysis will follow an intent-to-treat approach, such that all participants are included in the analyses, irrespective of whether they have complete or incomplete outcome data. Maximum likelihood (ML) and multiple imputation (MI) procedures will be used to address missing data with sensitivity analyses. Sensitivity analyses will be performed using pattern-based MI to examine the robustness of the results under different missing data assumptions. We will use random intercepts for school/clinic ID to account for clustering of persons within schools and their affiliated clinics and include random intercepts, random slopes, and their covariance for person ID to account for clustering of repeated measurements within persons. Reflecting the binary HIV viral suppression outcome, a binomial distribution and log link will be used to fit a log-binomial model to estimate the relative risks. If the log-binomial model does not converge, we will substitute a Poisson model with robust SEs [159,160]. To maximize rigor, quasi-likelihood methods will not be used. Instead, maximum likelihood estimation via adaptive Gaussian quadrature with 15 integration points will be used to ensure stable solutions [161]. To test hypotheses H1a to H1c, we will perform 3 time-averaged comparisons of repeatedly measured observations across study arms to examine the intervention effects over the duration of the study period. As all possible comparisons among the 3 study arms will be evaluated, the α will be set at .05/3=.017 for each of these 3 planned comparisons. Any additional post hoc comparisons (eg, paired comparisons of groups at each time point) will maintain a nominal α of .05 using simulation-based step-down multiple comparison methods [114]. Our team has

considerable experience fitting 3-level generalized LMMs to analyze data from our cluster randomized asset-based intervention trials [113,162].

Primary Analyses for Aim 2

To examine the effect of M-Suubi on HIV stigma, we hypothesize the following:

1. H2a: MFG-HIVSR plus FEE will have lower mean HIV stigma than control participants (bolstered usual care).
2. H2b: MFG-HIVSR plus FEE plus GED-HIVSR will have lower mean HIV stigma than control participants.
3. H2c: MFG-HIVSR plus FEE plus GED-HIVSR will have lower mean HIV stigma than MFG-HIVSR plus FEE.

To test these hypotheses, we will fit LMMs using the same fixed effects (study arm, time, and study arm-by-time) and random effects for the school/clinic (random intercepts) and person levels (random intercepts, random slopes, and their covariance) as proposed in the H1 analyses described earlier. To test hypotheses H2a to H2c, we will perform 3 time-averaged comparisons of repeatedly measured observations of stigma across study arms to examine the intervention effects over the duration of the study. To maintain a nominal type 1 error rate of 5% across tests of H2a to H2c, α will be set at .05/3=.017 for each planned time-averaged comparison. Our analyses will follow an intent-to-treat approach, and ML and MI approaches will be used to address missing data (as described in aim 1 earlier). To maximize rigor, the assumptions of normality and constant variance of residuals for these continuous outcomes in LMMs will be evaluated by examining histograms of the residuals and scatter plots of predicted values-by-Cholesky-scaled residuals, respectively. Transformations of outcomes will be used as needed to improve data conformance with model assumptions. Inferences for models whose residual statistics still do not fully meet assumptions following transformations will be generated via robust heteroskedastic-consistent Huber-White "sandwich" variance estimators [163]. All analyses will include outlier and influential case screening via the computation of Cook *D*, DF β values, and likelihood displacement statistics. If outliers are found, the results will be reported with and without outliers included [164,165].

Randomization, Sample Size, and Power Analysis

We used NCSS Statistical Software Program PASS [166] to compute the minimum detectable effect size estimates for hypotheses H1a to H1c and H2a to H2c proposed to fulfill specific aims 1 and 2, respectively. For all power analyses, we assume power=0.80, α=.05/3=.017, and 4 repeated assessments from 714 participants conservatively assuming 15% attrition. Standardized minimum detectable effect sizes range from .26 to .35. Therefore, our study will have the power to detect small to medium effects for the proposed hypotheses

Aim 3: Evaluate the Cost-effectiveness of Each Intervention Condition

Following the standard practice of measuring the cost-effectiveness of interventions, we will measure costs on a per-person basis. The intervention costs will include all program costs incurred for running the GED-HIVSR and MFG-HIVSR plus FEE programs and not just the savings match of the youth development account. The research costs will not be included in this study. Data on the savings match costs will be readily available from the management information system. Data on the costs of other program elements will be drawn from the project administrative records collected throughout the intervention period. In the analyses, the costs from multiple years will be adjusted for inflation, depreciation, and discounting. The outcome analyses described earlier will be used to estimate the extent to which the *Combined Intervention (MFG-HIVSR plus FEE plus GED-HIVSR)* versus *MFG-HIVSR plus FEE alone* increased particular outcomes (eg, viral suppression). The per-person costs of *MFG-HIVSR plus FEE and GED-HIVSR* and *MFG-HIVSR plus FEE alone* will then be divided by the relevant effect sizes to produce estimates of cost-effectiveness. We will calculate CIs for point estimates using two methods: Monte Carlo [167] and bootstrap [168].

Aim 4: Qualitative Component Analysis

The interviews will be transcribed and uploaded to NVivo (version 12; QSR International) [169]. Data will be analyzed using a recurrent cross-sectional approach. Each wave of data will first be analyzed independently to understand experiences at each time point of data collection [170]. Analytic induction techniques [171] will be used for coding. Initially, 10 interview transcripts randomly selected across the 2 study groups will be read multiple times and independently coded by the team using sensitizing concepts to identify emergent themes (open coding) [172]. Broader themes will be divided into smaller, more specific units until no further subcategories are necessary. Analytic memos will be written to further develop categories, themes, and subthemes, and to integrate the ideas that emerge from the data [172,173]. Codes and the inclusion/exclusion criteria for assigning codes [174] will be discussed as a team to create the final codebook in NVivo. Each transcript will then be independently coded by 2 investigators using the codebook. Intercoder reliability will be established. A level of agreement ranging from 66% to 97% based on the level of coding indicates good reliability [155]. Disagreements will be resolved through team discussions. The secondary analysis will compare/contrast themes and categories within and across groups to identify similarities, differences, and relationships among the findings. Member checking, peer debriefing, and audit trails will be used to ensure rigor [158]. The data will be analyzed using both recurrent cross-sectional and trajectory approaches. After this initial analysis is completed, a second analysis will focus on the differences and similarities between the time points. Central themes from each wave of data collection will be compared using these 3 subsets of questions. The coded data will be organized into matrices with major themes (along the y-axis) and time points (along the x-axis) to explore how the data, in the existing thematic groupings, changed or did not change over time (eg, new concerns and change in priorities), as well as new major themes that emerge from one time point to another.

Results

The M-Suubi study was initiated in September 2021. The first 6 months of this 5-year study were a preparation period for obtaining IRB approval, mobilizing financial institutions, and recruiting clinics and adolescents. Data collection commenced in April 2022, with screening and recruitment of study participants, as well as completion of baseline assessments. Implementation of the MFG-HIVSR, GED-HIVSR, and FEE components will follow after randomization of the study participants, and the intervention will be delivered over a period of 20 months. Follow-up assessments will be conducted at 12, 24, and 36 months after completion of the baseline assessments.

Discussion

Overview

To the best of our knowledge, this is the first study to evaluate a culturally acceptable multilevel intervention to reduce HIV stigma within homes and schools and to improve HIV treatment adherence among in-school adolescents living with HIV in Uganda. HIV stigma reduction interventions targeting adolescents living with HIV in boarding school sections are nonexistent, and multilevel interventions addressing intrapersonal, interpersonal, and institutional stigma are scarce. The MFG approach is culturally consistent with SSA's collective approach of families raising children "together," which strengthens its appeal to communities and its likelihood of success. The asset-savings–led approach has demonstrated efficacy in reducing HIV-risk behaviors among HIV-affected adolescents [78,104,105,131,175,176] and has improved ART adherence among adolescents living with HIV [26]. The focus on schools is consistent with the United Nations Educational, Scientific and Cultural Organization's Good Policy and Practice on HIV in Schools report [176], which established a road map for supporting schools as caring contexts for children affected by HIV/AIDS. M-Suubi makes use of existing community institutions to deliver the intervention and builds local capacity, which will ensure an eventual scale-up. M-Suubi will provide much-needed evidence on effective strategies for reducing HIV stigma among school-attending adolescents living with HIV in Uganda. More importantly, this study will provide evidence on the effects of a multilevel intervention comprising of family-based economic empowerment and financial literacy combined with a school-based HIV stigma reduction intervention for educators. In so doing, it will enable an ecological assessment of the cascading effects of multilevel HIV stigma reduction strategies. In addition, the inclusion of educators as a target population will provide a unique opportunity to generate data on the prevalence and impact of HIV stigma among educators and effective intervention strategies to reduce HIV stigma within schools. To date, these data are nonexistent.

Limitations

This study has some limitations. First, it targets adolescents living with HIV in southwestern Uganda, so the study findings may not be generalizable to adolescents living with HIV in Uganda or other high HIV burden countries in SSA. Second, the study focuses on adolescents living with HIV attending primary or secondary school. adolescents living with HIV in vocational schools and other nontraditional school settings are not included in the study, which may bias the generalization of the study findings. Nonetheless, this study uses a sound methodological approach, which will enhance the quality of data generated in this study. The study findings, if successful, would advance knowledge to bridge the existing gap in evidence-based scalable HIV stigma interventions for adolescents living with HIV in resource-limited settings such as Uganda.

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Data Availability

Data sets from this study will be available to researchers through the National Institutes of Health Central Data Repository.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the Risk, Prevention and Health Behavior Integrated Review Group - Center for Scientific Review (CSR) Special Emphasis Panel - (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 122 KB - resprot_v11i10e40101_app1.pdf]

References

1. HIV and AIDS in adolescents. United Nations International Children's Emergency Fund. 2021 Jul. URL: https://data.unicef.org/topic/hiv-aids/ [accessed 2022-06-22]
2. Harrison S, Li X. Toward an enhanced understanding of psychological resilience for HIV youth populations. AIDS Care 2018;30(sup4):1-4 [FREE Full text] [doi: 10.1080/09540121.2018.1556384] [Medline: 30551725]
3. Schuyler AC, Edelstein ZR, Mathur S, Sekasanvu J, Nalugoda F, Gray R, et al. Mobility among youth in Rakai, Uganda: trends, characteristics, and associations with behavioural risk factors for HIV. Glob Public Health 2017 Aug;12(8):1033-1050 [FREE Full text] [doi: 10.1080/17441692.2015.1074715] [Medline: 26313708]
4. United Nations International Children's Emergency Fund. 320,000 children and adolescents newly infected with HIV in 2019, 1 every 100 seconds – UNICEF. United Nations International Children's Emergency Fund. 2020 Nov 25. URL: https://tinyurl.com/39cau5m5 [accessed 2022-06-22]
5. Peter T, Ellenberger D, Kim AA, Boeras D, Messele T, Roberts T, et al. Early antiretroviral therapy initiation: access and equity of viral load testing for HIV treatment monitoring. Lancet Infect Dis 2017 Jan;17(1):e26-e29 [FREE Full text] [doi: 10.1016/S1473-3099(16)30212-2] [Medline: 27773596]
6. Asiki G, Reniers G, Newton R, Baisley K, Nakiyingi-Miiro J, Slaymaker E, et al. Adult life expectancy trends in the era of antiretroviral treatment in rural Uganda (1991-2012). AIDS 2016 Jan 28;30(3):487-493 [FREE Full text] [doi: 10.1097/QAD.0000000000000930] [Medline: 26765939]
7. Rutakumwa R, Zalwango F, Richards E, Seeley J. Exploring the care relationship between grandparents/older carers and children infected with HIV in south-western Uganda: implications for care for both the children and their older carers. Int J Environ Res Public Health 2015 Feb 13;12(2):2120-2134 [FREE Full text] [doi: 10.3390/ijerph120202120] [Medline: 25689350]
8. Global Burden of Disease Pediatrics Collaboration, Kyu HH, Pinho C, Wagner JA, Brown JC, Bertozzi-Villa A, et al. Global and national burden of diseases and injuries among children and adolescents between 1990 and 2013: findings from the global burden of disease 2013 study. JAMA Pediatr 2016 Mar;170(3):267-287 [FREE Full text] [doi: 10.1001/jamapediatrics.2015.4276] [Medline: 26810619]
9. Fish R, Judd A, Jungmann E, O'Leary C, Foster C, HIV Young Persons Network (HYPNet). Mortality in perinatally HIV-infected young people in England following transition to adult care: an HIV Young Persons Network (HYPNet) audit. HIV Med 2014 Apr;15(4):239-244 [FREE Full text] [doi: 10.1111/hiv.12091] [Medline: 24112550]
10. Mirani G, Williams PL, Chernoff M, Abzug MJ, Levin MJ, Seage 3rd GR, IMPAACT P1074 Study Team. Changing trends in complications and mortality rates among US youth and young adults with HIV infection in the era of combination antiretroviral therapy. Clin Infect Dis 2015 Dec 15;61(12):1850-1861 [FREE Full text] [doi: 10.1093/cid/civ687] [Medline: 26270680]
11. Zanoni BC, Mayer KH. The adolescent and young adult HIV cascade of care in the United States: exaggerated health disparities. AIDS Patient Care STDS 2014 Mar;28(3):128-135 [FREE Full text] [doi: 10.1089/apc.2013.0345] [Medline: 24601734]
12. Mutumba M, Bauermeister JA, Harper GW, Musiime V, Lepkowski J, Resnicow K, et al. Psychological distress among Ugandan adolescents living with HIV: examining stressors and the buffering role of general and religious coping strategies. Glob Public Health 2017 Dec;12(12):1479-1491. [doi: 10.1080/17441692.2016.1170871] [Medline: 28278753]
13. Mutumba M, Musiime V, Lepkwoski JM, Harper GW, Snow RC, Resnicow K, et al. Examining the relationship between psychological distress and adherence to anti-retroviral therapy among Ugandan adolescents living with HIV. AIDS Care 2016 Jul;28(7):807-815. [doi: 10.1080/09540121.2015.1131966] [Medline: 27294696]
14. Nasuuna E, Kigozi J, Babirye L, Muganzi A, Sewankambo NK, Nakanjako D. Low HIV viral suppression rates following the intensive adherence counseling (IAC) program for children and adolescents with viral failure in public health facilities in Uganda. BMC Public Health 2018 Aug 22;18(1):1048 [FREE Full text] [doi: 10.1186/s12889-018-5964-x] [Medline: 30134880]
15. Arrivé E, Dicko F, Amghar H, Aka AE, Dior H, Bouah B, Pediatric IeDEA West Africa Working Group. HIV status disclosure and retention in care in HIV-infected adolescents on antiretroviral therapy (ART) in West Africa. PLoS One 2012;7(3):e33690 [FREE Full text] [doi: 10.1371/journal.pone.0033690] [Medline: 22457782]
16. Agwu AL, Lee L, Fleishman JA, Voss C, Yehia BR, Althoff KN, et al. Aging and loss to follow-up among youth living with human immunodeficiency virus in the HIV Research Network. J Adolesc Health 2015 Mar;56(3):345-351 [FREE Full text] [doi: 10.1016/j.jadohealth.2014.11.009] [Medline: 25703322]
17. Lamb MR, Fayorsey R, Nuwagaba-Biribonwoha H, Viola V, Mutabazi V, Alwar T, et al. High attrition before and after ART initiation among youth (15-24 years of age) enrolled in HIV care. AIDS 2014 Feb 20;28(4):559-568 [FREE Full text] [doi: 10.1097/QAD.0000000000000054] [Medline: 24076661]
18. Evans D, Menezes C, Mahomed K, Macdonald P, Untiedt S, Levin L, et al. Treatment outcomes of HIV-infected adolescents attending public-sector HIV clinics across Gauteng and Mpumalanga, South Africa. AIDS Res Hum Retroviruses 2013 Jun;29(6):892-900 [FREE Full text] [doi: 10.1089/AID.2012.0215] [Medline: 23373540]
19. Blower SM, Aschenbach AN, Gershengorn HB, Kahn JO. Predicting the unpredictable: transmission of drug-resistant HIV. Nat Med 2001 Sep;7(9):1016-1020. [doi: 10.1038/nm0901-1016] [Medline: 11533704]

20. Mills EJ, Nachega JB, Buchan I, Orbinski J, Attaran A, Singh S, et al. Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. JAMA 2006 Aug 09;296(6):679-690. [doi: 10.1001/jama.296.6.679] [Medline: 16896111]
21. Eisinger RW, Dieffenbach CW, Fauci AS. HIV viral load and transmissibility of HIV infection: undetectable equals untransmittable. JAMA 2019 Feb 05;321(5):451-452. [doi: 10.1001/jama.2018.21167] [Medline: 30629090]
22. Fast-Track - Ending the AIDS epidemic by 2030. Joint United Nations Programme on HIV/AIDS. 2014 Nov 18. URL: https://www.unaids.org/en/resources/documents/2014/JC2686_WAD2014report#:~:text=The%20world%20is%20embarking%20on,no%20one%20is%20left%20behind [accessed 2022-06-22]
23. Mutumba M, Bauermeister JA, Musiime V, Byaruhanga J, Francis K, Snow RC, et al. Psychosocial challenges and strategies for coping with HIV among adolescents in Uganda: a qualitative study. AIDS Patient Care STDS 2015 Feb;29(2):86-94. [doi: 10.1089/apc.2014.0222] [Medline: 25607900]
24. Martinez J, Harper G, Carleton RA, Hosek S, Bojan K, Clum G, Adolescent Medicine Trials Network. The impact of stigma on medication adherence among HIV-positive adolescent and young adult females and the moderating effects of coping and satisfaction with health care. AIDS Patient Care STDS 2012 Feb;26(2):108-115 [FREE Full text] [doi: 10.1089/apc.2011.0178] [Medline: 22149767]
25. Katz IT, Ryu AE, Onuegbu AG, Psaros C, Weiser SD, Bangsberg DR, et al. Impact of HIV-related stigma on treatment adherence: systematic review and meta-synthesis. J Int AIDS Soc 2013 Nov 13;16(3 Suppl 2):18640 [FREE Full text] [doi: 10.7448/IAS.16.3.18640] [Medline: 24242258]
26. Bermudez LG, Ssewamala FM, Neilands TB, Lu L, Jennings L, Nakigozi G, et al. Does economic strengthening improve viral suppression among adolescents living with HIV? Results from a cluster randomized trial in Uganda. AIDS Behav 2018 Nov;22(11):3763-3772 [FREE Full text] [doi: 10.1007/s10461-018-2173-7] [Medline: 29846836]
27. Ssewamala FM, Dvalishvili D, Mellins CA, Geng EH, Makumbi F, Neilands TB, et al. The long-term effects of a family based economic empowerment intervention (Suubi+Adherence) on suppression of HIV viral loads among adolescents living with HIV in southern Uganda: findings from 5-year cluster randomized trial. PLoS One 2020 Feb 10;15(2):e0228370 [FREE Full text] [doi: 10.1371/journal.pone.0228370] [Medline: 32040523]
28. Dow DE, Turner EL, Shayo AM, Mmbaga B, Cunningham CK, O'Donnell K. Evaluating mental health difficulties and associated outcomes among HIV-positive adolescents in Tanzania. AIDS Care 2016 Jul;28(7):825-833 [FREE Full text] [doi: 10.1080/09540121.2016.1139043] [Medline: 26837437]
29. Kang E, Delzell DA, Chhabra M, Oberdorfer P. Factors associated with high rates of antiretroviral medication adherence among youth living with perinatal HIV in Thailand. Int J STD AIDS 2015 Jul;26(8):534-541. [doi: 10.1177/0956462414545524] [Medline: 25080289]
30. Murphy DA, Wilson CM, Durako SJ, Muenz LR, Belzer M, Adolescent Medicine HIV/AIDS Research Network. Antiretroviral medication adherence among the REACH HIV-infected adolescent cohort in the USA. AIDS Care 2001 Feb;13(1):27-40. [doi: 10.1080/09540120020018161] [Medline: 11177463]
31. Williams PL, Storm D, Montepiedra G, Nichols S, Kammerer B, Sirois PA, PACTG 219C Team. Predictors of adherence to antiretroviral medications in children and adolescents with HIV infection. Pediatrics 2006 Dec;118(6):e1745-e1757. [doi: 10.1542/peds.2006-0493] [Medline: 17101712]
32. Nabunya P, Bahar OS, Chen B, Dvalishvili D, Damulira C, Ssewamala FM. The role of family factors in antiretroviral therapy (ART) adherence self-efficacy among HIV-infected adolescents in southern Uganda. BMC Public Health 2020 Mar 17;20(1):340 [FREE Full text] [doi: 10.1186/s12889-020-8361-1] [Medline: 32183762]
33. Ashaba S, Cooper-Vince C, Maling S, Rukundo GZ, Akena D, Tsai AC. Internalized HIV stigma, bullying, major depressive disorder, and high-risk suicidality among HIV-positive adolescents in rural Uganda. Glob Ment Health (Camb) 2018 Jun 18;5:e22 [FREE Full text] [doi: 10.1017/gmh.2018.15] [Medline: 29997894]
34. Cluver L, Orkin M. Cumulative risk and AIDS-orphanhood: interactions of stigma, bullying and poverty on child mental health in South Africa. Soc Sci Med 2009 Oct;69(8):1186-1193. [doi: 10.1016/j.socscimed.2009.07.033] [Medline: 19713022]
35. Hardon AP, Akurut D, Comoro C, Ekezie C, Irunde HF, Gerrits T, et al. Hunger, waiting time and transport costs: time to confront challenges to ART adherence in Africa. AIDS Care 2007 May;19(5):658-665. [doi: 10.1080/09540120701244943] [Medline: 17505927]
36. Weiser SD, Tuller DM, Frongillo EA, Senkungu J, Mukiibi N, Bangsberg DR. Food insecurity as a barrier to sustained antiretroviral therapy adherence in Uganda. PLoS One 2010 Apr 28;5(4):e10340 [FREE Full text] [doi: 10.1371/journal.pone.0010340] [Medline: 20442769]
37. Weiser SD, Palar K, Frongillo EA, Tsai AC, Kumbakumba E, Depee S, et al. Longitudinal assessment of associations between food insecurity, antiretroviral adherence and HIV treatment outcomes in rural Uganda. AIDS 2014 Jan 02;28(1):115-120 [FREE Full text] [doi: 10.1097/01.aids.0000433238.93986.35] [Medline: 23939234]
38. Young S, Wheeler AC, McCoy SI, Weiser SD. A review of the role of food insecurity in adherence to care and treatment among adult and pediatric populations living with HIV and AIDS. AIDS Behav 2014 Oct;18 Suppl 5(0 5):S505-S515 [FREE Full text] [doi: 10.1007/s10461-013-0547-4] [Medline: 23842717]

39. Chan BT, Weiser SD, Boum Y, Siedner MJ, Mocello AR, Haberer JE, et al. Persistent HIV-related stigma in rural Uganda during a period of increasing HIV incidence despite treatment expansion. AIDS 2015 Jan 02;29(1):83-90 [FREE Full text] [doi: 10.1097/QAD.0000000000000495] [Medline: 25268886]
40. Chan BT, Tsai AC, Siedner MJ. HIV treatment scale-up and HIV-related stigma in Sub-Saharan Africa: a longitudinal cross-country analysis. Am J Public Health 2015 Aug;105(8):1581-1587 [FREE Full text] [doi: 10.2105/AJPH.2015.302716] [Medline: 26066939]
41. Heijnders M, Van Der Meij S. The fight against stigma: an overview of stigma-reduction strategies and interventions. Psychol Health Med 2006 Aug;11(3):353-363. [doi: 10.1080/13548500600595327] [Medline: 17130071]
42. Cross HA, Heijnders M, Dalal A, Sermrittirong S, Mak S. Interventions for stigma reduction–part 1: theoretical considerations. Disabil CBR Inclus Dev 2012 Feb 15;22(3):62-70. [doi: 10.5463/dcid.v22i3.70]
43. Boyes ME, Cluver LD. Relationships between familial HIV/AIDS and symptoms of anxiety and depression: the mediating effect of bullying victimization in a prospective sample of South African children and adolescents. J Youth Adolesc 2015 Apr;44(4):847-859. [doi: 10.1007/s10964-014-0146-3] [Medline: 24996836]
44. Casale M, Boyes M, Pantelic M, Toska E, Cluver L. Suicidal thoughts and behaviour among South African adolescents living with HIV: can social support buffer the impact of stigma? J Affect Disord 2019 Feb 15;245:82-90. [doi: 10.1016/j.jad.2018.10.102] [Medline: 30368074]
45. Cluver L, Bowes L, Gardner F. Risk and protective factors for bullying victimization among AIDS-affected and vulnerable children in South Africa. Child Abuse Negl 2010 Oct;34(10):793-803. [doi: 10.1016/j.chiabu.2010.04.002] [Medline: 20880588]
46. Mutabazi-Mwesigire D, Katamba A, Martin F, Seeley J, Wu AW. Factors that affect quality of life among people living with HIV attending an urban clinic in Uganda: a cohort study. PLoS One 2015 Jun 3;10(6):e0126810 [FREE Full text] [doi: 10.1371/journal.pone.0126810] [Medline: 26039733]
47. Mutumba M, Mugerwa H, Musiime V, Gautam A, Nakyambadde H, Matama C, et al. Perceptions of strategies and intervention approaches for HIV self-management among Ugandan adolescents: a qualitative study. J Int Assoc Provid AIDS Care 2019;18:2325958218823246 [FREE Full text] [doi: 10.1177/2325958218823246] [Medline: 30798668]
48. Earnshaw VA, Smith LR, Chaudoir SR, Amico KR, Copenhaver MM. HIV stigma mechanisms and well-being among PLWH: a test of the HIV stigma framework. AIDS Behav 2013 Jun;17(5):1785-1795 [FREE Full text] [doi: 10.1007/s10461-013-0437-9] [Medline: 23456594]
49. Buseh AG, Kelber ST, Stevens PE, Park CG. Relationship of symptoms, perceived health, and stigma with quality of life among urban HIV-infected African American men. Public Health Nurs 2008;25(5):409-419. [doi: 10.1111/j.1525-1446.2008.00725.x] [Medline: 18816358]
50. Earnshaw VA, Lang SM, Lippitt M, Jin H, Chaudoir SR. HIV stigma and physical health symptoms: do social support, adaptive coping, and/or identity centrality act as resilience resources? AIDS Behav 2015 Jan;19(1):41-49 [FREE Full text] [doi: 10.1007/s10461-014-0758-3] [Medline: 24715226]
51. Holzemer WL, Human S, Arudo J, Rosa ME, Hamilton MJ, Corless I, et al. Exploring HIV stigma and quality of life for persons living with HIV infection. J Assoc Nurses AIDS Care 2009;20(3):161-168. [doi: 10.1016/j.jana.2009.02.002] [Medline: 19427593]
52. Siedner MJ, Musinguzi N, Tsai AC, Muzoora C, Kembabazi A, Weiser SD, et al. Treatment as long-term prevention: sustained reduction in HIV sexual transmission risk with use of antiretroviral therapy in rural Uganda. AIDS 2014 Jan 14;28(2):267-271 [FREE Full text] [doi: 10.1097/QAD.0000000000000136] [Medline: 24361683]
53. Closson EF, Mimiaga MJ, Sherman SG, Tangmunkongvorakul A, Friedman RK, Limbada M, HPTN063 study team. Intimacy versus isolation: a qualitative study of sexual practices among sexually active HIV-infected patients in HIV care in Brazil, Thailand, and Zambia. PLoS One 2015 Mar 20;10(3):e0120957 [FREE Full text] [doi: 10.1371/journal.pone.0120957] [Medline: 25793283]
54. Mutwa PR, Van Nuil JI, Asiimwe-Kateera B, Kestelyn E, Vyankandondera J, Pool R, et al. Living situation affects adherence to combination antiretroviral therapy in HIV-infected adolescents in Rwanda: a qualitative study. PLoS One 2013;8(4):e60073 [FREE Full text] [doi: 10.1371/journal.pone.0060073] [Medline: 23573232]
55. Nabukeera-Barungi N, Elyanu P, Asire B, Katureebe C, Lukabwe I, Namusoke E, et al. Adherence to antiretroviral therapy and retention in care for adolescents living with HIV from 10 districts in Uganda. BMC Infect Dis 2015 Nov 14;15:520 [FREE Full text] [doi: 10.1186/s12879-015-1265-5] [Medline: 26573923]
56. Denison JA, Packer C, Stalter RM, Banda H, Mercer S, Nyambe N, et al. Factors related to incomplete adherence to antiretroviral therapy among adolescents attending three HIV clinics in the copperbelt, Zambia. AIDS Behav 2018 Mar;22(3):996-1005. [doi: 10.1007/s10461-017-1944-x] [Medline: 29103190]
57. Rao D, Kekwaletswe TC, Hosek S, Martinez J, Rodriguez F. Stigma and social barriers to medication adherence with urban youth living with HIV. AIDS Care 2007 Jan;19(1):28-33. [doi: 10.1080/09540120600652303] [Medline: 17129855]
58. Kimera E, Vindevogel S, Reynaert D, Justice KM, Rubaihayo J, De Maeyer J, et al. Experiences and effects of HIV-related stigma among youth living with HIV/AIDS in Western Uganda: a photovoice study. PLoS One 2020 Apr 24;15(4):e0232359 [FREE Full text] [doi: 10.1371/journal.pone.0232359] [Medline: 32330206]

59. Kimera E, Vindevogel S, De Maeyer J, Reynaert D, Engelen AM, Nuwaha F, et al. Challenges and support for quality of life of youths living with HIV/AIDS in schools and larger community in East Africa: a systematic review. Syst Rev 2019 Feb 26;8(1):64 [FREE Full text] [doi: 10.1186/s13643-019-0980-1] [Medline: 30808419]
60. Kimera E, Vindevogel S, Kintu MJ, Rubaihayo J, De Maeyer J, Reynaert D, et al. Experiences and perceptions of youth living with HIV in Western Uganda on school attendance: barriers and facilitators. BMC Public Health 2020 Jan 17;20(1):79 [FREE Full text] [doi: 10.1186/s12889-020-8198-7] [Medline: 31952483]
61. Strauss M, Rhodes B, George G. A qualitative analysis of the barriers and facilitators of HIV counselling and testing perceived by adolescents in South Africa. BMC Health Serv Res 2015 Jun 30;15:250 [FREE Full text] [doi: 10.1186/s12913-015-0922-0] [Medline: 26123133]
62. Mavhu W, Berwick J, Chirawu P, Makamba M, Copas A, Dirawo J, et al. Enhancing psychosocial support for HIV positive adolescents in Harare, Zimbabwe. PLoS One 2013 Jul 23;8(7):e70254 [FREE Full text] [doi: 10.1371/journal.pone.0070254] [Medline: 23894625]
63. Takada S, Weiser SD, Kumbakumba E, Muzoora C, Martin JN, Hunt PW, et al. The dynamic relationship between social support and HIV-related stigma in rural Uganda. Ann Behav Med 2014 Aug;48(1):26-37 [FREE Full text] [doi: 10.1007/s12160-013-9576-5] [Medline: 24500077]
64. Earnshaw VA, Chaudoir SR. From conceptualizing to measuring HIV stigma: a review of HIV stigma mechanism measures. AIDS Behav 2009 Dec;13(6):1160-1177 [FREE Full text] [doi: 10.1007/s10461-009-9593-3] [Medline: 19636699]
65. Baxen J, Haipinge E. School experiences of HIV-positive secondary school learners on ARV treatment in Namibia. Int J Educ Dev 2015 Mar;41(C):237-244 [FREE Full text] [doi: 10.1016/j.ijedudev.2014.11.002]
66. Kelly MJ. Planning for Education in the Context of HIV/AIDS. Paris, France: Unesco, International Institute for Educational Planning; 2000.
67. Kimera E, Vindevogel S, Rubaihayo J, Reynaert D, De Maeyer J, Engelen AM, et al. Youth living with HIV/AIDS in secondary schools: perspectives of peer educators and patron teachers in Western Uganda on stressors and supports. SAHARA J 2019 Dec;16(1):51-61 [FREE Full text] [doi: 10.1080/17290376.2019.1626760] [Medline: 31179837]
68. Tsai AC. Socioeconomic gradients in internalized stigma among 4,314 persons with HIV in sub-Saharan Africa. AIDS Behav 2015 Feb;19(2):270-282 [FREE Full text] [doi: 10.1007/s10461-014-0993-7] [Medline: 25572833]
69. Castro A, Farmer P. Understanding and addressing AIDS-related stigma: from anthropological theory to clinical practice in Haiti. Am J Public Health 2005 Jan;95(1):53-59. [doi: 10.2105/AJPH.2003.028563] [Medline: 15623859]
70. Collins DL, Leibbrandt M. The financial impact of HIV/AIDS on poor households in South Africa. AIDS 2007 Nov;21 Suppl 7:S75-S81. [doi: 10.1097/01.aids.0000300538.28096.1c] [Medline: 18040168]
71. Hosegood V, Preston-Whyte E, Busza J, Moitse S, Timaeus IM. Revealing the full extent of households' experiences of HIV and AIDS in rural South Africa. Soc Sci Med 2007 Sep;65(6):1249-1259 [FREE Full text] [doi: 10.1016/j.socscimed.2007.05.002] [Medline: 17570572]
72. Masanjala W. The poverty-HIV/AIDS nexus in Africa: a livelihood approach. Soc Sci Med 2007 Mar;64(5):1032-1041. [doi: 10.1016/j.socscimed.2006.10.009] [Medline: 17126972]
73. Marais BJ, Esser M, Godwin S, Rabie H, Cotton MF. Poverty and human immunodeficiency virus in children: a view from the Western Cape, South Africa. Ann N Y Acad Sci 2008;1136:21-27. [doi: 10.1196/annals.1425.012] [Medline: 17954682]
74. Ramadhani HO, Thielman NM, Landman KZ, Ndosi EM, Gao F, Kirchherr JL, et al. Predictors of incomplete adherence, virologic failure, and antiviral drug resistance among HIV-infected adults receiving antiretroviral therapy in Tanzania. Clin Infect Dis 2007 Dec 01;45(11):1492-1498. [doi: 10.1086/522991] [Medline: 17990233]
75. Tuller DM, Bangsberg DR, Senkungu J, Ware NC, Emenyonu N, Weiser SD. Transportation costs impede sustained adherence and access to HAART in a clinic population in southwestern Uganda: a qualitative study. AIDS Behav 2010 Aug;14(4):778-784 [FREE Full text] [doi: 10.1007/s10461-009-9533-2] [Medline: 19283464]
76. Weiser S, Wolfe W, Bangsberg D, Thior I, Gilbert P, Makhema J, et al. Barriers to antiretroviral adherence for patients living with HIV infection and AIDS in Botswana. J Acquir Immune Defic Syndr 2003 Nov 01;34(3):281-288. [doi: 10.1097/00126334-200311010-00004] [Medline: 14600572]
77. Nabunya P, Ssewamala FM, Ilic V. Family economic strengthening and parenting stress among caregivers of AIDS-orphaned children: results from a cluster randomized clinical trial in Uganda. Child Youth Serv Rev 2014 Sep 01;44:417-421 [FREE Full text] [doi: 10.1016/j.childyouth.2014.07.018] [Medline: 25136142]
78. Ismayilova L, Ssewamala FM, Karimli L. Family support as a mediator of change in sexual risk-taking attitudes among orphaned adolescents in rural Uganda. J Adolesc Health 2012 Mar;50(3):228-235 [FREE Full text] [doi: 10.1016/j.jadohealth.2011.06.008] [Medline: 22325127]
79. Ssewamala FM, Karimli L, Chang-Keun H, Ismayilova L. Social capital, savings, and educational performance of orphaned adolescents in Sub-Saharan Africa. Child Youth Serv Rev 2010 Dec 01;32(12):1704-1710 [FREE Full text] [doi: 10.1016/j.childyouth.2010.07.013] [Medline: 20948971]
80. Ismayilova L, Karimli L. Harsh parenting and violence against children: a trial with ultrapoor families in Francophone West Africa. J Clin Child Adolesc Psychol 2020;49(1):18-35. [doi: 10.1080/15374416.2018.1485103] [Medline: 30110179]
81. Lachman J, Wamoyi J, Spreckelsen T, Wight D, Maganga J, Gardner F. Combining parenting and economic strengthening programmes to reduce violence against children: a cluster randomised controlled trial with predominantly male caregivers

in rural Tanzania. BMJ Glob Health 2020 Jul;5(7):e002349 [FREE Full text] [doi: 10.1136/bmjgh-2020-002349] [Medline: 32641291]
82. Amerikaner M, Monks G, Wolfe P, Thomas S. Family interaction and individual psychological health. J Couns Dev 1994;72(6):614-620. [doi: 10.1002/j.1556-6676.1994.tb01691.x]
83. Kotchick BA, Dorsey S, Miller KS, Forehand R. Adolescent sexual risk-taking behavior in single-parent ethnic minority families. J Fam Psychol 1999;13(1):93-102. [doi: 10.1037/0893-3200.13.1.93]
84. McNeely C, Shew ML, Beuhring T, Sieving R, Miller BC, Blum RW. Mothers' influence on the timing of first sex among 14- and 15-year-olds. J Adolesc Health 2002 Sep;31(3):256-265. [doi: 10.1016/s1054-139x(02)00350-6] [Medline: 12225738]
85. Miller KS, Forehand R, Kotchick BA. Adolescent sexual behavior in two ethnic minority samples: the role of family variables. J Marriage Fam 1999 Feb;61(1):85-98. [doi: 10.2307/353885]
86. Resnick MD, Bearman PS, Blum RW, Bauman KE, Harris KM, Jones J, et al. Protecting adolescents from harm. Findings from the National Longitudinal Study on Adolescent Health. JAMA 1997 Sep 10;278(10):823-832. [doi: 10.1001/jama.278.10.823] [Medline: 9293990]
87. Ansell N. Substituting for families? Schools and social reproduction in AIDS-affected Lesotho. Antipode 2008 Nov;40(5):802-824. [doi: 10.1111/j.1467-8330.2008.00638.x]
88. Smith G, Kippax S, Aggleton P, Tyrer P. HIV/AIDS school-based education in selected Asia-Pacific countries. Sex Educ 2003 Apr;3(1):3-21. [doi: 10.1080/1468181032000052126]
89. Atwiine B, Kiwanuka J, Musinguzi N, Atwine D, Haberer JE. Understanding the role of age in HIV disclosure rates and patterns for HIV-infected children in southwestern Uganda. AIDS Care 2015;27(4):424-430. [doi: 10.1080/09540121.2014.978735] [Medline: 25397994]
90. Kajubi P, Whyte S, Muhumuza S, Kyaddondo D, Katahoire AR. Communication between HIV-infected children and their caregivers about HIV medicines: a cross-sectional study in Jinja district, Uganda. J Int AIDS Soc 2014 Jul 7;17(1):19012 [FREE Full text] [doi: 10.7448/IAS.17.1.19012] [Medline: 25005046]
91. Mutumba M, Musiime V, Tsai AC, Byaruhanga J, Kiweewa F, Bauermeister JA, et al. Disclosure of HIV status to perinatally infected adolescents in urban Uganda: a qualitative study on timing, process, and outcomes. J Assoc Nurses AIDS Care 2015;26(4):472-484. [doi: 10.1016/j.jana.2015.02.001] [Medline: 26066697]
92. Hartog K, Hubbard CD, Krouwer AF, Thornicroft G, Kohrt BA, Jordans MJ. Stigma reduction interventions for children and adolescents in low- and middle-income countries: systematic review of intervention strategies. Soc Sci Med 2020 Feb;246:112749 [FREE Full text] [doi: 10.1016/j.socscimed.2019.112749] [Medline: 31978636]
93. Chambers LA, Rueda S, Baker DN, Wilson MG, Deutsch R, Raeifar E, Stigma Review Team. Stigma, HIV and health: a qualitative synthesis. BMC Public Health 2015 Sep 03;15:848 [FREE Full text] [doi: 10.1186/s12889-015-2197-0] [Medline: 26334626]
94. Mak WW, Mo PK, Ma GY, Lam MY. Meta-analysis and systematic review of studies on the effectiveness of HIV stigma reduction programs. Soc Sci Med 2017 Sep;188:30-40. [doi: 10.1016/j.socscimed.2017.06.045] [Medline: 28704645]
95. Sengupta S, Banks B, Jonas D, Miles MS, Smith GC. HIV interventions to reduce HIV/AIDS stigma: a systematic review. AIDS Behav 2011 Aug;15(6):1075-1087 [FREE Full text] [doi: 10.1007/s10461-010-9847-0] [Medline: 21088989]
96. Rao D, Elshafei A, Nguyen M, Hatzenbuehler ML, Frey S, Go VF. A systematic review of multi-level stigma interventions: state of the science and future directions. BMC Med 2019 Feb 15;17(1):41 [FREE Full text] [doi: 10.1186/s12916-018-1244-y] [Medline: 30770756]
97. Stangl AL, Lloyd JK, Brady LM, Holland CE, Baral S. A systematic review of interventions to reduce HIV-related stigma and discrimination from 2002 to 2013: how far have we come? J Int AIDS Soc 2013 Nov 13;16(3 Suppl 2):18734 [FREE Full text] [doi: 10.7448/IAS.16.3.18734] [Medline: 24242268]
98. MacPherson P, Munthali C, Ferguson J, Armstrong A, Kranzer K, Ferrand RA, et al. Service delivery interventions to improve adolescents' linkage, retention and adherence to antiretroviral therapy and HIV care. Trop Med Int Health 2015 Aug;20(8):1015-1032 [FREE Full text] [doi: 10.1111/tmi.12517] [Medline: 25877007]
99. Ssewamala FM, Bermudez LG, Neilands TB, Mellins CA, McKay MM, Garfinkel I, et al. Suubi4Her: a study protocol to examine the impact and cost associated with a combination intervention to prevent HIV risk behavior and improve mental health functioning among adolescent girls in Uganda. BMC Public Health 2018 Jun 05;18(1):693 [FREE Full text] [doi: 10.1186/s12889-018-5604-5] [Medline: 29871619]
100. Ridgeway K, Dulli LS, Murray KR, Silverstein H, Dal Santo L, Olsen P, et al. Interventions to improve antiretroviral therapy adherence among adolescents in low- and middle-income countries: a systematic review of the literature. PLoS One 2018 Jan 2;13(1):e0189770 [FREE Full text] [doi: 10.1371/journal.pone.0189770] [Medline: 29293523]
101. Shaw S, Amico KR. Antiretroviral therapy adherence enhancing interventions for adolescents and young adults 13-24 years of age: a review of the evidence base. J Acquir Immune Defic Syndr 2016 Aug 01;72(4):387-399 [FREE Full text] [doi: 10.1097/QAI.0000000000000977] [Medline: 26959190]
102. Bermudez LG, Jennings L, Ssewamala FM, Nabunya P, Mellins C, McKay M. Equity in adherence to antiretroviral therapy among economically vulnerable adolescents living with HIV in Uganda. AIDS Care 2016 Mar;28 Suppl 2:83-91 [FREE Full text] [doi: 10.1080/09540121.2016.1176681] [Medline: 27392003]

103. Han CK, Ssewamala FM, Wang JS. Family economic empowerment and mental health among AIDS-affected children living in AIDS-impacted communities: evidence from a randomised evaluation in southwestern Uganda. J Epidemiol Community Health 2013 Mar;67(3):225-230 [FREE Full text] [doi: 10.1136/jech-2012-201601] [Medline: 23410851]
104. Jennings L, Ssewamala FM, Nabunya P. Effect of savings-led economic empowerment on HIV preventive practices among orphaned adolescents in rural Uganda: results from the Suubi-Maka randomized experiment. AIDS Care 2016;28(3):273-282 [FREE Full text] [doi: 10.1080/09540121.2015.1109585] [Medline: 26548549]
105. Ssewamala FM, Han C, Neilands TB, Ismayilova L, Sperber E. Effect of economic assets on sexual risk-taking intentions among orphaned adolescents in Uganda. Am J Public Health 2010 Mar;100(3):483-488 [FREE Full text] [doi: 10.2105/AJPH.2008.158840] [Medline: 20075323]
106. Maluccio JA, Wu F, Rokon RB, Rawat R, Kadiyala S. Assessing the impact of food assistance on stigma among people living with HIV in Uganda using the HIV/AIDS stigma instrument-PLWA (HASI-P). AIDS Behav 2017 Mar;21(3):766-782. [doi: 10.1007/s10461-016-1476-9] [Medline: 27372803]
107. McCoy SI, Njau PF, Fahey C, Kapologwe N, Kadiyala S, Jewell NP, et al. Cash vs. food assistance to improve adherence to antiretroviral therapy among HIV-infected adults in Tanzania. AIDS 2017 Mar 27;31(6):815-825 [FREE Full text] [doi: 10.1097/QAD.0000000000001406] [Medline: 28107221]
108. Rawat R, Faust E, Maluccio JA, Kadiyala S. The impact of a food assistance program on nutritional status, disease progression, and food security among people living with HIV in Uganda. J Acquir Immune Defic Syndr 2014 May 01;66(1):e15-e22. [doi: 10.1097/QAI.0000000000000079] [Medline: 24326603]
109. Singer AW, Weiser SD, McCoy SI. Does food insecurity undermine adherence to antiretroviral therapy? A systematic review. AIDS Behav 2015 Aug;19(8):1510-1526. [doi: 10.1007/s10461-014-0873-1] [Medline: 25096896]
110. Tirivayi N, Groot W. Health and welfare effects of integrating AIDS treatment with food assistance in resource constrained settings: a systematic review of theory and evidence. Soc Sci Med 2011 Sep;73(5):685-692. [doi: 10.1016/j.socscimed.2011.06.056] [Medline: 21824702]
111. Ssewamala FM, Shu-Huah Wang J, Brathwaite R, Sun S, Mayo-Wilson LJ, Neilands TB, et al. Impact of a family economic intervention (Bridges) on health functioning of adolescents orphaned by HIV/AIDS: A 5-year (2012-2017) cluster randomized controlled trial in Uganda. Am J Public Health 2021 Mar;111(3):504-513. [doi: 10.2105/AJPH.2020.306044] [Medline: 33476237]
112. Tozan Y, Sun S, Capasso A, Shu-Huah Wang J, Neilands TB, Bahar OS, et al. Evaluation of a savings-led family-based economic empowerment intervention for AIDS-affected adolescents in Uganda: a four-year follow-up on efficacy and cost-effectiveness. PLoS One 2019 Dec 31;14(12):e0226809 [FREE Full text] [doi: 10.1371/journal.pone.0226809] [Medline: 31891601]
113. Wang JS, Ssewamala FM, Neilands TB, Bermudez LG, Garfinkel I, Waldfogel J, et al. Effects of financial incentives on saving outcomes and material well-being: evidence from a randomized controlled trial in Uganda. J Policy Anal Manage 2018;37(3):602-629 [FREE Full text] [doi: 10.1002/pam.22065] [Medline: 30122799]
114. Ssewamala FM, Wang JS, Neilands TB, Bermudez LG, Garfinkel I, Waldfogel J, et al. Cost-effectiveness of a savings-led economic empowerment intervention for AIDS-affected adolescents in Uganda: implications for scale-up in low-resource communities. J Adolesc Health 2018 Jan;62(1S):S29-S36 [FREE Full text] [doi: 10.1016/j.jadohealth.2017.09.026] [Medline: 29273115]
115. Harper GW, Lemos D, Hosek SG. Stigma reduction in adolescents and young adults newly diagnosed with HIV: findings from the Project ACCEPT intervention. AIDS Patient Care STDS 2014 Oct;28(10):543-554 [FREE Full text] [doi: 10.1089/apc.2013.0331] [Medline: 25216106]
116. Ssewamala FM, Sperber E, Zimmerman JM, Karimli L. The potential of asset‐based development strategies for poverty alleviation in Sub‐Saharan Africa. Int J Soc Welfare 2010 Aug 13;19(4):433-443. [doi: 10.1111/j.1468-2397.2010.00738.x]
117. Sherraden M, Gilbert N. Assets and the Poor: New American Welfare Policy. New York, NY, USA: Routledge; 1991.
118. Broderick CB. Understanding Family Process: Basics of Family Systems Theory. Thousand Oaks, CA, USA: Sage Publications; 1993.
119. Brown J. Bowen family systems theory and practice: illustration and critique. Aust N Z J Fam Ther 1999 Jun;20(2):94-103. [doi: 10.1002/j.1467-8438.1999.tb00363.x]
120. Karimli L, Ssewamala FM. Do savings mediate changes in adolescents' future orientation and health-related outcomes? Findings from randomized experiment in Uganda. J Adolesc Health 2015 Oct;57(4):425-432 [FREE Full text] [doi: 10.1016/j.jadohealth.2015.06.011] [Medline: 26271162]
121. Ssewamala FM, Karimli L, Torsten N, Wang JS, Han CK, Ilic V, et al. Applying a family-level economic strengthening intervention to improve education and health-related outcomes of school-going AIDS-orphaned children: lessons from a randomized experiment in Southern Uganda. Prev Sci 2016 Jan;17(1):134-143 [FREE Full text] [doi: 10.1007/s11121-015-0580-9] [Medline: 26228480]
122. Ssewamala FM, Byansi W, Bahar OS, Nabunya P, Neilands TB, Mellins C, et al. Suubi+Adherence study protocol: a family economic empowerment intervention addressing HIV treatment adherence for perinatally infected adolescents. Contemp Clin Trials Commun 2019 Dec;16:100463 [FREE Full text] [doi: 10.1016/j.conctc.2019.100463] [Medline: 31872152]

123. Michalopoulos LM, Meinhart M, Barton SM, Kuhn J, Mukasa MN, Namuwonge F, et al. Adaptation and validation of the shame questionnaire among Ugandan youth living with HIV. Child Indic Res 2019 Jun 15;12(3):1023-1042 [FREE Full text] [doi: 10.1007/s12187-018-9570-3] [Medline: 34721728]
124. Uganda AIDS Commission. Uganda AIDS country progress report July 2017-June 2018. Government of Uganda. 2018 Sep. URL: https://www.unaids.org/sites/default/files/country/documents/UGA_2019_countryreport.pdf [accessed 2022-07-26]
125. Consolidated Guidelines for Prevention and Treatment of HIV in Uganda. Ministry of Health Knowledge Management Portal, Uganda. 2018. URL: http://library.health.go.ug/publications/hivaids/consolidated-guidelines-prevention-and-treatment-hiv-uganda-1 [accessed 2022-06-22]
126. Bhana A, Petersen I, Mason A, Mahintsho Z, Bell C, McKay M. Children and youth at risk: adaptation and pilot study of the CHAMP (Amaqhawe) programme in South Africa. Afr J AIDS Res 2004 May;3(1):33-41. [doi: 10.2989/16085900409490316] [Medline: 25874981]
127. Bhana A, McKay MM, Mellins C, Petersen I, Bell C. Family-based HIV prevention and intervention services for youth living in poverty-affected contexts: the CHAMP model of collaborative, evidence-informed programme development. J Int AIDS Soc 2010 Jun 23;13 Suppl 2:S8 [FREE Full text] [doi: 10.1186/1758-2652-13-S2-S8] [Medline: 20573290]
128. Petersen I, Mason A, Bhana A, Bell CC, McKay M. Mediating social representations using a cartoon narrative in the context of HIV/AIDS: the AmaQhawe Family Project in South Africa. J Health Psychol 2006 Mar;11(2):197-208. [doi: 10.1177/1359105306061180] [Medline: 16464919]
129. McKay MM, Chasse KT, Paikoff R, McKinney LD, Baptiste D, Coleman D, et al. Family-level impact of the CHAMP Family Program: a community collaborative effort to support urban families and reduce youth HIV risk exposure. Fam Process 2004 Mar;43(1):79-93. [doi: 10.1111/j.1545-5300.2004.04301007.x] [Medline: 15359716]
130. Karimli L, Ssewamala FM, Ismayilova L. Extended families and perceived caregiver support to AIDS orphans in Rakai district of Uganda. Child Youth Serv Rev 2012 Jul;34(7):1351-1358 [FREE Full text] [doi: 10.1016/j.childyouth.2012.03.015] [Medline: 23188930]
131. Dennison ST. A Multiple Family Group Therapy Program for at Risk Adolescents and their Families. Springfield, IL, USA: Charles C Thomas Publisher; 2005.
132. Karimli L, Ssewamala FM, Neilands TB, McKay MM. Matched child savings accounts in low-resource communities: who saves? Glob Soc Welf 2015 Jun;2(2):53-64 [FREE Full text] [doi: 10.1007/s40609-015-0026-0] [Medline: 26636025]
133. Karimli L, Ssewamala FM, Neilands TB. Poor families striving to save in matched children's savings accounts: findings from a randomized experimental design in Uganda. Soc Serv Rev 2014 Dec;88(4):658-694 [FREE Full text] [doi: 10.1086/679256] [Medline: 25525282]
134. McKay MM, Gonzales JJ, Stone S, Ryland D, Kohner K. Multiple family therapy groups: a responsive intervention model for inner city families. Soc Work Group 1995;18(4):41-56. [doi: 10.1300/j009v18n04_04]
135. Curley J, Ssewamala F, Han CK. Assets and educational outcomes: child development accounts (CDAs) for orphaned children in Uganda. Child Youth Serv Rev 2010 Nov 01;32(11):1585-1590 [FREE Full text] [doi: 10.1016/j.childyouth.2009.07.016] [Medline: 21076646]
136. Curley J, Ssewamala FM, Nabunya P, Ilic V, Keun HC. Child development accounts (CDAs): an asset-building strategy to empower girls in Uganda. Int Soc Work 2016 Jan 01;59(1):18-31 [FREE Full text] [doi: 10.1177/0020872813508569] [Medline: 26900173]
137. Tozan Y, Sun S, Capasso A, Shu-Huah Wang J, Neilands T, Bahar OS, et al. Cost-effectiveness of an economic empowerment intervention for AIDS-affected adolescents in Uganda: four-year follow-up. In: Proceedings of the 9th Annual Conference of the American Society of Health Economists. 2020 Presented at: ASHEcon '20; June 7-10, 2020; St. Louis, MO, USA URL: https://ashecon.confex.com/ashecon/2020/meetingapp.cgi/Paper/8498
138. Nabunya P, Ssewamala FM. The effects of parental loss on the psychosocial wellbeing of AIDS-orphaned children living in AIDS-impacted communities: does gender matter? Child Youth Serv Rev 2014 Aug 01;43:131-137 [FREE Full text] [doi: 10.1016/j.childyouth.2014.05.011] [Medline: 25067869]
139. Ssewamala FM, Ismayilova L, McKay M, Sperber E, Bannon Jr W, Alicea S. Gender and the effects of an economic empowerment program on attitudes toward sexual risk-taking among AIDS-orphaned adolescent youth in Uganda. J Adolesc Health 2010 Apr;46(4):372-378 [FREE Full text] [doi: 10.1016/j.jadohealth.2009.08.010] [Medline: 20307827]
140. Ssewamala FM, Neilands TB, Waldfogel J, Ismayilova L. The impact of a comprehensive microfinance intervention on depression levels of AIDS-orphaned children in Uganda. J Adolesc Health 2012 Apr;50(4):346-352 [FREE Full text] [doi: 10.1016/j.jadohealth.2011.08.008] [Medline: 22443837]
141. Ssewamala FM, Nabunya P, Mukasa NM, Ilic V, Nattabi J. Integrating a mentorship component in programming for care and support of AIDS-orphaned and vulnerable children: lessons from the suubi and bridges programs in sub-Saharan Africa. Glob Soc Welf 2014 Mar 01;1(1):9-24 [FREE Full text] [doi: 10.1007/s40609-014-0008-7] [Medline: 24999449]
142. Ssewamala FM, Sherraden M. Integrating saving into microenterprise programs for the poor: do institutions matter? Soc Serv Rev 2004 Sep;78(3):404-428 [FREE Full text] [doi: 10.1086/421919]
143. Ssewamala FM, Alicea S, Bannon Jr WM, Ismayilova L. A novel economic intervention to reduce HIV risks among school-going AIDS orphans in rural Uganda. J Adolesc Health 2008 Jan;42(1):102-104 [FREE Full text] [doi: 10.1016/j.jadohealth.2007.08.011] [Medline: 18155037]

144. Ssewamala FM, Curley J. School attendance of orphaned children in sub-Saharan Africa: the role of family assets. In: Johnson WG, Tracy MB, editors. Social Development Issues: Alternative Approaches to Global Human Needs. Iowa city, Iowa, USA: University of Iowa; 2006:84-105.
145. Ssewamala FM, Ismayilova L. Integrating children's savings accounts in the care and support of orphaned adolescents in rural Uganda. Soc Serv Rev 2009 Sep 01;83(3):453-472 [FREE Full text] [doi: 10.1086/605941] [Medline: 20445763]
146. Brown L, Macintyre K, Trujillo L. Interventions to reduce HIV/AIDS stigma: what have we learned? AIDS Educ Prev 2003 Feb;15(1):49-69. [doi: 10.1521/aeap.15.1.49.23844] [Medline: 12627743]
147. Gronholm PC, Henderson C, Deb T, Thornicroft G. Interventions to reduce discrimination and stigma: the state of the art. Soc Psychiatry Psychiatr Epidemiol 2017 Mar;52(3):249-258 [FREE Full text] [doi: 10.1007/s00127-017-1341-9] [Medline: 28144713]
148. Ruria EC, Masaba R, Kose J, Woelk G, Mwangi E, Matu L, et al. Optimizing linkage to care and initiation and retention on treatment of adolescents with newly diagnosed HIV infection. AIDS 2017 Jul 01;31 Suppl 3:S253-S260 [FREE Full text] [doi: 10.1097/QAD.0000000000001538] [Medline: 28665883]
149. Ferreira R, Ebersöhn L. Formative evaluation of the STAR intervention: improving teachers' ability to provide psychosocial support for vulnerable individuals in the school community. Afr J AIDS Res 2011 Apr;10(1):63-72. [doi: 10.2989/16085906.2011.575549] [Medline: 25859621]
150. Ebersöhn L, Ferreira R. Coping in an HIV/AIDS-dominated context: teachers promoting resilience in schools. Health Educ Res 2011 Aug;26(4):596-613. [doi: 10.1093/her/cyr016] [Medline: 21441389]
151. Chan JY, Mak WW, Law LS. Combining education and video-based contact to reduce stigma of mental illness: "The Same or Not the Same" anti-stigma program for secondary schools in Hong Kong. Soc Sci Med 2009 Apr;68(8):1521-1526. [doi: 10.1016/j.socscimed.2009.02.016] [Medline: 19282079]
152. Pettigrew TF, Tropp LR. How does intergroup contact reduce prejudice? Meta-analytic tests of three mediators. Eur J Soc Psychol 2008 Sep;38(6):922-934. [doi: 10.1002/ejsp.504]
153. Levine S. Documentary film and HIV/AIDS: new directions for applied visual anthropology in Southern Africa. Vis Anthropol Rev 2003 Mar;19(1-2):57-72. [doi: 10.1525/var.2003.19.1-2.57]
154. Boyatzis RE. Transforming Qualitative Information: Thematic Analysis and Code Development. Thousand Oaks, CA, USA: Sage Publications; 1998.
155. Guest G, Bunce A, Johnson L. How many interviews are enough?: an experiment with data saturation and variability. Field Methods 2006 Feb 1;18(1):59-82. [doi: 10.1177/1525822X05279903]
156. Morse JM. Determining sample size. Qual Health Res 2000 Jan 1;10(1):3-5. [doi: 10.1177/104973200129118183]
157. Padgett DK. Qualitative Methods in Social Work Research. 2nd edition. Thousand Oaks, CA, USA: Sage Publications; 2008.
158. Zou GY, Donner A. Extension of the modified Poisson regression model to prospective studies with correlated binary data. Stat Methods Med Res 2013 Dec;22(6):661-670. [doi: 10.1177/0962280211427759] [Medline: 22072596]
159. Pedroza C, Truong VT. Estimating relative risks in multicenter studies with a small number of centers - which methods to use? A simulation study. Trials 2017 Nov 02;18(1):512 [FREE Full text] [doi: 10.1186/s13063-017-2248-1] [Medline: 29096682]
160. Rodriguez G, Goldman N. An assessment of estimation procedures for multilevel models with binary responses. J R Stat Soc Ser A Stat Soc 1995;158(1):73-89. [doi: 10.2307/2983404]
161. Westfall PH, Young SS. Resampling-Based Multiple Testing: Examples and Methods for p-Value Adjustment. New York, NY, USA: John Wiley and Sons; 1993.
162. Mancl LA, DeRouen TA. A covariance estimator for GEE with improved small-sample properties. Biometrics 2001 Mar;57(1):126-134. [doi: 10.1111/j.0006-341x.2001.00126.x] [Medline: 11252587]
163. Cook RD, Weisberg S. Residuals and Influence in Regression. New York, NY, USA: Chapman and Hall; 1982.
164. Stroup WW, Milliken GA, Claasen EA, Wolfinger RD. SAS for Mixed Models: Introduction and Basic Applications. 2nd edition. Cary, NC, USA: SAS Institute; 2018.
165. Hintze J. NCSS PASS 2020. 16 ed. Kaysville, UT, USA: NCSS Statistical Software; 2020. URL: https://www.ncss.com/ [accessed 2022-06-22]
166. Zarkin GA, Bala MV, Wood LL, Bennett CL, Simpson K, Dohn MN. Estimating the cost effectiveness of atovaquone versus intravenous pentamidine in the treatment of mild-to-moderate Pneumocystis carinii pneumonia. Pharmacoeconomics 1996 Jun;9(6):525-534. [doi: 10.2165/00019053-199609060-00007] [Medline: 10160480]
167. Doubilet P, McNeil BJ. Clinical decisionmaking. Med Care 1985 May;23(5):648-662. [doi: 10.1097/00005650-198505000-00021] [Medline: 3892182]
168. NVIVO 12. QSR International. 2018. URL: https://www.qsrinternational.com/nvivo-qualitative-data-analysis-software/home [accessed 2022-06-22]
169. Nevedal AL, Ayalon L, Briller SH. A qualitative evidence synthesis review of longitudinal qualitative research in gerontology. Gerontologist 2019 Nov 16;59(6):e791-e801. [doi: 10.1093/geront/gny134] [Medline: 30395232]
170. Lincoln SY, Guba EG. Naturalistic inquiry. Newbury Park, CA, USA: Sage Publications; 1985.

171. Strauss A, Corbin J. Basics of Qualitative Research: Techniques and Procedures for Developing Grounded Theory. 2nd edition. Thousand Oaks, CA, USA: Sage Publications; 1998.
172. Charmaz K. Grounded theory: objectivist and constructivist methods. In: Denzin NK, Lincoln YS, Lincoln YS, editors. Strategies of Qualitative Inquiry. Thousand Oaks, CA: Sage Publications; 2003:249-291.
173. Miles MB, Huberman MA. Qualitative Data Analysis: An Expanded Sourcebook. 2nd edition. Thousand Oaks, CA, USA: Sage Publications; 1994.
174. Wang JS, Ssewamala FM, Han CK. Family economic strengthening and mental health functioning of caregivers for AIDS-affected children in rural Uganda. Vulnerable Child Youth Stud 2014;9(3):258-269 [FREE Full text] [doi: 10.1080/17450128.2014.920119] [Medline: 26246846]
175. Kivumbi A, Byansi W, Ssewamala FM, Proscovia N, Damulira C, Namatovu P. Utilizing a family-based economic strengthening intervention to improve mental health wellbeing among female adolescent orphans in Uganda. Child Adolesc Psychiatry Ment Health 2019 Mar 11;13:14 [FREE Full text] [doi: 10.1186/s13034-019-0273-4] [Medline: 30899327]
176. Attawekll K, Elder K. United Nations Educational, Scientific and Cultural Organization. Paris, France: United Nations Educational, Scientific and Cultural Organization; 2008. URL: https://unesdoc.unesco.org/ark:/48223/pf0000146122 [accessed 2022-06-22]

Abbreviations

ART: antiretroviral therapy
FEE: family economic empowerment
GED-HIVSR: group-based HIV stigma reduction for educators
IRB: institutional review board
LMM: linear mixed model
MFG: multiple family group
MFG-HIVSR: MFG HIV stigma reduction for educators
MI: maximum imputation
ML: maximum likelihood
SSA: sub-Saharan Africa
VL: viral load

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Protocol

Nurse Practitioner–Led Integrated Rapid Access to HIV Prevention for People Who Inject Drugs (iRaPID): Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: The ongoing volatile opioid epidemic remains a significant public health concern, alongside continued outbreaks of HIV and hepatitis C virus among people who inject drugs. The limited access to and scale-up of medications for opioid use disorder (MOUD) among people who inject drugs, coupled with multilevel barriers to pre-exposure prophylaxis (PrEP) uptake, makes it imperative to integrate evidence-based risk reduction and HIV prevention strategies in innovative ways. To address this need, we developed an integrated rapid access to HIV prevention program for people who inject drugs (iRaPID) that incorporates same-day PrEP and MOUD for this population.

Objective: The primary objective of this pilot study is to assess the feasibility and acceptability of the program and evaluate its preliminary efficacy on PrEP and MOUD uptake for a future randomized controlled trial (RCT). We also aim to explore information on the implementation of the program in a real-world setting using a type I hybrid implementation trial design.

Methods: Using a type I hybrid implementation trial design, we are pilot testing the nurse practitioner–led iRaPID program while exploring information on its implementation in a real-world setting. Specifically, we will assess the feasibility and acceptability of the iRaPID program and evaluate its preliminary efficacy on PrEP and MOUD uptake in a pilot RCT. The enrolled 50 people who inject drugs will be randomized (1:1) to either iRaPID or treatment as usual (TAU). Behavioral assessments will occur at baseline, and at 1, 3, and 6 months. Additionally, we will conduct a process evaluation of the delivery and implementation of the iRaPID program to collect information for future implementation.

Results: Recruitment began in July 2021 and was completed in August 2022. Data collection is planned through February 2023. The Institutional Review Boards at Yale University and the University of Connecticut approved this study (2000028740).

Conclusions: This prospective pilot study will test a nurse practitioner–led, integrated HIV prevention program that incorporates same-day PrEP and MOUD for people who inject drugs. This low-threshold protocol delivers integrated prevention via one-stop shopping under the direction of nurse practitioners. iRaPID seeks to overcome barriers to delayed PrEP and MOUD initiation, which is crucial for people who inject drugs who have had minimal access to evidence-based prevention.

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KEYWORDS

HIV prevention; people who inject drugs; sexual risk; pre-exposure prophylaxis; opioid agonist therapy; medications for opioid use disorder; opioid use disorder

Introduction

With opioid use disorder being intricately linked to HIV transmission via drug injection, the United States is witnessing resurgent twin opioid and HIV epidemics, fueled by concurrent rises in opioid-related overdoses [1-6]. People who inject drugs remain disproportionately affected by HIV [7] despite their engagement in preventable drug- and sex-related risk behaviors [8-14]. There is an urgent need to combine evidence-based harm reduction services and HIV prevention strategies in innovative ways to effectively curb HIV incidence.

Critical elements in the HIV prevention toolbox for people who inject drugs include medication for opioid use disorder (MOUD), syringe services programs (SSPs), pre-exposure prophylaxis (PrEP), and HIV treatment as prevention. MOUD minimizes the risk of fatal overdose and effectively reduces HIV transmission by decreasing or eliminating the frequency of injection [15-21], while SSPs narrow transmission risk with each protected injection [22,23]. Nevertheless, access to these programs among people who inject drugs is often limited, with overall coverage remaining low [24-27] despite data documenting increased HIV incidence in people who inject drugs where MOUD and SSPs are unavailable [28-30]. HIV treatment as prevention requires active case-finding and effective linkage to HIV treatment, which is markedly improved when people with HIV gain access to MOUD [31].

PrEP is an essential additional tool for people who inject drugs [32,33]. It is not restricted to specially licensed prescribers and reduces HIV transmission from not only drug injection but also sex. Although integrating PrEP into existing evidence-based risk reduction programs can strengthen HIV prevention efforts for people who inject drugs [16,17,19-21,34], its scale-up has been hampered for several reasons. First, PrEP and MOUD each require a separate prescription. They are often delivered in different settings and by clinicians with varying areas of expertise [35], generating excess demands on patients and making access to care more difficult for people who inject drugs. Furthermore, the provision of PrEP and MOUD prescriptions is unnecessarily complex. The traditional PrEP delivery model requires multiple visits before the prescription. Existing data show high attrition rates between initial screening and PrEP initiation, adding to the attrition observed between PrEP referral and initiation [36,37]. The prescription of MOUD also has its own set of demands [38], some of which are regulated by the Drug Enforcement Agency. PrEP and MOUD have been mainly prescribed in a "centralized" care delivery model that focuses more on physicians, is costly, and limits accessibility. There also remains a suboptimal supply of prescribers [39-41], with many physicians reluctant to prescribe medications to people who inject drugs [42-45].

An innovative approach of coprescribing PrEP and MOUD on the same day can streamline delivery, as it addresses impediments to PrEP and MOUD uptake. Same-day PrEP prescription is a safe, feasible, and acceptable approach to linking at-risk individuals to much-needed PrEP care early on [46-48] while decreasing attrition rates between the initial visit and prescription time and increasing adherence [49]. This approach also sets the stage to boost PrEP uptake and makes the current standard of care, which already comprises streamlined access to and initiation of MOUD, more inclusive. The provision of same-day MOUD, when integrated with PrEP, provides the added benefit of stabilizing patients and can therefore strongly complement and facilitate PrEP initiation, adherence, and persistence as has been observed with antiretroviral therapy [34,50]. Additionally, it has the potential to overcome provider-level barriers, increasing the confidence that patients will maintain their treatment regimen [43,45].

With ongoing calls for task shifting to support the expansion of HIV prevention services [51], there is a need to "decentralize" PrEP delivery by incorporating it into front-line prevention services provided by nurse practitioners (NPs). Nurse-led PrEP delivery is a viable strategy that can lead to rapid increases in PrEP service capacity without additional resources [39,52]. Furthermore, the 2016 Comprehensive Addiction and Recovery Act permits NPs to prescribe buprenorphine with waivers, paving the way for PrEP and MOUD coprescription. This decentralized delivery model represents an innovative approach to scale-up integrated HIV prevention services among people who inject drugs.

We developed an NP-led, integrated rapid access to HIV prevention program for people who inject drugs (iRaPID) that incorporates same-day access to PrEP and MOUD. The primary objective of this pilot study is to assess the feasibility and acceptability of the program and evaluate its preliminary efficacy on PrEP and MOUD uptake for a future randomized controlled trial (RCT). We also aim to explore information on the implementation of the program in a real-world setting using a type I hybrid implementation trial design.

Methods

Study Design

The protocol involves a type I hybrid implementation trial design [53], where we pilot test the NP-led iRaPID program. The study is a 2-arm RCT that examines the feasibility and acceptability of the program among people who inject drugs and clinical stakeholders. In the process, we can provide a preliminary estimate of the efficacy of PrEP and MOUD uptake by comparing the iRaPID program against treatment as usual (TAU) among HIV-negative people who inject drugs. We hypothesize that the iRaPID program will be more efficacious than will TAU on PrEP and MOUD uptake and adherence.

In this type I hybrid implementation trial design, we collect process measures to inform future implementation efforts. We will explore potential patient- and provider-level barriers and facilitators of the program regarding its implementation in

real-world settings. More specifically, we will assess at both these levels the overall satisfaction, perceived utility, and relevance of each intervention component; determine the relevant needs of the target population (ie, people who inject drugs), thereby delineating intervention characteristics that address those needs; and explore the barriers to implementation of the iRaPID program, such as logistical barriers and time and resource constraints. Finally, changes needed to accommodate same-day coprescription of PrEP and MOUD will be established, along with the resources and structural changes necessary for the successful implementation of the program.

Ethics Approval

The institutional review board at Yale University approved this protocol (#2000028740) with an institutional reliance agreement with the University of Connecticut. This study is registered at ClinicalTrials.gov (NCT04531670).

Study Setting

This study is being conducted at the New Haven Syringe Service Program (NHSSP) in Connecticut, the first SSP in the United States (established 1986). With steadily high-ranking and rising fatal and nonfatal accidental overdose rates over the past few years, New Haven continues to bear the detrimental impacts of a severe opioid crisis and reflects the nationwide picture of a twin opioid and HIV epidemic, with a high HIV prevalence among people who inject drugs in the city [54,55]. The NHSSP offers services beyond New Haven to exurban and rural communities and integrated medical services through the Community Health Care Van, a 40-foot mobile medical clinic, and minivans that provide personalized services [56-60].

Study Procedures

Recruitment and Screening

Recruitment for the trial started in July 2021 at the NHSSP and lasted until August 31, 2022. People who inject drugs were recruited on-site through posted flyers at the central and mobile distribution locations of the NHSSP, word of mouth, and community-based outreach. Individuals are screened initially by phone or in person to assess whether they meet the eligibility criteria, which include being 18 years or older; having a confirmed HIV-negative status; self-reported injection drug use in the past 6 months; OUD based on *The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria; and substantial ongoing HIV risk factors (eg, condomless sex, needle sharing) in the past 6 months. Uninsured participants were referred to an on-site case manager for assistance with insurance enrollment.

Informed Consent, Enrollment, and Randomization

After confirming eligibility criteria and providing informed consent, all participants underwent a baseline assessment, which took approximately 90 minutes and was administered electronically by a trained research staff member in a private room at NHSSP. Participants were then randomized (1:1) to receive either the iRaPID intervention or TAU. Randomization was done via REDCap software (Vanderbilt University), a secure, HIPAA (Health Insurance Portability and Accountability Act)-compliant web app with a built-in randomization feature that allows the development of a defined randomization model. Randomization was stratified by sex to ensure that an equal proportion of participants is present in both arms. Participants are assessed at baseline, and 1-, 3-, and 6-month time points. This approach allows us to examine short-term outcomes and the decay and emergence of intervention effects. Study participants are reimbursed for the time required to complete the assessments (US $35 for the baseline assessment and US $25 for each follow-up assessment).

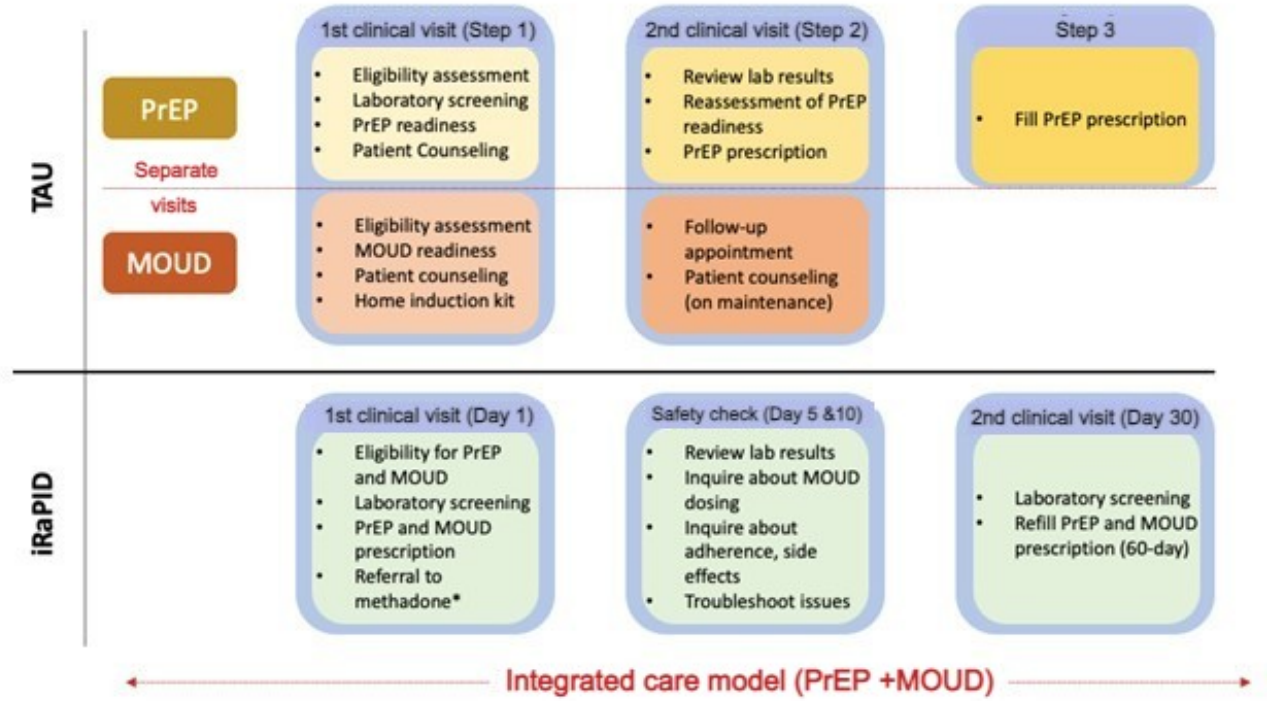
Intervention Procedures

Treatment as Usual

Participants randomized to the TAU group will follow the existing clinical guidelines to receive PrEP, MOUD, or both medications. They are provided with a comprehensive list of PrEP and MOUD programs available in the area. Since PrEP and MOUD services are not integrated within the current standard of care, participants will have to be screened at separate visits (one for PrEP and another for MOUD) if they are interested in both programs unless they find a prescriber who will provide both.

For PrEP, the current standard of care generally involves 2 clinical appointments. During the first visit, patients are assessed for eligibility and PrEP readiness and receive additional counseling on using PrEP. Additionally, laboratory screenings are ordered. During the second visit, which usually occurs 1 to 3 weeks later, the laboratory results are reviewed, PrEP readiness is reassessed, and the patient is provided with a PrEP prescription that they will need to fill at a pharmacy. Access to MOUD also entails 2 separate clinic visits at least 3 days apart. The first encompasses an eligibility assessment, patient counseling, and an evaluation of the patient's readiness to start therapy. Patients are also given a home induction kit and asked to follow up in 3 days for further counseling on maintenance therapy (Figure 1).

Figure 1. Integrated care process for same-day PrEP and MOUD compared to TAU. iRaPID: integrated rapid access to HIV prevention program for people who inject drugs; MOUD: medication for opioid use disorder; PrEP: pre-exposure prophylaxis; TAU: treatment as usual. *Patients interested in methadone prescriptions are referred to a methadone (or other appropriate) addiction treatment center.



iRaPID Intervention

The iRaPID program was developed by adapting TAU services for PrEP and MOUD to accommodate same-day coprescription for both medications through a single nurse provider. We used the modified participatory, evidence-based, patient-focused process for advanced practice nursing [61] to guide the optimal use of the NP-led model and refined it to incorporate the same-day coprescription of PrEP and MOUD. Participants randomized to the iRaPID group will receive a prescription for PrEP and MOUD and educational counseling by an NP, followed by safety checks via phone calls or SMS text messages on days 5 and 10; and a clinical visit on day 30 (Figure 1).

During the first day, the NP evaluates the participant's eligibility for PrEP and assesses PrEP readiness. Participants eligible for PrEP are evaluated using the Centers for Disease Control and Prevention's PrEP clinical practice guidelines [62], including acute HIV infection symptoms and laboratory testing for HIV, hepatitis (ie, hepatitis A, B, and C viruses), creatinine, pregnancy (for females), and sexually transmitted infections (ie, gonorrhea, chlamydia, and syphilis). During the same visit, they will also be offered a PrEP prescription for a 30-day supply.

Additionally, the NP assesses MOUD readiness. Participants are screened for buprenorphine maintenance therapy (BMT) eligibility according to the Drug Addiction Treatment Act of 2000 and Treatment Improvement Protocol Series 43 criteria [63]. As methadone maintenance therapy (MMT) is only provided in specialty settings, only BMT is offered at the study site (NHSSP). Patients preferring MMT over BMT are referred to initiate same-day MMT. If the participant is eligible for BMT, a drug toxicology screen is performed, and participants are provided with office or home induction and resources to assist them in self-managing their opioid treatment [64]. The resources provided include a home induction kit with an instruction sheet, BMT film packets, nonsteroidal anti-inflammatory drugs (for body pain), hydroxyzine (for anxiety and insomnia), and loperamide (for diarrhea). Additionally, patients receive adherence and potential medical adverse events counseling.

After the laboratory results become available (typically within 3 days following the visit), the NP contacts the participant (on day 5) via a phone call or SMS text message to review the test results and inquire about MOUD stabilization. If test results are concerning and warrant PrEP discontinuation (which is typically rare) [65-68], participants are urged to cease PrEP immediately. On day 10, the NP contacts the participant using the same modality to inquire about PrEP adherence, possible side effects, and MOUD dosing as well as to troubleshoot potential billing issues. On day 30, the NP prescribes a 60-day supply of PrEP and a 30-day supply of MOUD and provides counseling related to long-term maintenance of PrEP and MOUD. In the case of a positive test result for any disease or laboratory value outside the normal range, participants are referred to appropriate clinical care according to the standard of care at any time point during the study. The study's timeline and activities are summarized in Table 1.

Table 1. Study activity and measures.

Study activity	Timeline						
	Screening (prebaseline)	Evaluation (baseline)	Treatment		Retention		
			Day 5	Day 10	1 month	3 months	6 months
Eligibility assessment	✓						
Informed consent		✓					
TAU[a] PrEP[b]							
PrEP educational counseling[c]		✓				✓	✓
Lab screenings		✓				✓	✓
Lab result review[c]		✓				✓	✓
PrEP prescription[c]		✓				✓	✓
TAU MOUD[d]							
Office/home induction		✓					
Buprenorphine kit		✓					
Follow-up appointment				✓		✓	✓
iRaPID[e]							
Educational counseling[f]		✓		✓			
PrEP prescription		✓			✓	✓	✓
Safety check			✓	✓			
Day 30 check-up		✓					
Follow-up appointment				✓		✓	✓
Research interview		✓				✓	✓
DBS[g]					✓	✓	✓
Qualitative interview						✓	✓
Payment		✓			✓	✓	✓

[a] TAU: treatment as usual.

[b]PrEP: pre-exposure prophylaxis.

[c]Exact day depends on when the laboratory results are available for the clinician (usually 3-7 days after baseline assessment).

[d]MOUD: medication for opioid use disorder.

[e]iRaPID: integrated rapid access to HIV prevention program for people who inject drugs.

[f]PrEP and MOUD educational counseling.

[g]DBS: dried blood spot.

Strategies To Maximize Recruitment and Retention

Based on our previous research experience [69-72], we are using several strategies to maximize recruitment and minimize attrition rates. Our recruitment strategies include community-based outreach (eg, through flyers and public advertisements), cross-organizational collaborations, and referrals from harm reduction services such as SSPs and mobile clinics. Moreover, the research team routinely meets with the community-based stakeholders (eg, clinical team members, counselors at the MMP, and staff at the SSPs) to ensure proper screening of participants and the smooth function and operation of all study components.

Strategies to promote retention include rapid enrollment, thorough explanation of study requirements, integration of the research program within community-based clinical and nonclinical settings (eg, SSPs, mobile clinics, addiction treatment centers), close monitoring of participants' clinical status, and accessibility of study staff to patients for questions and problems. Participant locator forms, which include name, address, phone number, and family or friend contact, are collected and updated at each visit. Members of the research staff call or message each participant (according to their previously stated preferred contact method) 1 week and 1 day before the date of their visit. We also issue appointment cards at each visit for subsequent ones. Furthermore, participants are compensated based on the time and effort required to complete the assessments based on the market rate, which has also been an essential retention strategy.

Outcome Measures

The study will assess the feasibility, acceptability, and preliminary efficacy of the iRaPID intervention using a range of instruments administered at various time points throughout the study. The feasibility and acceptability of the program will be evaluated using both quantitative (in-depth interview) and qualitative (one-to-one interview) mechanisms. Data collected include the following: a quantitative assessment of process indicators, standardized acceptability measures collected through quantitative interviews, and measures of fidelity gauged through implementation checklists. Feasibility will be assessed by quantitative process indicators collected by the research staff, including the number of participants screened, recruited, randomized, retained, and adherent to treatment. Acceptability of the intervention will include a 10-item acceptability rating profile and an intervention fidelity assessment. The acceptability profile [73] will be collected through in-depth quantitative interviews at each follow-up point. We will also examine participants' views on acceptability, areas of perceived usefulness of the program, and their confidence in starting PrEP and MOUD. Ultimately, intervention fidelity will be collected using an implementation checklist specific for each part of the program (ie, baseline visit, safety check, follow-up, and clinical visit on day 30), which NPs will complete, documenting the activities covered in each program domain.

We will also estimate the preliminary efficacy of PrEP and MOUD uptake in this pilot RCT of the iRaPID intervention versus TAU (primary outcome). This will be determined by assessing PrEP and MOUD uptake (ie, current use). For those who initiate PrEP, we will also evaluate the time to PrEP initiation, along with adherence and persistence on PrEP, as part of the secondary outcome. Time to PrEP initiation will be calculated by recording the number of days between the first encounter with the NP or health care provider and the day of initiation of PrEP, validated by the pharmacy PrEP pick-up date. We will measure PrEP adherence using the visual analog scale [74] and confirm with dried blood spot testing [75-77]. Persistence on PrEP will be measured by assessing pharmacy data, including both refill (if refilled within 30 days after exhausting PrEP from previous fill or not) and pick-up information. Given the importance of moderating factors on the effect of efficacy, we will measure individual (eg, sociodemographic, sexually transmitted infection, drug use, depression), social (eg, social support), and structural (eg, stigma, physician distrust) factors at each in-depth interview.

Statistical Analyses

Feasibility will be assessed through the analysis of data collected by the research team, including the number of participants screened and enrolled per month, the proportion of eligible participants who enroll in the study, the treatment-specific proportion of participants completing follow-up visits, rates of adherence to the intervention protocol, and fidelity of implementation measured by the percentage of domains captured by the NPs at each time point. Acceptability analysis will be based on descriptive statistics from the acceptability measures, such as simple means and percentages between treatment arms, and thematic analysis of qualitative data collected in postimplementation focus groups.

Meanwhile, preliminary efficacy analysis will assess the hypothesis that the iRaPID intervention will perform better than TAU over time using a primary outcome (ie, PrEP uptake) and secondary outcomes (ie, time to PrEP initiation, PrEP adherence and persistence). We will first test baseline characteristics for homogeneity between treatment arms using an independent-samples *t* test or Wilcoxon rank sum test (if unequal variances are assessed) for continuous variables and chi-square tests or Fisher exact tests (if any small cell sizes) for categorical variables. This analysis of baseline characteristics will be used to determine significantly different factors to include in the final model for adjustment. To assess our hypotheses relating to preliminary efficacy, we will use a generalized linear mixed model [78] with random subject effects to account for the correlation in repeated measurements that occur within subjects. Treatment assignment, time, and the interaction between time and treatment assignment, including confounders such as sociodemographic characteristics and prior PrEP or MOUD engagement, will be included as covariates. The proportion of participants that initiate PrEP will be estimated and compared using the linear contrast statement in SAS PROC GLIMMIX (SAS Institute). Similar analyses will be conducted for other outcomes, including MOUD uptake, time to PrEP initiation, optimal adherence to PrEP, and PrEP persistence.

Sample Size

This study aims to test the feasibility and acceptability of the iRaPID program and obtain preliminary estimates of potential effects on HIV prevention outcomes among people who inject drugs. Previous research has shown that pilot studies of 20 to 30 participants per arm are considered adequate to meet proposed study aims similar to this study [79,80]. Our sample size of 50 participants would be ideal for detecting a moderate treatment effect and informing a future RCT. The recruitment of this sample size is feasible based on our formative work.

Implementation Science Research

As previously mentioned, we are using a type I hybrid implementation trial design, where we will pilot test the NP-led iRaPID program while exploring multilevel implementation factors for future refinement and adoption. As such, we will conduct open-ended interviews with iRaPID participants (n=20) and relevant stakeholders (n=10), including recruitment staff, clinical providers, and administrators at the participating clinic.

We will administer a process measure to assess the overall satisfaction and perceived utility of each intervention component regarding organization-level factors (eg, perceived relevance of intervention components and characteristics to target population needs, the usefulness of the intervention to the organization, and barriers to intervention implementation as designed). These questions will elicit feedback about the potential barriers and facilitators to implementing the iRaPID program—as currently designed—regarding issues ranging from specific intervention components to the more general organizational dynamics (eg., time and resource constraints). The process evaluation will provide a nuanced understanding

of the intervention effects, barriers, and facilitators to the intervention implementation and refinement needed to maximize implementation success in a real-world setting. Based on this feedback, the iRaPID program will then be adjusted and adapted for future implementation in various clinical settings.

Results

Study recruitment began on July 28, 2021, and lasted until August 31, 2022. A total of 174 participants completed screening, yielding 99 eligible participants. The main reasons for ineligibility included not injecting drugs or not having ongoing HIV risk (eg, not engaging in risky sexual or injection drug use practices such as needle sharing). Among eligible participants, 85% (50/99) successfully enrolled in the study and were randomized to a study arm. The remaining eligible participants refused to participate in the study. Enrolled participants had a mean age of 45.98 (SD 8.19) years, 70% (35/50) were male, and 78% (39/50) identified as being heterosexual. They had a diverse portfolio of HIV risk behaviors, as most of them (47/50, 94%) had condomless sex in the past 6 months, and 84% (42/50) injected drugs in the past month. The final study follow-up is expected to be completed by February 2023, and the results will be available by mid-2023.

Discussion

Principal Findings and Implications

This ongoing trial aims to test an NP-led integrated HIV prevention program for people who inject drugs that combines same-day coprescribing of PrEP and MOUD. This strategy addresses delayed initiation and low linkage to HIV prevention (PrEP) and substance use (MOUD) care in traditional models. We hypothesize that the iRaPID intervention will be feasible and acceptable among people who inject drugs and will prove to be more efficacious than the standard of care for PrEP and MOUD services. We also anticipate that the results and qualitative feedback from participants and stakeholders will inform the refinement of the iRaPID intervention for a future large-scale RCT.

Same-day access to HIV preventive care may be particularly crucial for people who inject drugs with MOUD as they remain a hard-to-reach group and have significantly higher rates of attrition and poor linkage to care. Since HIV acquisition risk persists during delays, timely PrEP and MOUD initiation are critical in at-risk populations. Individuals with streamlined care initiation may also experience enhanced self-efficacy, encouraging continued engagement. Hence, our results could impact local and international PrEP and MOUD scale-up policies and promote engagement in HIV prevention services.

Given the risk of continued HIV outbreaks amidst the ongoing opioid crisis, scaling up PrEP alongside MOUD for people who inject drugs is crucial for HIV prevention. If successful, subsequent stand-alone tailored programs can be developed to support communities where opioid use is high and HIV outbreaks are likely, thereby promoting a transition to integrative care. Considering the limited access to and scale-up of harm-reduction strategies among people who inject drugs and the existing multilevel barriers to PrEP uptake, effective interventions are urgently needed to fill this critical gap. Given the significant growth in the waivered NP workforce, trained nurses are ideally situated to deliver this integrated care model. The iRaPID program represents a paradigm shift in HIV prevention and may be a particularly crucial strategy for people who inject drugs with OUD, as they remain an easy-to-miss subgroup with high rates of loss to follow-up and poor linkage to care.

Limitations and Setbacks

The pilot trial has several limitations. Our study is restricted to 1 geographical location (Greater New Haven area, CT), potentially limiting the generalizability of our findings to all people who inject drugs across different geographic settings, particularly areas with fewer or absent SSPs. Further, the prescribing privileges of NPs have geographical disparities of their own, as they only have fully independent practice authority in 29 US commonwealths, states, and territories [81], which undermines nationwide program implementation in areas with physician shortages. Additionally, the study relies on self-reported measures of prior drug use, HIV-related risk behaviors, sexual behaviors, and some measures of primary outcomes (eg, adherence to PrEP using the visual analog scale). Impression management might occur to heighten protocol eligibility, which could potentially lead to the overreporting of risk behaviors during screening and subsequent discrepancies between data collected at different time points. Participants in the pilot trial include both out-of-treatment and in-treatment people who inject drugs (ie, those who were on BMT or MMT at the time of enrollment), which can affect treatment and adherence outcomes, especially as participants who were already on BMT or MMT at the time of enrollment did not undergo induction as compared to their out-of-treatment counterparts.

We also encountered many setbacks regarding participant recruitment due to the COVID-19 pandemic and the recurrent surge of cases in the area. Due to the nature of our program mandating in-person laboratory tests and assessments, ensuing research laboratory closures, and programmatic policies and changes that were developed to ensure research staff safety at the workplace (such as shift schedule changes and remote work) negatively affected recruitment efforts.

Future Directions

Although shutdown conditions were lifted, insightful strategies implemented by the Addiction Medicine Program at Yale during the COVID-19 pandemic and grasped by the research and clinical staff for future potential use included establishing safe pick-up and delivery of medication and setting up telehealth access for patients. Comparably, the centralization of PrEP dispensing to clinical settings and the in-person nature of its delivery prompted a recent call in the literature for the integration of telehealth to alleviate patient- and provider-level demands [82]. Recent studies, especially in the context of the COVID-19 pandemic, established the feasibility of PrEP and MOUD delivery among people who inject drugs via telehealth [82,83]. Integrating telehealth services within harm reduction settings (eg, SSPs) could not only boost access and address demands imposed on patients [84-86] but also relieve some of

the excess pressures imposed on people who inject drugs specifically, including logistical barriers to in-person care and concerns related to stigma. Future directions in implementing the iRaPID program also include expanding access to newly available HIV prevention tools. Preliminary trials have shown that the new Federal Drug Administration–approved, long-acting injectable cabotegravir (given intramuscularly every 8 weeks) is likely to be superior to daily oral tenofovir disoproxil fumarate-emtricitabine (marketed under the name Truvada) in at-risk cisgender men who have sex with men [87]. With the advent of a new mode of administration for PrEP and its ensuing impact on HIV prevention strategies and adherence rates, the iRaPID program will likely have to be restructured to include a long-acting injectable option for participants.

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Data Availability

All data generated or analyzed up to this point are included in this published article.

Conflicts of Interest

FLA has grants from Gilead and Merck Pharmaceuticals and research consulting from Gilead Sciences. RS has research grants from Gilead Sciences. The authors have no further interests to declare.

Multimedia Appendix 1
External Peer Review Report from the Population and Public Health Approaches to HIV/AIDS (PPAH) Study Section - Exploratory/Developmental Grants (R21) - National Institute on Drug Abuse (NIDA) (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 180 KB - resprot_v11i10e42585_app1.pdf]

References

1. Des Jarlais DC, Kerr T, Carrieri P, Feelemyer J, Arasteh K. HIV infection among persons who inject drugs: ending old epidemics and addressing new outbreaks. AIDS 2016 Mar 27;30(6):815-826 [FREE Full text] [doi: 10.1097/QAD.0000000000001039] [Medline: 26836787]
2. Mirzazadeh A, Evans J, Hahn J, Jain J, Briceno A, Shiboski S, et al. Continued transmission of HIV among young adults who inject drugs in San Francisco: still room for improvement. AIDS Behav 2018 Apr;22(4):1383-1394 [FREE Full text] [doi: 10.1007/s10461-017-1988-y] [Medline: 29168067]
3. Schranz A, Barrett J, Hurt C, Malvestutto C, Miller W. Challenges facing a rural opioid epidemic: treatment and prevention of HIV and Hepatitis C. Curr HIV/AIDS Rep 2018 Jun;15(3):245-254 [FREE Full text] [doi: 10.1007/s11904-018-0393-0] [Medline: 29796965]
4. Hodder SL, Feinberg J, Strathdee SA, Shoptaw S, Altice FL, Ortenzio L, et al. The opioid crisis and HIV in the USA: deadly synergies. Lancet 2021 Mar 20;397(10279):1139-1150. [doi: 10.1016/S0140-6736(21)00391-3] [Medline: 33617769]
5. Green TC, McGowan SK, Yokell MA, Pouget ER, Rich JD. HIV infection and risk of overdose: a systematic review and meta-analysis. AIDS 2012 Feb 20;26(4):403-417 [FREE Full text] [doi: 10.1097/QAD.0b013e32834f19b6] [Medline: 22112599]
6. HIV and injection drug use. Centers for Disease Control and Prevention. 2021. URL: https://www.cdc.gov/hiv/basics/hiv-transmission/injection-drug-use.html [accessed 2022-08-06]
7. Injection drug use. Centers for Disease Control and Prevention. 2019. URL: https://www.cdc.gov/hiv/risk/drugs/ [accessed 2022-08-06]
8. Arasteh K, Des Jarlais DC, Perlis TE. Alcohol and HIV sexual risk behaviors among injection drug users. Drug Alcohol Depend 2008 May 1;95(1-2):54-61 [FREE Full text] [doi: 10.1016/j.drugalcdep.2007.12.008] [Medline: 18242009]
9. Marshall BDL, Friedman SR, Monteiro JFG, Paczkowski M, Tempalski B, Pouget ER, et al. Prevention and treatment produced large decreases in HIV incidence in a model of people who inject drugs. Health Aff (Millwood) 2014 Mar;33(3):401-409 [FREE Full text] [doi: 10.1377/hlthaff.2013.0824] [Medline: 24590937]
10. Noar SM. Behavioral interventions to reduce HIV-related sexual risk behavior: review and synthesis of meta-analytic evidence. AIDS Behav 2008 May;12(3):335-353. [doi: 10.1007/s10461-007-9313-9] [Medline: 17896176]
11. Strathdee SA, Hallett TB, Bobrova N, Rhodes T, Booth R, Abdool R, et al. HIV and risk environment for injecting drug users: the past, present, and future. Lancet 2010 Jul 24;376(9737):268-284 [FREE Full text] [doi: 10.1016/S0140-6736(10)60743-X] [Medline: 20650523]
12. Volkow ND, Montaner J. The urgency of providing comprehensive and integrated treatment for substance abusers with HIV. Health Aff (Millwood) 2011 Aug;30(8):1411-1419 [FREE Full text] [doi: 10.1377/hlthaff.2011.0663] [Medline: 21821558]

13. Martin M, Vanichseni S, Sangkum U, Mock PA, Leethochawalit M, Chiamwongpaet S, et al. HIV Incidence and Risk Behaviours of People Who Inject Drugs in Bangkok, 1995-2012. EClinicalMedicine 2019 Mar;9:44-51 [FREE Full text] [doi: 10.1016/j.eclinm.2019.03.012] [Medline: 31143881]
14. Gangi MF, Karamouzian M, Nedjat S, Rahimi-Movaghar A, Yazdani K, Shokoohi M, et al. HIV prevention cascades for injection and sexual risk behaviors among HIV-negative people who inject drug in Iran. Int J Drug Policy 2020 Oct;84:102868 [FREE Full text] [doi: 10.1016/j.drugpo.2020.102868] [Medline: 32717706]
15. Bhatia R, Modali L, Lowther M, Glick N, Bell M, Rowan S, et al. . Outcomes of preexposure prophylaxis referrals from public STI clinics and implications for the preexposure prophylaxis continuum. Sex Transm Dis 2018 Jan;45(1):50-55. [doi: 10.1097/OLQ.0000000000000690] [Medline: 28876282]
16. Gowing L, Farrell MF, Bornemann R, Sullivan LE, Ali R. Oral substitution treatment of injecting opioid users for prevention of HIV infection. Cochrane Database Syst Rev 2011 Aug 10(8):CD004145. [doi: 10.1002/14651858.CD004145.pub4] [Medline: 21833948]
17. Karki P, Shrestha R, Huedo-Medina TB, Copenhaver M. The impact of methadone maintenance treatment on HIV risk behaviors among high-risk injection drug users: a systematic revie. Evid Based Med Public Health 2016;2:e1129 [FREE Full text] [Medline: 27066590]
18. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev 2014 Feb 06(2):CD002207. [doi: 10.1002/14651858.CD002207.pub4] [Medline: 24500948]
19. Mazhnaya A, Marcus R, Bojko MJ, Zelenev A, Makarenko I, Pykalo I, et al. Opioid Agonist Treatment and Improved Outcomes at Each Stage of the HIV Treatment Cascade in People Who Inject Drugs in Ukraine. J Acquir Immune Defic Syndr 2018 Nov 01;79(3):288-295 [FREE Full text] [doi: 10.1097/QAI.0000000000001827] [Medline: 30312275]
20. Mukandavire C, Low A, Mburu G, Trickey A, May MT, Davies CF, et al. Impact of opioid substitution therapy on the HIV prevention benefit of antiretroviral therapy for people who inject drugs. AIDS 2017 May 15;31(8):1181-1190. [doi: 10.1097/QAD.0000000000001458] [Medline: 28323752]
21. Nosyk B, Min JE, Evans E, Li L, Liu L, Lima VD, et al. The Effects of Opioid Substitution Treatment and Highly Active Antiretroviral Therapy on the Cause-Specific Risk of Mortality Among HIV-Positive People Who Inject Drugs. Clin Infect Dis 2015 Oct 01;61(7):1157-1165 [FREE Full text] [doi: 10.1093/cid/civ476] [Medline: 26113656]
22. Pierce M, Bird SM, Hickman M, Marsden J, Dunn G, Jones A, et al. Impact of treatment for opioid dependence on fatal drug-related poisoning: a national cohort study in England. Addiction 2016 Feb;111(2):298-308 [FREE Full text] [doi: 10.1111/add.13193] [Medline: 26452239]
23. Schwartz RP, Gryczynski J, O'Grady KE, Sharfstein JM, Warren G, Olsen Y, et al. Opioid agonist treatments and heroin overdose deaths in Baltimore, Maryland, 1995-2009. Am J Public Health 2013 May;103(5):917-922. [doi: 10.2105/AJPH.2012.301049] [Medline: 23488511]
24. Larney S, Peacock A, Leung J, Colledge S, Hickman M, Vickerman P, et al. Global, regional, and country-level coverage of interventions to prevent and manage HIV and hepatitis C among people who inject drugs: a systematic review. The Lancet Global Health 2017 Dec;5(12):e1208-e1220. [doi: 10.1016/s2214-109x(17)30373-x]
25. Priest KC, Gorfinkel L, Klimas J, Jones AA, Fairbairn N, McCarty D. Comparing Canadian and United States opioid agonist therapy policies. Int J Drug Policy 2019 Dec;74:257-265 [FREE Full text] [doi: 10.1016/j.drugpo.2019.01.020] [Medline: 30765118]
26. Medicaid coverage of medication-assisted treatment for alcohol and opioid use disorders and of medication for the reversal of opioid overdose. Substance Abuse and Mental Health Services Administration. 2018. URL: https://store.samhsa.gov/sites/default/files/d7/priv/medicaidfinancingmatreport_0.pdf [accessed 2022-08-09]
27. The FFAIDSR. Toward an effective strategy to combat HIV. Hepatitis C and the opioid epidemic: recommendations for policy makers. URL: https://www.amfar.org/wp-content/uploads/2022/03/DC-2018-Combat-the-Op-Epidemic-Rec-040518-single-pg.pdf [accessed 2022-08-07]
28. Alpren C, Dawson E, John B, Cranston K, Panneer N, Fukuda H, et al. Opioid Use Fueling HIV Transmission in an Urban Setting: An Outbreak of HIV Infection Among People Who Inject Drugs-Massachusetts, 2015-2018. Am J Public Health 2020 Jan;110(1):37-44. [doi: 10.2105/AJPH.2019.305366] [Medline: 31725317]
29. Conrad C. Morbidity and mortality weekly report: outbreak of HIV infection linked to injection drug use of oxymorphone. Centers for Disease Control and Prevention. URL: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6416a4.htm [accessed 2022-08-06]
30. Gonsalves GS, Crawford FW. Dynamics of the HIV outbreak and response in Scott County, IN, USA, 2011-15: a modelling study. Lancet HIV 2018 Oct;5(10):e569-e577 [FREE Full text] [doi: 10.1016/S2352-3018(18)30176-0] [Medline: 30220531]
31. Low AJ, Mburu G, Welton NJ, May MT, Davies CF, French C, et al. Impact of Opioid Substitution Therapy on Antiretroviral Therapy Outcomes: A Systematic Review and Meta-Analysis. Clin Infect Dis 2016 Oct 15;63(8):1094-1104 [FREE Full text] [doi: 10.1093/cid/ciw416] [Medline: 27343545]
32. Preexposure prophylaxis for the prevention of HIV infection in the United States. Centers for Disease Control and Prevention. 2017. URL: https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf [accessed 2022-08-07]

33. Alpren C, Dawson EL, John B, Cranston K, Panneer N, Fukuda HD, et al. Opioid Use Fueling HIV Transmission in an Urban Setting: An Outbreak of HIV Infection Among People Who Inject Drugs-Massachusetts, 2015-2018. Am J Public Health 2020 Jan;110(1):37-44. [doi: 10.2105/AJPH.2019.305366] [Medline: 31725317]
34. Bhatia R, Modali L, Lowther M, Glick N, Bell M, Rowan S, et al. Outcomes of preexposure prophylaxis referrals from public STI clinics and implications for the preexposure prophylaxis continuum. Sex Transm Dis 2018 Jan;45(1):50-55. [doi: 10.1097/OLQ.0000000000000690] [Medline: 28876282]
35. Spector AY, Remien RH, Tross S. PrEP in substance abuse treatment: a qualitative study of treatment provider perspectives. Subst Abuse Treat Prev Policy 2015 Jan 8;10(1):1. [doi: 10.1186/1747-597x-10-1]
36. Shrestha R, Alias H, Wong LP, Altice FL, Lim SH. Using individual stated-preferences to optimize HIV self-testing service delivery among men who have sex with men (MSM) in Malaysia: results from a conjoint-based analysis. BMC Public Health 2020 Nov 25;20(1):1777 [FREE Full text] [doi: 10.1186/s12889-020-09832-w]
37. Mistler CB, Curley CM, Rosen AO, El-Krab R, Wickersham JA, Copenhaver MM, et al. The Impact of COVID-19 on Access to HIV Prevention Services Among Opioid-Dependent Individuals. J Community Health 2021 Oct;46(5):960-966 [FREE Full text] [doi: 10.1007/s10900-021-00979-0] [Medline: 33770334]
38. Substance AHSA. Medications for Opioid Use Disorder for Healthcare and Addiction Professionals, Policymakers, Patients, and Families. Treatment Improved Protocol TIP 63. URL: https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP21-02-01-002.pdf [accessed 2022-08-06]
39. Nelson LE, McMahon JM, Leblanc NM, Braksmajer A, Crean HF, Smith K, et al. Advancing the case for nurse practitioner-based models to accelerate scale-up of HIV pre-exposure prophylaxis. J Clin Nurs 2019 Jan;28(1-2):351-361. [doi: 10.1111/jocn.14675] [Medline: 30230068]
40. Petroll AE, Walsh JL, Owczarzak JL, McAuliffe TL, Bogart LM, Kelly JA. PrEP Awareness, Familiarity, Comfort, and Prescribing Experience among US Primary Care Providers and HIV Specialists. AIDS Behav 2017 May;21(5):1256-1267. [doi: 10.1007/s10461-016-1625-1] [Medline: 27885552]
41. Spetz J, Toretsky C, Chapman S, Phoenix B, Tierney M. Nurse practitioner and physician assistant waivers to prescribe buprenorphine and state scope of practice restrictions. JAMA 2019 Apr 09;321(14):1407-1408 [FREE Full text] [doi: 10.1001/jama.2019.0834] [Medline: 30964519]
42. Edelman EJ, Moore BA, Calabrese SK, Berkenblit G, Cunningham C, Patel V, et al. Primary Care Physicians' Willingness to Prescribe HIV Pre-exposure Prophylaxis for People who Inject Drugs. AIDS Behav 2017 Apr;21(4):1025-1033 [FREE Full text] [doi: 10.1007/s10461-016-1612-6] [Medline: 27896552]
43. Ferro EG, Culbert GJ, Wickersham JA, Marcus R, Steffen AD, Pauls HA, et al. Physician Decisions to Defer Antiretroviral Therapy in Key Populations: Implications for Reducing Human Immunodeficiency Virus Incidence and Mortality in Malaysia. Open Forum Infect Dis 2017;4(1):ofw219 [FREE Full text] [doi: 10.1093/ofid/ofw219] [Medline: 28480230]
44. Shrestha R, Altice FL, Karki P, Copenhaver MM. Integrated Bio-behavioral Approach to Improve Adherence to Pre-exposure Prophylaxis and Reduce HIV Risk in People Who Use Drugs: A Pilot Feasibility Study. AIDS Behav 2018 Aug;22(8):2640-2649 [FREE Full text] [doi: 10.1007/s10461-018-2099-0] [Medline: 29582199]
45. Westergaard RP, Ambrose BK, Mehta SH, Kirk GD. Provider and clinic-level correlates of deferring antiretroviral therapy for people who inject drugs: a survey of North American HIV providers. J Int AIDS Soc 2012 Feb 23;15(1):10 [FREE Full text] [doi: 10.1186/1758-2652-15-10] [Medline: 22360788]
46. Kamis KF, Marx GE, Scott KA, Gardner EM, Wendel KA, Scott ML, et al. Same-Day HIV Pre-Exposure Prophylaxis (PrEP) Initiation During Drop-in Sexually Transmitted Diseases Clinic Appointments Is a Highly Acceptable, Feasible, and Safe Model that Engages Individuals at Risk for HIV into PrEP Care. Open Forum Infect Dis 2019 Jul;6(7):ofz310 [FREE Full text] [doi: 10.1093/ofid/ofz310] [Medline: 31341933]
47. Khosropour CM, Backus KV, Means AR, Beauchamps L, Johnson K, Golden MR, et al. A Pharmacist-Led, Same-Day, HIV Pre-Exposure Prophylaxis Initiation Program to Increase PrEP Uptake and Decrease Time to PrEP Initiation. AIDS Patient Care STDS 2020 Jan;34(1):1-6 [FREE Full text] [doi: 10.1089/apc.2019.0235] [Medline: 31944854]
48. Kamis KF, Marx GE, Scott KA, Gardner EM, Wendel KA, Scott ML, et al. Same-Day HIV Pre-Exposure Prophylaxis (PrEP) Initiation During Drop-in Sexually Transmitted Diseases Clinic Appointments Is a Highly Acceptable, Feasible, and Safe Model that Engages Individuals at Risk for HIV into PrEP Care. Open Forum Infect Dis 2019 Jul;6(7):ofz310 [FREE Full text] [doi: 10.1093/ofid/ofz310] [Medline: 31341933]
49. Rowan SE, Patel RR, Schneider JA, Smith DK. Same-day prescribing of daily oral pre-exposure prophylaxis for HIV prevention. Lancet HIV 2021 Feb;8(2):e114-e120. [doi: 10.1016/S2352-3018(20)30256-3] [Medline: 33128874]
50. Herrick AL, Lim SH, Plankey MW, Chmiel JS, Guadamuz TE, Guadamuz TT, et al. Adversity and syndemic production among men participating in the multicenter AIDS cohort study: a life-course approach. Am J Public Health 2013 Jan;103(1):79-85 [FREE Full text] [doi: 10.2105/AJPH.2012.300810] [Medline: 23153154]
51. Task shifting: global recommendations and guidelines. World Health Organization. 2008. URL: https://apps.who.int/iris/bitstream/handle/10665/43821/9789241596312_eng.pdf [accessed 2022-08-15]
52. Schmidt HA, Schaefer R, Nguyen VTT, Radebe M, Sued O, Rodolph M, et al. Scaling up access to HIV pre-exposure prophylaxis (PrEP): should nurses do the job? Lancet HIV 2022 May;9(5):e363-e366 [FREE Full text] [doi: 10.1016/S2352-3018(22)00006-6] [Medline: 35358418]

53. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. Med Care 2012 Mar;50(3):217-226 [FREE Full text] [doi: 10.1097/MLR.0b013e3182408812] [Medline: 22310560]
54. Davila K. Overdose data to action: trends in substance use, overdose, and treatment in the Quinnipiack valley health district and new haven. ctdatahaven. 2021. URL: https://www.ctdatahaven.org/sites/ctdatahaven/files/OD2A_final.pdf [accessed 2022-08-15]
55. HIV infection cases by year of first diagnosis, sex, race, and risk, New Haven County, 2011 - 2020. Connecticut DOPH. 2021. URL: https://portal.ct.gov/-/media/Departments-and-Agencies/DPH/AIDS--Chronic-Diseases/Surveillance/city_county/county_New-Haven_hivaids_trends_table.pdf [accessed 2022-08-15]
56. Gibson BA, Ghosh D, Morano JP, Altice FL. Accessibility and utilization patterns of a mobile medical clinic among vulnerable populations. Health Place 2014 Jul;28:153-166 [FREE Full text] [doi: 10.1016/j.healthplace.2014.04.008] [Medline: 24853039]
57. Gibson BA, Morano JP, Walton MR, Marcus R, Zelenev A, Bruce RD, et al. Innovative Program Delivery and Determinants of Frequent Visitation to a Mobile Medical Clinic in an Urban Setting. J Health Care Poor Underserved 2017;28(2):643-662. [doi: 10.1353/hpu.2017.0065] [Medline: 28529215]
58. Morano JP, Gibson BA, Altice FL. The burgeoning HIV/HCV syndemic in the urban Northeast: HCV, HIV, and HIV/HCV coinfection in an urban setting. PLoS One 2013;8(5):e64321 [FREE Full text] [doi: 10.1371/journal.pone.0064321] [Medline: 23691197]
59. Morano JP, Zelenev A, Lombard A, Marcus R, Gibson BA, Altice FL. Strategies for hepatitis C testing and linkage to care for vulnerable populations: point-of-care and standard HCV testing in a mobile medical clinic. J Community Health 2014 Oct;39(5):922-934. [doi: 10.1007/s10900-014-9932-9] [Medline: 25135842]
60. Morano JP, Zelenev A, Walton MR, Bruce RD, Altice FL. Latent tuberculosis infection screening in foreign-born populations: a successful mobile clinic outreach model. Am J Public Health 2014 Aug;104(8):1508-1515. [doi: 10.2105/AJPH.2014.301897] [Medline: 24922157]
61. Bryant-Lukosius D, Dicenso A. A framework for the introduction and evaluation of advanced practice nursing roles. J Adv Nurs 2004 Dec;48(5):530-540. [doi: 10.1111/j.1365-2648.2004.03235.x] [Medline: 15533091]
62. Preexposure prophylaxis for the prevention of HIV infection in the United States. Centers for Disease Control and Prevention. 2021. URL: https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf [accessed 2022-08-16]
63. Center for Substance Abuse Treatment. Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs. Rockville, MD: Substance Abuse and Mental Health Services Administration (US); 2016.
64. Conway DP, Holt M, Couldwell DL, Smith DE, Davies SC, McNulty A, Sydney Rapid HIV Test Study. Barriers to HIV testing and characteristics associated with never testing among gay and bisexual men attending sexual health clinics in Sydney. J Int AIDS Soc 2015;18:20221 [FREE Full text] [doi: 10.7448/IAS.18.1.20221] [Medline: 26318960]
65. O Murchu E, Marshall L, Teljeur C, Harrington P, Hayes C, Moran P, et al. Oral pre-exposure prophylaxis (PrEP) to prevent HIV: a systematic review and meta-analysis of clinical effectiveness, safety, adherence and risk compensation in all populations. BMJ Open 2022 May 11;12(5):e048478 [FREE Full text] [doi: 10.1136/bmjopen-2020-048478] [Medline: 35545381]
66. Marcus JL, Hurley LB, Hare CB, Nguyen DP, Phengrasamy T, Silverberg MJ, et al. Preexposure Prophylaxis for HIV Prevention in a Large Integrated Health Care System: Adherence, Renal Safety, and Discontinuation. J Acquir Immune Defic Syndr 2016 Dec 15;73(5):540-546 [FREE Full text] [doi: 10.1097/QAI.0000000000001129] [Medline: 27851714]
67. Riddell J, Amico KR, Mayer KH. HIV preexposure prophylaxis: a review. JAMA 2018 Mar 27;319(12):1261-1268. [doi: 10.1001/jama.2018.1917] [Medline: 29584848]
68. Sanchez Conde M, Vivancos Gallego MJ, Moreno Guillen S. Pre-exposure prophylaxis (PrEP) against HIV: efficacy, safety and uncertainties. Farm Hosp 2017 Sep 01;41(5):630-637 [FREE Full text] [doi: 10.7399/fh.10821] [Medline: 28847253]
69. Dumchev K, Dvoryak S, Chernova O, Morozova O, Altice FL. Retention in medication-assisted treatment programs in Ukraine-Identifying factors contributing to a continuing HIV epidemic. Int J Drug Policy 2017 Oct;48:44-53 [FREE Full text] [doi: 10.1016/j.drugpo.2017.05.014] [Medline: 28800420]
70. Mazhnaya A, Meteliuk A, Barnard T, Zelenev A, Filippovych S, Altice FL. Implementing and scaling up HCV treatment services for people who inject drugs and other high risk groups in Ukraine: An evaluation of programmatic and treatment outcomes. Int J Drug Policy 2017 Sep;47:187-195 [FREE Full text] [doi: 10.1016/j.drugpo.2017.07.023] [Medline: 28811159]
71. Muthulingam D, Bia J, Madden LM, Farnum SO, Barry DT, Altice FL. Using nominal group technique to identify barriers, facilitators, and preferences among patients seeking treatment for opioid use disorder: A needs assessment for decision making support. J Subst Abuse Treat 2019 May;100:18-28 [FREE Full text] [doi: 10.1016/j.jsat.2019.01.019] [Medline: 30898324]
72. Shrestha R, Altice F, Karki P, Copenhaver M. Developing an Integrated, Brief Biobehavioral HIV Prevention Intervention for High-Risk Drug Users in Treatment: The Process and Outcome of Formative Research. Front Immunol 2017;8:561 [FREE Full text] [doi: 10.3389/fimmu.2017.00561] [Medline: 28553295]
73. Tarnowski KJ, Simonian SJ. Assessing treatment acceptance: the Abbreviated Acceptability Rating Profile. J Behav Ther Exp Psychiatry 1992 Jun;23(2):101-106. [doi: 10.1016/0005-7916(92)90007-6] [Medline: 1460097]

74. Giordano TP, Guzman D, Clark R, Charlebois ED, Bangsberg DR. Measuring adherence to antiretroviral therapy in a diverse population using a visual analogue scale. HIV Clin Trials 2004;5(2):74-79. [doi: 10.1310/JFXH-G3X2-EYM6-D6UG] [Medline: 15116282]
75. Castillo-Mancilla J, Seifert S, Campbell K, Coleman S, McAllister K, Zheng J, et al. Emtricitabine-Triphosphate in Dried Blood Spots as a Marker of Recent Dosing. Antimicrob Agents Chemother 2016 Nov;60(11):6692-6697 [FREE Full text] [doi: 10.1128/AAC.01017-16] [Medline: 27572401]
76. Castillo-Mancilla JR, Zheng J, Rower JE, Meditz A, Gardner EM, Predhomme J, et al. Tenofovir, emtricitabine, and tenofovir diphosphate in dried blood spots for determining recent and cumulative drug exposure. AIDS Res Hum Retroviruses 2013 Feb;29(2):384-390. [doi: 10.1089/AID.2012.0089] [Medline: 22935078]
77. Zheng J, Rower C, McAllister K, Castillo-Mancilla J, Klein B, Meditz A, et al. Application of an intracellular assay for determination of tenofovir-diphosphate and emtricitabine-triphosphate from erythrocytes using dried blood spots. J Pharm Biomed Anal 2016 Apr 15;122:16-20 [FREE Full text] [doi: 10.1016/j.jpba.2016.01.038] [Medline: 26829517]
78. Palmgren J, Diggle PJ, Heagarty P, Liang KY, Zeger SL. Analysis of longitudinal data (2nd ed.). Statist. Med 2004 Nov 15;23(21):3399-3401 [FREE Full text] [doi: 10.1002/sim.1701]
79. Muller KE, Lavange LM, Ramey SL, Ramey CT. Power Calculations for General Linear Multivariate Models Including Repeated Measures Applications. J Am Stat Assoc 1992 Dec 01;87(420):1209-1226 [FREE Full text] [doi: 10.1080/01621459.1992.10476281] [Medline: 24790282]
80. Edwards L. Applied Analysis of Variance in Behavioral Science. New York: M. Dekker; 1993.
81. State Practice Environment. American Association of Nurse Practitioners. 2022. URL: https://www.aanp.org/advocacy/state/state-practice-environment [accessed 2022-06-25]
82. Vanhamel J, Rotsaert A, Reyniers T, Nöstlinger C, Laga M, Van Landeghem E, et al. The current landscape of pre-exposure prophylaxis service delivery models for HIV prevention: a scoping review. BMC Health Serv Res 2020 Jul 31;20(1):704 [FREE Full text] [doi: 10.1186/s12913-020-05568-w] [Medline: 32736626]
83. Mark TL, Treiman K, Padwa H, Henretty K, Tzeng J, Gilbert M. Addiction Treatment and Telehealth: Review of Efficacy and Provider Insights During the COVID-19 Pandemic. Psychiatr Serv 2022 May;73(5):484-491. [doi: 10.1176/appi.ps.202100088] [Medline: 34644125]
84. Allen ST, O'Rourke A, White RH, Smith KC, Weir B, Lucas GM, et al. Barriers and facilitators to PrEP use among people who inject drugs in rural Appalachia: A Qualitative Study. AIDS Behav 2020 Jun;24(6):1942-1950 [FREE Full text] [doi: 10.1007/s10461-019-02767-3] [Medline: 31853771]
85. Broz D, Carnes N, Chapin-Bardales J, Des Jarlais DC, Handanagic S, Jones CM, et al. Syringe Services Programs' Role in Ending the HIV Epidemic in the U.S.: Why We Cannot Do It Without Them. Am J Prev Med 2021 Nov;61(5 Suppl 1):S118-S129 [FREE Full text] [doi: 10.1016/j.amepre.2021.05.044] [Medline: 34686281]
86. Degenhardt L, Mathers B, Vickerman P, Rhodes T, Latkin C, Hickman M. Prevention of HIV infection for people who inject drugs: why individual, structural, and combination approaches are needed. Lancet 2010 Jul 24;376(9737):285-301. [doi: 10.1016/S0140-6736(10)60742-8] [Medline: 20650522]
87. Landovitz RJ, Donnell D, Clement ME, Hanscom B, Cottle L, Coelho L, HPTN 083 Study Team. Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women. N Engl J Med 2021 Aug 12;385(7):595-608 [FREE Full text] [doi: 10.1056/NEJMoa2101016] [Medline: 34379922]

Abbreviations

BMT: buprenorphine maintenance therapy
HIPAA: Health Insurance Portability and Accountability Act
iRaPID: integrated rapid access to HIV prevention program for people who inject drugs
MMT: methadone maintenance therapy
MOUD: medication for opioid use disorder
NHSSP: New Haven Syringe Service Program
NP: nurse practitioner
PrEP: pre-exposure prophylaxis
RCT: randomized controlled trial
SSP: syringe services program
TAU: treatment as usual

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Protocol

A Tailored Occupational Therapist–Led Vocational Intervention for People With Stroke: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Resuming work after stroke is a common goal of working-age adults, yet there are few vocational rehabilitation programs designed to address the unique challenges faced following stroke. The Work intervention was developed to address these gaps.

Objective: This paper presents a protocol that outlines the steps that will be undertaken to pilot both the intervention and trial processes for the Work trial.

Methods: The Work trial is a 2-arm, prospective, randomized, blinded-assessor study with intention-to-treat analysis. A total of 54 adults of working age who have experienced a stroke <4 months prior will be randomized 1:1 to either (1) an experimental group who will receive a 12-week early vocational intervention (Work intervention) plus usual clinical rehabilitation or (2) a control group who will receive only their usual clinical rehabilitation.

Results: Outcomes include study and intervention feasibility and intervention benefit. In addition to evaluating the feasibility of delivering vocational intervention early after stroke, benefit will be assessed by measuring rates of vocational participation and quality-of-life improvements at the 3- and 6-month follow-ups. Process evaluation using data collected during the study, as well as postintervention individual interviews with participants and surveys with trial therapists, will complement quantitative data.

Conclusions: The results of the trial will provide details on the feasibility of delivering the Work intervention embedded within the clinical rehabilitation context and inform future trial processes. Pilot data will enable a future definitive trial to determine the clinical effectiveness of vocational rehabilitation when delivered in the early subacute phase of stroke recovery.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12619001164189; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=378112&isReview=true

International Registered Report Identifier (IRRID): DERR1-10.2196/40548

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KEYWORDS

return to work; vocational rehabilitation; acquired brain injury; stroke; traumatic brain injury; neuroscience; rehabilitation; intervention; feasibility; stroke recovery; resume work

Introduction

Background

After a stroke, returning to work is challenging, and many people never return to employment [1]. Stroke leads to physical limitations (such as walking), cognitive impairments (such as memory or reasoning difficulties), as well as emotional and psychological challenges (including depression and apathy). Together, these limitations can result in challenges in returning to usual activities, especially work [2,3]. Nearly one-third of all strokes occur in adults who are of working age, and as many as 60% of people identify an unmet need with regard to work after stroke in Australia [4].

Resuming work is important for stroke survivors [5,6]. Evidence supports the benefits of working, including the economic resources to enable participation in society, meeting essential psychosocial needs, and being central to a person's identity, social roles, and social status [6,7]. Conversely, there is a well-established association between unemployment and poor health in terms of higher mortality, poorer general health, and poorer mental health [8]. Unfortunately, at present, stroke survivors have limited and variable access to vocational rehabilitation that supports reintegration to work or rehabilitation for work-related activities [5,9]. Community rehabilitation, where available, rarely addresses needs beyond the traditional model of rehabilitation (gait, hand-therapy, speech, cognitive, and self-care rehabilitation) [5,9]. Such models of rehabilitation (focusing on the short-term delivery of rehabilitation interventions) may reduce impairments such as mobility but do not provide stroke survivors with the skills to confidently return to participating in important, everyday activities such as work. In other words, traditional rehabilitation does not currently equip stroke survivors to transition successfully from the rehabilitation environment to the work environment.

It is likely that early vocational rehabilitation, including work ability (how well someone's health, skills, and experience match the demands of their work role) assessment, work visits, and the involvement of the employee, health professionals, and the employer, has the potential to improve participation in work for stroke survivors [2,10]. Yet it has become accepted that vocational rehabilitation is not a standard feature of poststroke rehabilitation programs [5,9]. Opportunities to provide vocational rehabilitation alongside clinical rehabilitation were an important consideration for the development of the Work intervention.

The Work Intervention: An Occupational Therapist–Led Vocational Intervention for People With Stroke

The Work intervention is an individually provided, vocational intervention that is tailored to each participant's return-to-work goals so as to enhance work ability. A total of 12 weekly sessions (1 hour per session) in either the inpatient or community setting commence with assessing the participant's role as a worker alongside their stroke-related impairments. The occupational therapist then compares the client's capabilities to the worker role requirements to forecast potential challenges that may be faced in the workplace; determine work limits and capabilities; coordinate appropriate supports and resources required from health care professionals, employers, and community services; as well as negotiate workplace adjustments, monitor return to work, and explore alternatives where current work is not feasible or sustainable [10-12]. Rehabilitation interventions then commence with establishing a daily routine in the home and building awareness of the worker role before all participants receive rehabilitation to address core work skills (such as problem solving complex situations or working as part of a team) [13]. The intervention may also address poststroke fatigue and enable community access through transport training or provide work conditioning to restore physical and cognitive capacity for work, work hardening programs [14], functional or cognitive capacity evaluations [15], or job task training before establishing an individualized return-to-work plan for each participant. The employer and relevant occupational health and safety staff from the workplace may be involved in the vocational rehabilitation program with permission from the participant, or the participant may only want to accept advice only about employer liaison.

To date, there has been no evaluation of the Work intervention, which was developed to be provided early after stroke (ie, within the first 4 months following a stroke while the participant is also receiving traditional clinical rehabilitation). Therefore, the aim of this pilot randomized controlled trial is to test the feasibility and potential benefit of adding a 12-week, stroke-specific vocational rehabilitation intervention to standard (clinical) rehabilitation, in either an inpatient or community context. The specific research questions posed in this pilot study are as follows:

1. What is the feasibility of adding early vocational rehabilitation alongside usual care for patients after a stroke?
2. What are the benefits of adding early vocational rehabilitation after stroke to those returning to work? Does

it increase the number of working hours and improve confidence to work and self-reported quality of life?

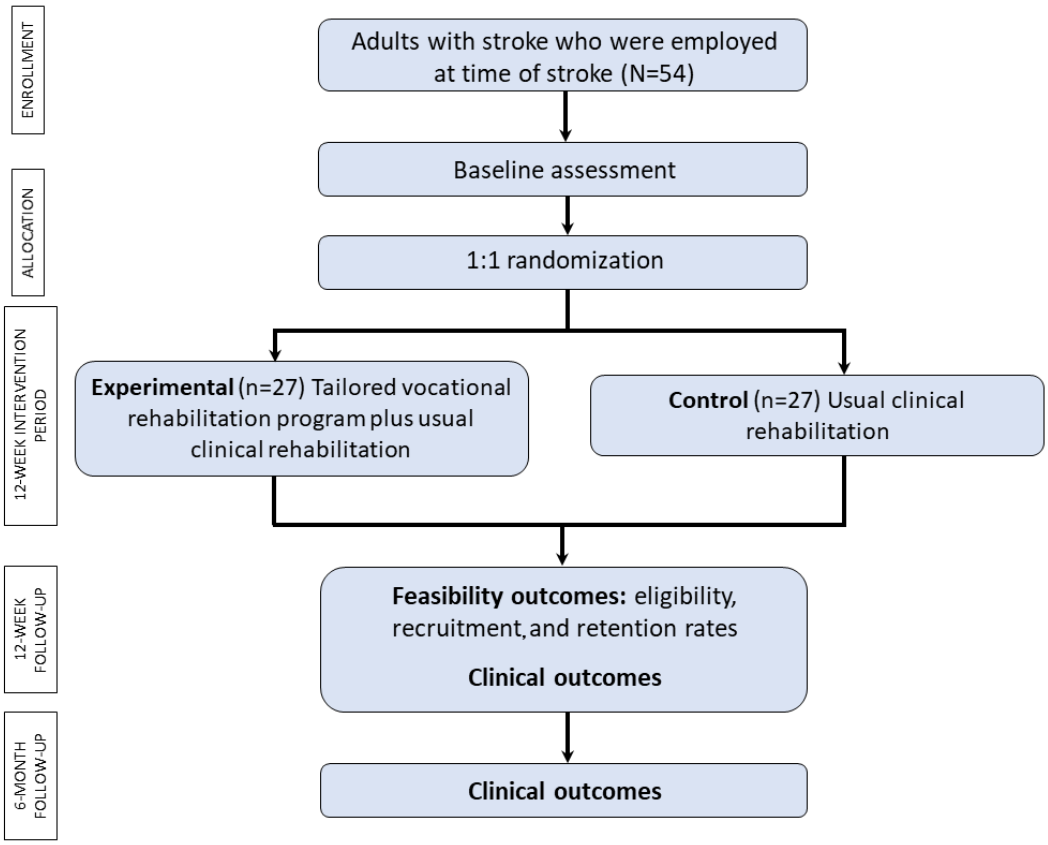
While the main purpose of this study is to determine feasibility, regarding the effect of the Work intervention, we hypothesize that participants who receive vocational rehabilitation will experience higher rates of vocational participation and improved quality of life compared to the control group.

Methods

Study Design and Approach

The Work trial is an observer-blinded, pilot randomized controlled trial with concealed allocation, blinded measurement, and intention-to-treat analysis. We will recruit stroke survivors from acute, rehabilitation, and community settings at 1 health service in Australia. Participants will receive either (1) early vocational rehabilitation plus usual clinical rehabilitation or (2) usual clinical rehabilitation alone. Outcomes will be assessed at baseline, 3 months (end of intervention), and 6 months from randomization. Assessments will be collected by researchers blind to group allocation; it is not possible to blind participants or therapists to group allocation. Researchers blinded to group allocation will analyze the data. The design of the trial is presented in Figure 1.

Figure 1. The CONSORT (Consolidated Standards of Reporting Trials) diagram of the Work trial.



Ethics Approval

The Alfred Health Human Research Ethics Committee approved this study (HREC490/19, SERP56225; date of authorization: October 30, 2019), and La Trobe and Monash Universities' human research ethics committees provided reciprocal registration. All participants will provide informed consent before data collection. This protocol was prospectively registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12619001164189; date of registration: August 20, 2019).

Consumer and Community Engagement

The views of people with lived experience of a stroke have been sought from the inception of this trial, including during a review of the funding application and protocol and selection of the primary outcome, and as representatives on the expert panel who will have oversight across the lifetime of the research. The expert panel consists of stroke survivors with lived experience of undertaking vocational rehabilitation as well as the failure to sustain working post stroke. The expert panel will continue to meet at least 3 times per year to provide input into the trial processes, documents, and intervention resources. These experts will be invited to review preliminary findings at the completion of data collection and will also inform dissemination strategies based on the pilot trial's findings. All expert panel members receive a gift voucher following each consultation as recompense for their attendance at meetings.

Participants and Therapists

Participants will be included in the study if they have been admitted to Alfred Health, a large tertiary hospital in Melbourne, Australia, with a new stroke in the last 4 months and have an identified vocational goal. Vocational goals will be inclusive

of paid work, voluntary positions, and study, and be defined as being on sick leave due to stroke, unemployed, or underemployed. Participants will have the potential for a return to competitive employment within 6 months, which will be clinically determined based on a history of competitive employment within the last 3 years and a stated goal of returning to work.

People will be excluded if they do not speak English, have >10 years of formal education, have a history of nonstroke neuropsychological disorder resulting in cognitive impairment (eg, vascular dementia, brain injury, or Alzheimer disease), or have a receptive language or cognitive impairment significant enough to prevent the person from participating in the intervention. To determine the severity of cognitive impairment, the Oxford Cognitive Screen will be administered.

Therapists will be eligible to deliver the experimental intervention if they are registered occupational therapists with at least 3 years of experience in stroke rehabilitation. All therapists will be trained in vocational assessment and the intervention before intervention delivery by authors SOK and NAL.

Randomization

Following baseline measurement, participants will be randomized via a web-based randomization program into 1 of 2 groups (experimental or control) using a process of minimization. Minimization will aim to balance 3 factors: baseline return-to-work status (unemployed or underemployed), age, and gender. The allocation sequence has been generated and will be managed by the Leeds Randomization Service at Leeds University and overseen by author AF.

Intervention

Usual Clinical Rehabilitation

Both the control and experimental groups will receive usual clinical rehabilitation, which will be determined by their treating clinicians. Usual clinical rehabilitation may involve inpatient or outpatient/community physiotherapy, speech pathology, occupational therapy, psychology, or medical follow-up. Within the services involved in the pilot, the clinical teams work with the participant (and those important to them) to develop a rehabilitation plan directed by goals set by the participant and deliver interventions [16] that maximize their potential and independence [17].

Experimental Group Intervention: Early Vocational Rehabilitation Plus Usual Clinical Rehabilitation

Participants randomized to the experimental group will receive early vocational rehabilitation (the Work intervention) to address individualized goals set in relation to work and working in addition to usual clinical rehabilitation. The vocational intervention will be predominantly delivered face to face, but there is potential to deliver using telehealth [18]. Whether in-person or via telehealth, the intervention will be delivered on a one-to-one basis and be individually tailored to the participant in terms of content, dose, intensity, and duration according to participants' needs and preferences (eg, whether the participant consents to employer liaison and workplace visits).

Outcome Measures

Outcome measures will be collected by a health professional who is trained in the procedures and blinded to group allocation. Participants will be asked not to discuss any aspect of the trial with the assessor to protect assessor blinding.

Feasibility

Feasibility of the study will involve examining recruitment; adherence, acceptability, and safety of the intervention; and measurement of outcomes.

Feasibility of recruitment will be determined by calculating the number of enrolled participants as a proportion of the eligible population of stroke survivors who were working prior to admission to a hospital with a new case of stroke and retention of participants. Feasibility of providing early vocational rehabilitation will be determined by examining participant adherence to the intervention. Acceptability will be determined at the end of trial participation when each participant will be asked the following question: which intervention(s) would you prefer given the choice? Safety will be determined by recording injurious events. Feasibility of measurement will be determined by being able to measure the clinical outcomes in all participants.

Clinical Outcomes

All clinical outcomes will be assessed at each time point, that is, baseline, end of the intervention period (3 months), and follow-up (6 months), by a measurer who is blind to group allocation. The primary outcome is participation level in work, defined by the proportion of hours worked against a standard working week of 38 hours per week (7.6 hours per day) as well as days worked in the month prior.

Secondary outcomes include the following:

- Quality of life will be measured using the EuroQol Group's EQ-5D-5L [19]
- The presence of anxiety and depressive symptoms will be measured using the Hospital Anxiety and Depression Scale [20]
- Social functioning will be assessed using the Work and Social Adjustment Scale [21]
- Functional independence to perform self-care and community activities will be assessed using the Autonomy Measurement System [22] and the Nottingham Extended Activities of Daily Living Index [23]
- Global disability arising from stroke will be rated using the modified Rankin Scale [24]

COVID-19 Safety Measures and Contingency Planning

The Australian government and institutional COVID-19 safety procedures and public health regulations will be adhered to at all times. This includes: (1) pausing recruitment during periods of lockdown or stay-at-home orders; (2) having current COVID-19 safety plans in place for all research and community sites; (3) participant screening for COVID-19 symptoms, maintaining physical distancing requirements, cleaning and

hygiene practices in line with infection control requirements, and use of personal protective equipment at all times. All staff will undertake training in COVID-19 safety procedures (Alfred Health, Melbourne, Victoria). With respect to extenuating circumstances leading to unplanned methodological, ethical, and/or analytical changes, protocol modifications will be submitted for approval. We plan to report modifications using CONSERVE (CONSORT and SPIRIT Extension for RCTs Revised in Extenuating Circumstances) alongside the CONSORT (Consolidated Standards of Reporting Trials) statement.

Data Safety

Data safety and monitoring will be overseen by a health professional independent of the trial who will be responsible for reviewing all adverse events and ceasing of recruitment in the case of multiple, trial-related serious adverse events. For the purpose of this study, a serious adverse event will be defined as an event that (1) is life-threatening or results in death, (2) requires or prolongs existing hospitalization, or (3) results in persistent or significant disability. Adverse events will be monitored throughout the study period and compared across the intervention and control groups.

Sample Size Estimates

Formal power calculations for feasibility studies are not usually undertaken; however, as the study is randomized, and we wish to obtain a preliminary estimate of effectiveness in relation to demonstrating how the intervention affects return-to-work rates, we propose a sample size that will be adequate to estimate parameters such as recruitment rate and sample variability for a phase III trial [25]. Based on these recommendations, we therefore propose to pragmatically recruit up to 54 participants.

Statistical Analyses

Descriptive statistics will focus on CI estimation rather than formal hypothesis testing. Eligibility, consent, and recruitment rates will be reported to determine the acceptability of randomization. Reasons for ineligibility, nonconsent, and nonrandomization will be summarized. Rates of retention in, adherence to, and completion of treatment will be summarized by group. Follow-up rates and compliance with outcome measurement will similarly demonstrate the acceptability of the outcome measures. Reasons for dropout will also be summarized where possible. Interventions provided to all participants (ie, both groups) will be descriptively summarized. We will also report the difference and its CI for follow-up rates between the intervention and control groups to identify large differences between the two arms. Dropout rates over time will also be reported. Levels of missing data for outcomes will be summarized and compared between groups. All outcome measures will be summarized using appropriate descriptive statistics (ie, means and SDs, medians and IQRs or proportions) and 95% CIs constructed for the difference in outcomes between the control and intervention groups. To generate evidence of proof of principle, we will generate a range of CIs around the main estimate for the treatment effect to inform us of the likelihood of where the “true” estimate may lie and inform the power calculations for a definitive phase III trial. The analysis will be adjusted for key predictors, including job type, baseline hours of work, and stroke severity.

Study Organization

Monash University supports trial organization, data management, and monitoring.

Results

Funded in March 2019, organizational ethics authorization was provided in October 2019. Although the first participant was randomized in November 2019, COVID-19 restrictions have affected Work trial recruitment to date. Data collection was not complete at the time of manuscript submission. Expected results are to be published in January 2023.

Discussion

Anticipated Findings

Returning to work is important to stroke survivors [5]; however, more than 60% of working-age people in Australia who experience a stroke report an unmet need with regard to returning to work [4]. In fact, almost 40% of people report ongoing unemployment or underemployment following a stroke [1]. Prior research has shown that vocational rehabilitation enables return to work [2], but there has been little research to date into interventions to support people with returning to work after stroke. The Work trial will determine whether providing a tailored vocational rehabilitation intervention is feasible early after stroke, as well as estimate the potential benefit. Given this trial will be conducted during the COVID-19 pandemic, we acknowledge that flexibility in the delivery of the Work trial intervention using telehealth may be required. Recruitment may be affected by COVID-19–related government restrictions; changes to this protocol will be disclosed using the CONSERVE statement for reporting extenuating circumstances.

This paper describes the protocol of a pilot randomized controlled trial designed to estimate the feasibility and benefit of providing early vocational rehabilitation to stroke survivors. The data obtained in this trial will inform the development of a future clinical trial powered to detect clinically significant changes in the chosen outcome measures if feasible.

Conclusions

This pilot feasibility study will provide necessary information regarding the delivery of vocational rehabilitation and the potential vocational outcomes experienced by people who have had a stroke. Findings from this pilot trial will provide data on the initial efficacy of an early vocational rehabilitation intervention and valuable feedback on the design and implementation of the intervention in the real world.

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Data Availability

The data sets generated during this study are not publicly available due to ethics restrictions but are available from the corresponding author upon reasonable request and with permission provided by the Alfred Health Human Research Committee.

Conflicts of Interest

None declared.

References

1. Harris C. Return to work after stroke: a nursing state of the science. Stroke 2014 Sep;45(9):e174-e176. [doi: 10.1161/STROKEAHA.114.006205] [Medline: 25013019]
2. O'Brien AN, Wolf TJ. Determining work outcomes in mild to moderate stroke survivors. Work 2010;36(4):441-447. [doi: 10.3233/WOR-2010-1047] [Medline: 20714100]
3. Treger I, Shames J, Giaquinto S, Ring H. Return to work in stroke patients. Disabil Rehabil 2007 Sep 15;29(17):1397-1403. [doi: 10.1080/09638280701314923] [Medline: 17729085]
4. National stroke audit: rehabilitation services report 2018. Stroke Foundation. 2018. URL: https://informme.org.au/media/5omlum0k/rehab_strokeservicesreport_2018.pdf [accessed 2022-09-29]
5. Medin J, Barajas J, Ekberg K. Stroke patients' experiences of return to work. Disabil Rehabil 2006 Sep 15;28(17):1051-1060. [doi: 10.1080/09638280500494819] [Medline: 16950735]
6. Walsh ME, Galvin R, Loughnane C, Macey C, Horgan NF. Community re-integration and long-term need in the first five years after stroke: results from a national survey. Disabil Rehabil 2015;37(20):1834-1838. [doi: 10.3109/09638288.2014.981302] [Medline: 25391817]
7. Waddell G, Burton AK. Is work good for your health and well-being?. Norwich, UK: The Stationery Office; 2006. URL: https://cardinal-management.co.uk/wp-content/uploads/2016/04/Burton-Waddell-is-work-good-for-you.pdf [accessed 2022-09-29]
8. Glozier N, Hackett ML, Parag V, Anderson CS, Auckland Regional Community Stroke (ARCOS) Study Group. The influence of psychiatric morbidity on return to paid work after stroke in younger adults: the Auckland Regional Community Stroke (ARCOS) Study, 2002 to 2003. Stroke 2008 May;39(5):1526-1532. [doi: 10.1161/STROKEAHA.107.503219] [Medline: 18369172]
9. Röding J, Lindström B, Malm J, Ohman A. Frustrated and invisible--younger stroke patients' experiences of the rehabilitation process. Disabil Rehabil 2003 Aug 05;25(15):867-874. [doi: 10.1080/0963828031000122276] [Medline: 12851097]
10. O'Keefe S, Stanley M, Adam K, Lannin NA. A systematic scoping review of work interventions for hospitalised adults with an acquired neurological impairment. J Occup Rehabil 2019 Sep;29(3):569-584. [doi: 10.1007/s10926-018-9820-8] [Medline: 30515620]
11. Holmes J. Vocational Rehabilitation. Oxford, UK: Blackwell Publishing; 2007.
12. Radford KA, Phillips J, Jones T, Gibson A, Sutton C, Watkins C, et al. Facilitating return to work through early specialist health-based interventions (FRESH): protocol for a feasibility randomised controlled trial. Pilot Feasibility Stud 2015;1:24 [FREE Full text] [doi: 10.1186/s40814-015-0017-z] [Medline: 27965803]
13. O'Keefe S, Stanley M, Sansonetti D, Schneider EJ, Kras M, Morarty J, et al. Designing an intervention process that embeds work-focussed interventions within inpatient rehabilitation: an intervention mapping approach. Aust Occup Ther J 2021 Feb;68(1):65-77. [doi: 10.1111/1440-1630.12705] [Medline: 33078431]
14. Brewer CC, Storms BS. The final phase of rehabilitation: work hardening. Orthop Nurs 1993;12(6):9-15; quiz 16. [doi: 10.1097/00006416-199311000-00003] [Medline: 8121714]
15. Chappell I, Higham J, McLean AM. An occupational therapy work skills assessment for individuals with head injury. Can J Occup Ther 2003 Jun;70(3):163-169. [doi: 10.1177/000841740307000305] [Medline: 12846109]
16. Living clinical guidelines for stroke management. Stroke Foundation. URL: https://informme.org.au/guidelines/living-clinical-guidelines-for-stroke-management [accessed 2022-10-04]
17. Commissioning guidance for rehabilitation. NHS England. 2016 Apr 01. URL: https://www.england.nhs.uk/publication/commissioning-guidance-for-rehabilitation/ [accessed 2022-09-29]
18. Kettlewell J, Lindley R, Radford K, Patel P, Bridger K, Kellezi B, et al. Factors affecting the delivery and acceptability of the ROWTATE telehealth vocational rehabilitation intervention for traumatic injury survivors: a mixed-methods study. Int J Environ Res Public Health 2021 Sep 16;18(18) [FREE Full text] [doi: 10.3390/ijerph18189744] [Medline: 34574670]

19. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011 Dec;20(10):1727-1736 [FREE Full text] [doi: 10.1007/s11136-011-9903-x] [Medline: 21479777]
20. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983 Jun;67(6):361-370. [doi: 10.1111/j.1600-0447.1983.tb09716.x] [Medline: 6880820]
21. Mundt JC, Marks IM, Shear MK, Greist JH. The Work and Social Adjustment Scale: a simple measure of impairment in functioning. Br J Psychiatry 2002 May;180:461-464. [doi: 10.1192/bjp.180.5.461] [Medline: 11983645]
22. Hebert R, Carrier R, Bilodeau A. The Functional Autonomy Measurement System (SMAF): description and validation of an instrument for the measurement of handicaps. Age Ageing 1988 Sep;17(5):293-302. [doi: 10.1093/ageing/17.5.293] [Medline: 2976575]
23. Nouri F, Lincoln N. An extended activities of daily living scale for stroke patients. Clin Rehabil 2016 Jul 01;1(4):301-305. [doi: 10.1177/026921558700100409]
24. Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. Stroke 2007 Mar;38(3):1091-1096. [doi: 10.1161/01.STR.0000258355.23810.c6] [Medline: 17272767]
25. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. J Eval Clin Pract 2004 May;10(2):307-312. [doi: 10.1111/j.2002.384.doc.x] [Medline: 15189396]

Abbreviations

CONSERVE: CONSORT and SPIRIT Extension for RCTs Revised in Extenuating Circumstances
CONSORT: Consolidated Standards of Reporting Trials

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Protocol

Feasibility of Monitoring Patients Who Have Cancer With a Smart T-shirt: Protocol for the OncoSmartShirt Study

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Abstract

Background: Studies have shown that there may be dissimilar perceptions on symptoms or side effects between patients with cancer and health care professionals. This may lead to symptomatic patients notifying the clinic irregularly or not telling the clinic at all. Wearables could help identify symptoms earlier. Patients with low socioeconomic status and less self-awareness of their health may benefit from this. A new design of wearables is a smart t-shirt that, with embedded sensors, provides measurement flows such as electrocardiogram, thoracic and abdominal respiration, and temperature.

Objective: This study evaluates the feasibility of using a smart t-shirt for home monitoring of biometric sensor data in adolescent and young adult and elderly patients during cancer treatment.

Methods: The OncoSmartShirt study is an explorative study investigating the feasibility of using the Chronolife smart t-shirt during cancer treatment. This smart t-shirt is designed with multiple fully embedded sensors and electrodes that engender 6 different measurement flows continuously. A total of 20 Danish patients with cancer ≥18 years old in antineoplastic treatment at Department of Oncology Rigshospitalet Denmark will be recruited from all cancer wards, whether patients are in curative or palliative care. Of these 20 patients, 10 (50%) will be <39 years old, defined as adolescent and young adult, and 10 (50%) will be patients >65 years old, defined as elderly. Consenting patients will be asked to wear a smart t-shirt daily for 2 weeks during their treatment course.

Results: The primary outcome is to determine if it is feasible to wear a smart t-shirt throughout the day (preferably 8 hours per day) for 2 weeks. Inclusion of patients started in March 2022.

Conclusions: The study will assess the feasibility of using the Chronolife smart t-shirt for home monitoring of vital parameters in patients with cancer during their treatment and bring new insights into how wearables and biometric data can be used as part of symptom or side-effect recognition in patients with cancer during treatment, with the aim to increase patients' quality of life.

Trial Registration: ClinicalTrials.gov NCT05235594; https://beta.clinicaltrials.gov/study/NCT05235594

International Registered Report Identifier (IRRID): PRR1-10.2196/37626

(JMIR Res Protoc 2022;11(10):e37626) doi:10.2196/37626

KEYWORDS

biometric sensor technology; cancer; home monitoring; patient-generated health data; sensor; smart t-shirt; remote monitoring; adolescent; protocol; patient; youth; health care professional; cancer treatment

Introduction

Collecting biometric sensor data by wearables is an example of real-time patient-generated health data that can provide vital and detailed objective information about patients. Although previous results from our research group have shown that the literature on wearables is very heterogeneous and lacks consensus [1], studies show that wearables may have the potential to improve quality of oncological treatment and increase patients' quality of life [2-5].

During oncological treatment, most patients are primarily seen in outpatient clinics where the number of visits is determined by type of treatment and the expected side effects [6]. The symptoms and side effects, experienced by patients with cancer, depend on the type of cancer, the treatment modality, and the preexisting comorbidity [7-9]. Patients are informed to notify the clinic if they experience side effects or increased symptoms. In worst case scenarios, patients may need acute hospital treatment, while in other cases, side effects are more related to poorer treatment compliance and reduced quality of life [2].

A wearable is a noninvasive and wireless sensor device that can monitor and collect health parameters on various biometric data points such as skin temperature, respiration rate, heart rate, and physical activity. The device normally transmits the health data to an app (eg, on a smartphone), which registers the readings. The devices can be worn in different ways, depending on the design of the device (eg, a smartwatch around the wrist) [10,11].

Thus, wearables offer the opportunity of monitoring patients passively in their own environment while they are outside the hospital. This allows the patients to carry on with their daily life and thus minimize the burden from the decrease in their quality of life [12].

Studies have shown that there may be dissimilar assessments and perceptions on symptoms between patients and health care professionals [13,14], which is reflected by the fact that health care professionals often underestimate patients' symptoms [15]. This may cause patients with symptoms or side effects to notify the clinic irregularly or not to notify the clinic at all, which could lead to unnecessary discomfort for patients and suboptimal treatment. In such cases, wearables could help identify symptoms or side effects earlier. In particular, patients with low socioeconomic status and less self-awareness of their health are assumed to benefit from using wearables [3].

A new design of a wearable is the smart t-shirt. A smart t-shirt is designed with sensors embedded into the fabric, which allows for the 24/7 monitoring of electrocardiogram (ECG), thoracic and abdominal respiration, and so on. Originally, smart t-shirts were designed to support athletes in their performance analysis and preventing injuries but with an ambition to support and improve health care as a wearable medical device [16]. Compared to other wearables, the smart t-shirt enables health professionals to monitor an increased number of health parameters on various biometric data points. Furthermore, data collection is predicted to be exact and completely comparable to conventional medical measuring devices [17,18]. Studies have shown that smart t-shirts can monitor 12-lead ECG acquisition with the same quality of standard Holter recording [17-19].

These new technologies allow health professionals to track patients' health more extensively. At the same time, the new tools provide precise information without recall and reporting bias, which can lead to a better and more accurate cancer treatment [3,20-22]. However, knowledge in using wearables in an oncological setting is limited [12,20,23,24], and it has been highlighted that there is very little consensus and awareness of adherence to wearables. This is an essential part of being able to use and compare collected biometric sensor data [1], and it could be questioned whether oncological patients are able to adhere to the use of a smart t-shirt during their treatment.

In this paper, the study design of the OncoSmartShirt feasibility study is described. The purpose of this study is to evaluate the feasibility of using a smart t-shirt for remote monitoring of biometric sensor data in adolescent and young adult (AYA) and elderly patients during cancer treatment.

Methods

Study Design

The OncoSmartShirt study is an explorative study investigating the feasibility of using the Chronolife Smart t-shirt during cancer treatment. This smart t-shirt is designed with multiple sensors and electrodes fully embedded, which engender 6 different measurement flows continuously [25].

This trial is an investigator-driven partnership between Department of Oncology Rigshospitalet and Chronolife and is registered at ClinicalTrials.gov (NCT05235594). The study is conformed to the guidelines of General Data Protection Regulation and is registered at the Capital Region of Denmark (P-2021-357). The trial is approved by the local division for IT and Medico Technology in the Capital Region of Denmark and is a collaboration between Department of Oncology Rigshospitalet, Department of Innovation Rigshospitalet, and Telemedical Knowledge Center Capital Region of Denmark. Approval from the National Committee on Health Research Ethics is not required for this trial in the Danish context.

The acceptance and comfort of wearing the Chronolife smart t-shirt throughout the day (preferably 8 hours per day) for 2 weeks is investigated in all 20 enrolled patients. The intervention period will elapse at any time in the patient's antineoplastic treatment course.

Secondly, qualitative telephone interviews will be carried out, and patients will be asked to fill in a questionnaire concerning their experience with wearing the shirt. Topics included in the interviews are, among others, the material and design of the smart t-shirt, feeling social stigma, and surveillance. The interview guide and patient questionnaire are available in Multimedia Appendices 1 and 2, respectively. The study will be performed in a public health care system, and the smart t-shirt will be given to the patients by the hospital. Only the patient included in the trial will be allowed to wear the t-shirt during the study period. Patients will be responsible for charging and washing the shirt and are required to return the shirt at study

termination. No biometric data of vital parameters collected by the wearable will be published or monitored by health care professionals during the study. All other interventions, such as oncological care and treatment, will be kept to their normal routine. Participation in the study will not result in any payment or reward for the included patients.

Patients and Recruitment

A total of 20 Danish patients ≥18 years old who have cancer and are in antineoplastic treatment will be recruited continuously. Of these 20 patients with cancer, 10 (50%) will be <39 years old, defined as AYA, and 10 (50%) >65 years old, defined as elderly, will be included. These 2 age groups were included, as we expected that these would differ the most from each other in terms of acceptance of the smart t-shirt. There will be no requirements regarding specific cancer diagnosis, and both patients in curative and palliative care will be included meaning that all types of patients with cancer can be included. These broad inclusion criteria are designed to make inclusion in the study as simple as possible. Therefore, recruitment of patients with cancer in the study will take place consecutively in all cancer departments at the Department of Oncology Rigshospitalet, Denmark. Patients will be eligible if they read and speak Danish and have the capacity to provide written informed consent to participate in the study. Patients can withdraw their consent at any time. Patients with serious cognitive deficits and who cannot reliably provide informed consent will be excluded. Inclusion in the study will have no interference with the planned oncological treatment.

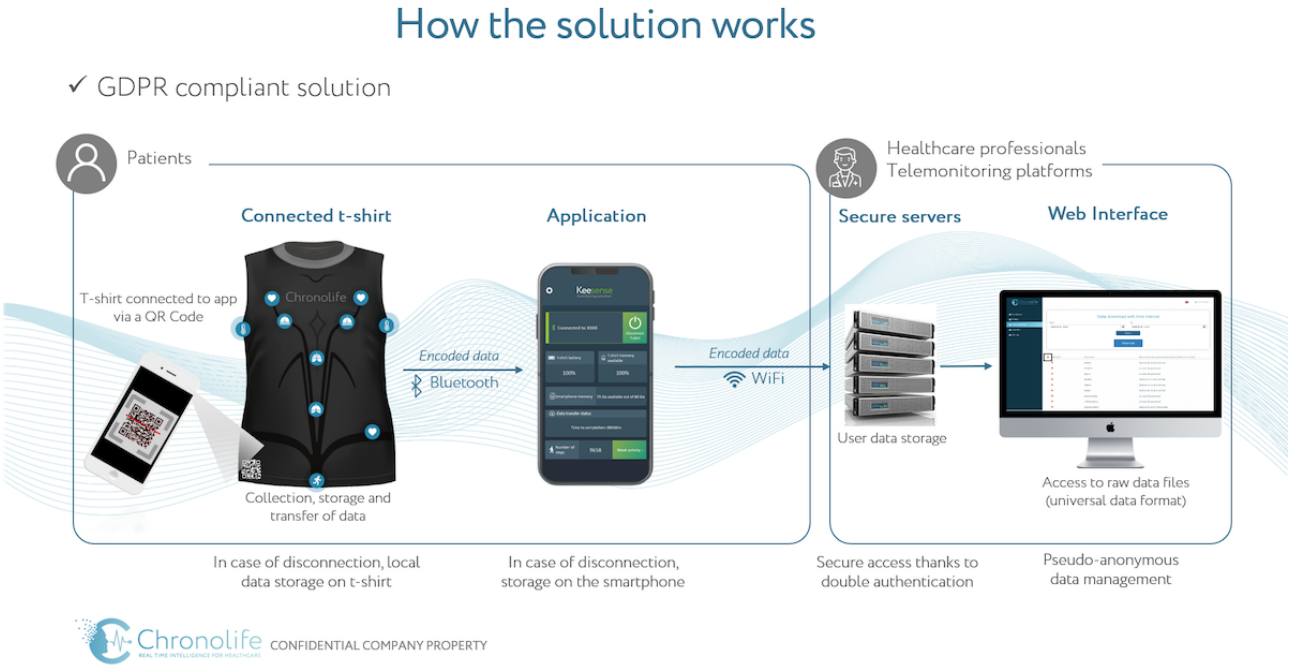
Hardware

The study device in the trial consists of four units; a washable smart t-shirt fitted with multiple sensors and electrodes from Chronolife, a companion smartphone or tablet app, an accredited secure data hosting server, and a web interface [25]. The Chronolife smart t-shirt is commercialized and “CE marked” for the consumer market. The smart t-shirt is designed for every-day use. The electrical sensors embedded in the shirt allows detection of 6 physiological parameters: ECG (beat per minute), thoracic and abdominal respiration (respiration per minute), thoracic impedance (kOhm), physical activity (steps), and skin temperature (°C) [25]. The sensors are powered by a nonremovable rechargeable battery. Additionally, the t-shirt is equipped with a memory card that stores data and a Bluetooth interface that transmits data. These are fully integrated into the t-shirt and have been sealed in water-resistant coatings.

Software

The smart t-shirt connects to the smartphone app via a QR code located on the shirt. The health data collected by the sensors in the shirt are transmitted by Bluetooth Low Energy to the connected smartphone app designed for storage (Figure 1). Furthermore, the smartphone app provides further data transmission through 3G or 4G Wi-Fi to an accredited data-hosting server that will store data and provide data for a web interface for analysis and algorithm training [25]. Figure 1 illustrates the four components and the flow of data.

Figure 1. Data flow from data collected by the t-shirt to the smartphone app to the accredited data hosting server. Illustration made public with allowance from Chronolife. GDPR: General Data Protection Regulation.



Statistical Analysis

Endpoints

The primary endpoint is to assess the feasibility of using the Chronolife smart t-shirt based on completion rate, which in this trial is defined as the number of included patients using the smart t-shirt at least 8 hours per day during the 2 weeks study period.

Secondary endpoints are to assess technical feasibility in a Danish health care system, including data acquisition rate and

data completeness. Qualitative interviews with the patients regarding the use of the smart t-shirt will be performed. Patients will be asked to fill in a questionnaire concerning their experience with wearing the t-shirt. As explorative endpoint changes in heart rate, skin temperature, physical activity, and respirations frequency will be presented descriptively.

Descriptive data will be collected and analyzed in the statistical software SPSS Statistics (IMB Corp).

Power

A power calculation is not required for this type of study because it is a feasibility study with no control group and no formal statistical hypothesis testing, and thus, the sample size is not driven by formal power calculations. This sample size corresponds to studies of the same nature in the literature [26-28].

Ethical Considerations

The inclusion of patients will not begin until the Data Protection Agency has granted their relevant approval for the study. Patients will receive verbal and written information and must provide written informed consent. Moreover, they can withdraw at any time during the study. The Scientific Ethics Committees for the Capital Region of Copenhagen has been informed; however, approval is not required for this type of study according to Danish law.

Results

Inclusion of patients started in March 2022. Data collection is expected to be completed in autumn 2022. Processing of data is expected to begin in autumn 2022 as well.

Discussion

The study will assess the feasibility of using the Chronolife smart t-shirt for remote home monitoring of vital parameters in AYA and elderly patients during their treatment course. This study will bring new insights into how wearables and biometric data potentially can be used as a part of symptom recognition in patients with cancer during the treatment course in the quest of increasing their quality of life, given that the use of smart t-shirts is feasible. Data from this study can be used in designing future prospective studies using the smart t-shirt as intervention, along with the recommendation from the Clinical Trials Transformation Initiative on Developing Novel Endpoints Generated by Mobile Technologies for Use in Clinical Trials 2017. In future studies, it would be relevant to examine the relationship between biometric data collected from wearables and the perception of symptoms and side effects from patients and clinicians.

Acknowledgments

The Chronolife smart t-shirts have been donated to the trials by Chronolife. The donation does not entail any financial obligations to the manufacturer. In addition to donating t-shirts, the manufacturer has contributed with education in the use of smart t-shirts and helped with technical support for included patients and clinicians.

Data Availability

Data from this study are not yet available. Data will not be publicly available due to institutional restrictions.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guide.
[PDF File (Adobe PDF File), 71 KB - resprot_v11i10e37626_app1.pdf]

Multimedia Appendix 2
Patient questionnaire.
[PDF File (Adobe PDF File), 154 KB - resprot_v11i10e37626_app2.pdf]

References

1. Beauchamp UL, Pappot H, Holländer-Mieritz C. The Use of Wearables in Clinical Trials During Cancer Treatment: Systematic Review. JMIR Mhealth Uhealth 2020 Nov 11;8(11):e22006 [FREE Full text] [doi: 10.2196/22006] [Medline: 33174852]
2. Kofoed S, Breen S, Gough K, Aranda S. Benefits of remote real-time side-effect monitoring systems for patients receiving cancer treatment. Oncol Rev 2012 Mar 05;6(1):e7 [FREE Full text] [doi: 10.4081/oncol.2012.e7] [Medline: 25992209]
3. Beg MS, Gupta A, Stewart T, Rethorst CD. Promise of Wearable Physical Activity Monitors in Oncology Practice. J Oncol Pract 2017 Feb;13(2):82-89 [FREE Full text] [doi: 10.1200/JOP.2016.016857] [Medline: 28387544]

4. Jim HSL, Hoogland AI, Brownstein NC, Barata A, Dicker AP, Knoop H, et al. Innovations in research and clinical care using patient-generated health data. CA Cancer J Clin 2020 May;70(3):182-199 [FREE Full text] [doi: 10.3322/caac.21608] [Medline: 32311776]
5. Chung AE, Jensen RE, Basch EM. Leveraging Emerging Technologies and the "Internet of Things" to Improve the Quality of Cancer Care. J Oncol Pract 2016 Oct;12(10):863-866 [FREE Full text] [doi: 10.1200/JOP.2016.015784] [Medline: 27624946]
6. Liao Y, Thompson C, Peterson S, Mandrola J, Beg MS. The Future of Wearable Technologies and Remote Monitoring in Health Care. Am Soc Clin Oncol Educ Book 2019 Jan;39:115-121 [FREE Full text] [doi: 10.1200/EDBK_238919] [Medline: 31099626]
7. Reilly CM, Bruner DW, Mitchell SA, Minasian LM, Basch E, Dueck AC, et al. A literature synthesis of symptom prevalence and severity in persons receiving active cancer treatment. Support Care Cancer 2013 Jun 12;21(6):1525-1550 [FREE Full text] [doi: 10.1007/s00520-012-1688-0] [Medline: 23314601]
8. Moreira-Pinto J, Leão I, Palmela C, Branco F, Godinho J, Simões P, et al. Febrile Neutropenia in Patients with Solid Tumors Undergoing Intravenous Chemotherapy. Oncol Res Treat 2020 Aug 20;43(11):605-612 [FREE Full text] [doi: 10.1159/000506109] [Medline: 32818937]
9. Niraula S, Seruga B, Ocana A, Shao T, Goldstein R, Tannock IF, et al. The Price We Pay for Progress: A Meta-Analysis of Harms of Newly Approved Anticancer Drugs. JCO 2012 Aug 20;30(24):3012-3019. [doi: 10.1200/jco.2011.40.3824]
10. Piwek L, Ellis DA, Andrews S, Joinson A. The Rise of Consumer Health Wearables: Promises and Barriers. PLoS Med 2016 Feb;13(2):e1001953 [FREE Full text] [doi: 10.1371/journal.pmed.1001953] [Medline: 26836780]
11. Dias D, Paulo Silva Cunha J. Wearable Health Devices-Vital Sign Monitoring, Systems and Technologies. Sensors (Basel) 2018 Jul 25;18(8):2414 [FREE Full text] [doi: 10.3390/s18082414] [Medline: 30044415]
12. Low CA, Dey AK, Ferreira D, Kamarck T, Sun W, Bae S, et al. Estimation of Symptom Severity During Chemotherapy From Passively Sensed Data: Exploratory Study. J Med Internet Res 2017 Dec 19;19(12):e420 [FREE Full text] [doi: 10.2196/jmir.9046] [Medline: 29258977]
13. Sonn GA, Sadetsky N, Presti JC, Litwin MS. Differing perceptions of quality of life in patients with prostate cancer and their doctors. J Urol 2013 Jan;189(1 Suppl):S59-65; discussion S65. [doi: 10.1016/j.juro.2012.11.032] [Medline: 23234635]
14. Litwin MS, Lubeck DP, Henning JM, Carrol PR. Differences in urologist and patient assessments of health related quality of life in men with prostate cancer: Results of the CaPSURE database. Journal of Urology 1998 Jun;159(6):1988-1992. [doi: 10.1016/s0022-5347(01)63222-1]
15. Xiao C, Polomano R, Bruner D. Comparison between patient-reported and clinician-observed symptoms in oncology. Cancer Nurs 2013;36(6):E1-E16. [doi: 10.1097/NCC.0b013e318269040f] [Medline: 23047799]
16. Smart textile. Chronolife. URL: https://www.chronolife.net/product/smart-textile [accessed 2022-09-19]
17. Steinberg C, Philippon F, Sanchez M, Fortier-Poisson P, O'Hara G, Molin F, et al. A Novel Wearable Device for Continuous Ambulatory ECG Recording: Proof of Concept and Assessment of Signal Quality. Biosensors (Basel) 2019 Jan 21;9(1):17 [FREE Full text] [doi: 10.3390/bios9010017] [Medline: 30669678]
18. Fouassier D, Roy X, Blanchard A, Hulot J. Assessment of signal quality measured with a smart 12-lead ECG acquisition T-shirt. Ann Noninvasive Electrocardiol 2020 Jan 24;25(1):e12682 [FREE Full text] [doi: 10.1111/anec.12682] [Medline: 31339208]
19. Tsukada YT, Tokita M, Murata H, Hirasawa Y, Yodogawa K, Iwasaki Y, et al. Validation of wearable textile electrodes for ECG monitoring. Heart Vessels 2019 Jul 24;34(7):1203-1211 [FREE Full text] [doi: 10.1007/s00380-019-01347-8] [Medline: 30680493]
20. Cox SM, Lane A, Volchenboum SL. Use of Wearable, Mobile, and Sensor Technology in Cancer Clinical Trials. JCO Clin Cancer Inform 2018 Dec;2:1-11 [FREE Full text] [doi: 10.1200/CCI.17.00147] [Medline: 30652590]
21. Basch E, Deal AM, Kris MG, Scher HI, Hudis CA, Sabbatini P, et al. Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial. J Clin Oncol 2016 Feb 20;34(6):557-565 [FREE Full text] [doi: 10.1200/JCO.2015.63.0830] [Medline: 26644527]
22. Komarzynski S, Wreglesworth NI, Griffiths D, Pecchia L, Subbe CP, Hughes SF, et al. Embracing Change: Learnings From Implementing Multidimensional Digital Remote Monitoring in Oncology Patients at a District General Hospital During the COVID-19 Pandemic. JCO Clinical Cancer Informatics 2021 Dec(5):216-220. [doi: 10.1200/cci.20.00136]
23. Lu T, Fu C, Ma MH, Fang C, Turner AM. Healthcare Applications of Smart Watches. A Systematic Review. Appl Clin Inform 2016 Sep 14;7(3):850-869 [FREE Full text] [doi: 10.4338/ACI-2016-03-R-0042] [Medline: 27623763]
24. Reeder B, David A. Health at hand: A systematic review of smart watch uses for health and wellness. J Biomed Inform 2016 Oct;63:269-276 [FREE Full text] [doi: 10.1016/j.jbi.2016.09.001] [Medline: 27612974]
25. Chronolife product description. Chronolife. URL: https://www.chronolife.net/product/keesense/2021 [accessed 2022-09-19]
26. Cnossen IC, van Uden-Kraan CF, Rinkel RN, Aalders IJ, de Goede CJ, de Bree R, et al. Multimodal guided self-help exercise program to prevent speech, swallowing, and shoulder problems among head and neck cancer patients: a feasibility study. J Med Internet Res 2014 Mar 06;16(3):e74 [FREE Full text] [doi: 10.2196/jmir.2990] [Medline: 24610383]

27. Wu R, Liaqat D, de Lara E, Son T, Rudzicz F, Alshaer H, et al. Feasibility of Using a Smartwatch to Intensively Monitor Patients With Chronic Obstructive Pulmonary Disease: Prospective Cohort Study. JMIR Mhealth Uhealth 2018 Jun 14;6(6):e10046 [FREE Full text] [doi: 10.2196/10046] [Medline: 29903700]
28. Holländer-Mieritz C, Vogelius I, Kristensen C, Green A, Rindum J, Pappot H. Using Biometric Sensor Data to Monitor Cancer Patients During Radiotherapy: Protocol for the OncoWatch Feasibility Study. JMIR Res Protoc 2021 May 13;10(5):e26096 [FREE Full text] [doi: 10.2196/26096] [Medline: 33983123]

Abbreviations

AYA: adolescent and young adult
ECG: electrocardiogram

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Protocol

Feasibility of Digital Cognitive Behavioral Therapy for Depressed Older Adults With the Moodbuster Platform: Protocol for 2 Pilot Feasibility Studies

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Abstract

Background: Internet-based interventions can be effective in the treatment of depression. However, internet-based interventions for older adults with depression are scarce, and little is known about their feasibility and effectiveness.

Objective: To present the design of 2 studies aiming to assess the feasibility of internet-based cognitive behavioral treatment for older adults with depression. We will assess the feasibility of an online, guided version of the Moodbuster platform among depressed older adults from the general population as well as the feasibility of a blended format (combining integrated face-to-face sessions and internet-based modules) in a specialized mental health care outpatient clinic.

Methods: A single-group, pretest-posttest design will be applied in both settings. The primary outcome of the studies will be feasibility in terms of (1) acceptance and satisfaction (measured with the Client Satisfaction Questionnaire-8), (2) usability (measured with the System Usability Scale), and (3) engagement (measured with the Twente Engagement with eHealth Technologies Scale). Secondary outcomes include (1) the severity of depressive symptoms (measured with the 8-item Patient Health Questionnaire depression scale), (2) participant and therapist experience with the digital technology (measured with qualitative interviews), (3) the working alliance between patients and practitioners (from both perspectives; measured with the Working Alliance Inventory–Short Revised questionnaire), (4) the technical alliance between patients and the platform (measured with the Working Alliance Inventory for Online Interventions–Short Form questionnaire), and (5) uptake, in terms of attempted and completed modules. A total of 30 older adults with mild to moderate depressive symptoms (Geriatric Depression Scale 15 score between 5 and 11) will be recruited from the general population. A total of 15 older adults with moderate to severe depressive symptoms (Geriatric Depression Scale 15 score between 8 and 15) will be recruited from a specialized mental health care outpatient clinic. A mixed methods approach combining quantitative and qualitative analyses will be adopted. Both the primary and secondary outcomes will be further explored with individual semistructured interviews and synthesized descriptively. Descriptive statistics (reported as means and SDs) will be used to examine the primary and secondary outcome measures. Within-group depression severity will be analyzed using a 2-tailed, paired-sample *t* test to investigate differences between time points. The interviews will be recorded and analyzed using thematic analysis.

Results: The studies were funded in October 2019. Recruitment started in September 2022.

Conclusions: The results of these pilot studies will show whether this platform is feasible for use by the older adult population in a blended, guided format in the 2 settings and will represent the first exploration of the size of the effect of Moodbuster in terms of decreased depressive symptoms.

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KEYWORDS

iCBT; study protocol; feasibility study; acceptance; satisfaction; usability; engagement; depression severity; older adults

Introduction

Background

Depression is a common mental disorder that is associated with the substantial loss of a person's well-being and quality of life [1]. Essential components of depression are depressed mood and loss of interest or pleasure in nearly all activities [2]. Depression constitutes a large and rising proportion of global disease [3] and is a major public health problem [4]. Late-life depression is the third leading contributor to the global burden of disease [5]. Late-life depression can be distinguished from adult depression in several ways. First, depressed older adults may show different or less obvious symptoms than their younger counterparts, and cognitive symptoms (eg, disorientation, memory loss, and distractibility) may be particularly prominent [6]. Cognitive impairment may mask the symptoms of late-life depression, as is often seen in vascular disease, Alzheimer dementia, and Parkinson disease [7]. Second, depression in later life is associated with increased risk of physical and psychological disability, decreased quality of life, and increased costs due to higher health care needs in general [7]. Lastly, depressive symptoms in later life increase the distress of family and friends and the burden of informal caregivers, such as spouses or other family members, which often contributes to social isolation of the older adult with depression [8].

Late-life depression is often not recognized or treated [6]. This is unfortunate, because treatment of late-life depression is effective, and decreases not only depressive symptoms [4], but also secondary symptoms, such as pain, general functioning, and health-related quality of life [9,10]. Depending on the diagnosed type of depression and the severity of the impairment, a variety of treatment interventions can be considered for older adults, such as psychoeducation, psychotherapy, and antidepressants [11]. Although antidepressants are effective as a treatment option for older adults [12], they can put them at greater risk for adverse events compared to younger adults with depression because of multiple medical comorbidities and drug-drug interactions, and can contribute to polypharmacy, which increases with aging [13]. Psychotherapies such as problem-solving therapy, cognitive behavioral therapy (CBT), and interpersonal psychotherapy are associated with fewer risks and have benefits equal to antidepressants [13]. CBT is an especially well studied [13,14] and effective type of psychotherapy for depression in later life [15,16]. Unfortunately, only a small proportion of older adults seek psychological treatment [17]. Internet-based interventions can help bridge this treatment gap [18].

Internet-Based CBT

In recent years, internet-based interventions for the treatment of various common mental disorders, including depression, have been developed and evaluated [19]. These online treatments may overcome barriers that hinder access to face-to-face treatment, such as costs, long waiting lists, limited access to psychological treatment in particular neighborhoods, and the perceived stigma of seeking treatment for a psychiatric disorder [20]. Internet-based CBT (iCBT) provides the same information and teaches similar skills as traditional face-to-face CBT, but does so through the internet with structured materials [21-23]. Additionally, iCBT interventions can be provided in different ways: with therapeutic guidance (ie, guided), without human support related to the therapeutic content (ie, unguided), or in a blended format (ie, integrating online and face-to-face sessions) [24-26]. Ample research has shown that iCBT interventions for depression are effective compared to inactive and active controls. Guided iCBT outperforms unguided interventions, especially among more severely depressed individuals [19,27,28].

Research into internet-based interventions for older depressed adults is scarce, underlining the need for more research to be able to assess the feasibility and effectiveness of these interventions for this specific group. A study by Spek et al [21] measured the effectiveness of an unguided CBT intervention for older adults (aged between 50 and 60 years) and found that it was at least as effective as face-to-face group CBT in reducing symptoms of depression. Furthermore, a randomized controlled trial (RCT) performed by Titov et al [29] supported the use of therapist-guided iCBT as an evidence-based approach to psychological treatment for older adults (aged between 60 and 76 years) with depression. Despite the fact that older adults are generally positive about internet-based interventions [30], there are hardly any digital interventions for the treatment of depression that specifically target older adults, either within the general population or in specialized mental health care outpatient clinics. Also, with the growing number of older adults in our society, there has been a large rise in the number of patients suffering from depression [31]. Furthermore, older adults are not always able to engage with traditional face-to-face interventions, as they might have limited access to health services due to physical health and constraints or due to limited mobility for other reasons, such as a lack of public transport. The need for innovative and effective digital interventions for older adults is thus a public health priority. Lastly, the study by Spek et al [21] recruited participants from the general population and provided the intervention in an unguided format. We

therefore plan to evaluate the feasibility of using the intervention in a specialized mental health care outpatient clinic with a blended format and in the general population with a guided format.

Aim of the Current Studies

The 2 current studies aim to evaluate the feasibility of an online treatment platform (Moodbuster) that targets depressive symptoms in older adults (aged at least 55 years) in 2 settings. The first study will test the feasibility of Moodbuster with an online guided treatment format for older adults with mild to moderate depressive symptoms recruited from the general population. The second study will test the intervention in a blended treatment format by integrating face-to-face and online sessions into one treatment protocol. It will target older adults with moderate to severe depression recruited from a specialized mental health care outpatient clinic. The primary aim of both studies is to evaluate the feasibility of the online platform in terms of (1) acceptance and satisfaction, (2) usability, and (3) engagement. Secondary outcomes include depressive symptom severity, participant experience with digital technologies, technical alliance, working alliance, and uptake.

Methods

Study Design

A single-group, pretest-posttest design will be used in both studies. Assessments will be taken at screening (T–1), at baseline (T0), and postintervention (T1). The intervention will last 8 weeks for the group with mild to moderate depressive symptoms from the general population and 16 to 20 weeks for the group with moderate to severe depressive symptoms from the specialized mental health care outpatient clinic. Written informed consent will be obtained from all participants. Figures 1 and 2 show the participant flow for both studies.

Figure 1. Flowchart of the study design for the group of older adult with mild to moderate depressive symptoms. GDS: Geriatric Depression Scale.

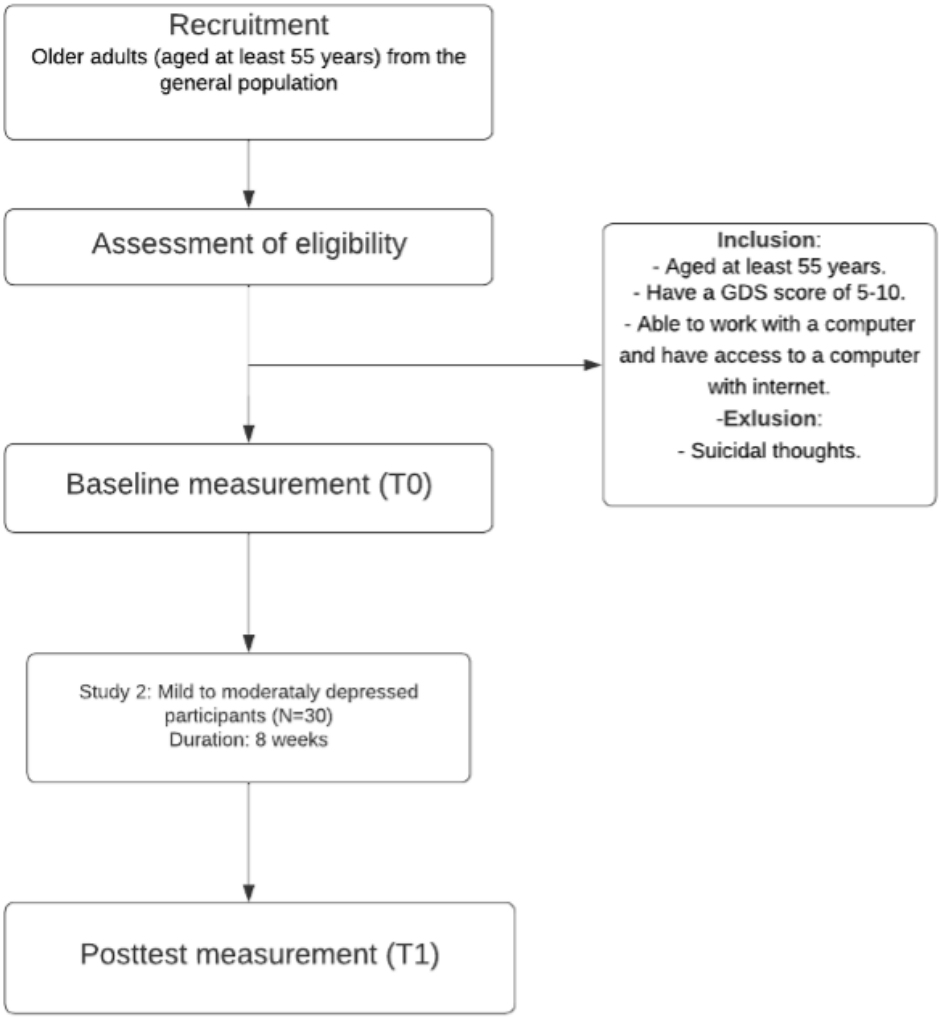
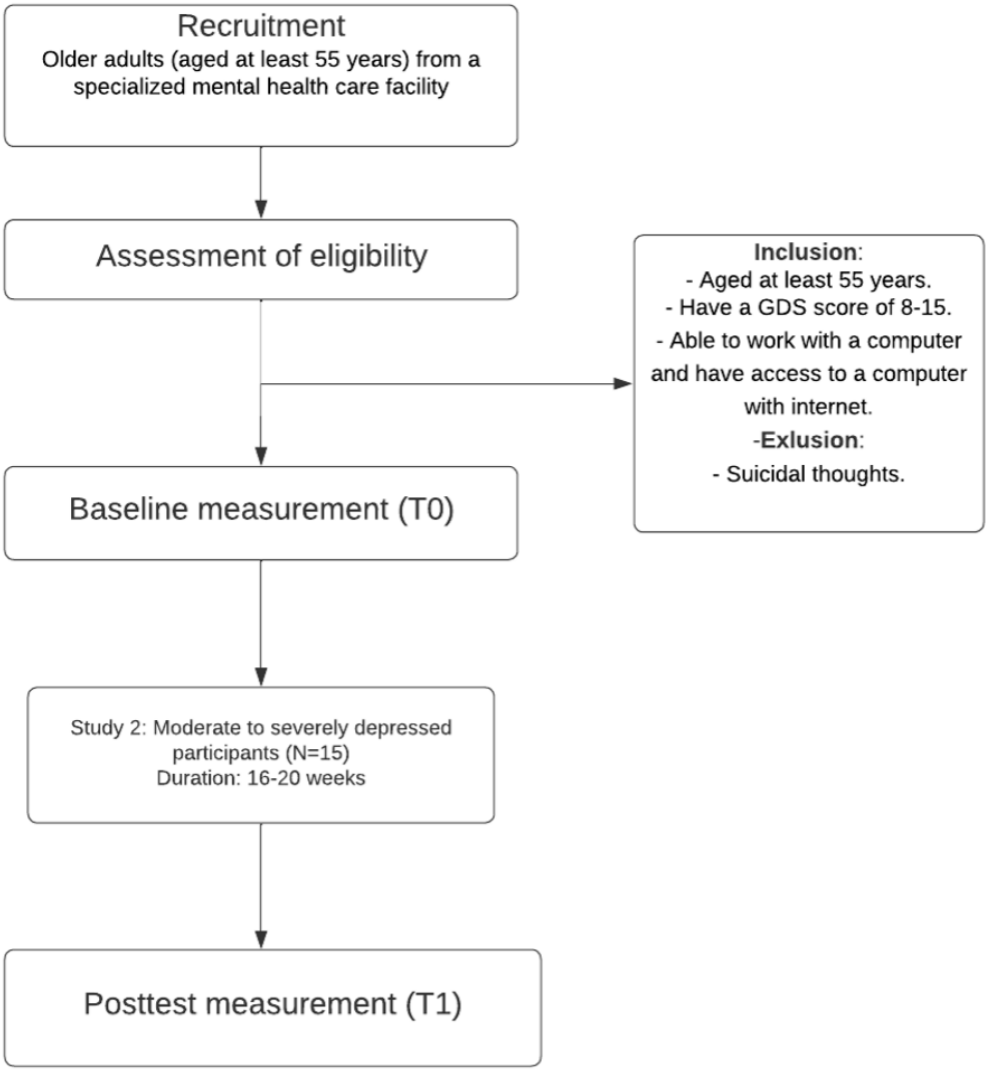


Figure 2. Flowchart of the study design for the group of older adult with moderate to severe depressive symptoms. GDS: Geriatric Depression Scale.



Participants

General Population

Participants with mild to moderate depressive symptoms will be recruited from the general population in the Netherlands. They will be eligible to participate if they (1) are aged at least 55 years, (2) have a Geriatric Depression Scale-15 (GDS-15) score between 5 and 10, (3) are able to work with a computer, and (4) have access to a computer with internet. Candidates will be excluded from the study if they (1) do not have adequate proficiency in the Dutch language or (2) have suicidal thoughts, assessed as having a score of 1 or higher on the 9th item of the Patient Health Questionnaire 9 (PHQ-9) [32]. Having suicidal ideation is considered an exclusion criterion to minimize the risk of an adverse event during the study period.

Specialized Mental Health Care Service

Participants with moderate to severe depressive symptoms will be recruited via a specialized mental health care outpatient clinic (Geestelijk gezondheidszorg [GGZ] inGeest, Amsterdam, the Netherlands). Patients who are in treatment at the clinic will be eligible to participate if they (1) are aged at least 55 years, (2) have a GDS-15 score between 8 and 15, (3) are able to work with a computer, and (4) have access to a computer with internet. Candidates will be excluded from the study if they (1) do not have adequate proficiency in the Dutch language or (2) have suicidal thoughts, assessed as having a score of 1 or higher on the 9th item of the PHQ-9 [32]. Having suicidal ideation is considered an exclusion criterion to minimize the risk of an adverse event during the study period.

Study Intervention: Online Treatment Platform

Moodbuster 2.0 has been developed and tested in a number of European projects. It is an innovative online and mobile solution for the treatment of adult depression and can be applied for research purposes. The platform has a patient and therapist portal (Figure 3) and can be used in unguided, guided, or blended formats and in different settings [33-35]. For the purpose of these studies, Moodbuster 2.0 has been adapted to meet the needs of depressed older adults. To make Moodbuster more aligned with the target group of older adults, the original Moodbuster modules were adjusted by making the content shorter and more relevant to older adults.

Figure 3. Screenshot of the patient portal of Moodbuster 2.0.

Moodbuster 2.0 for older adults consists of 7 web-based CBT modules. These modules are aimed at psychoeducation, behavioral activation, cognitive therapy, problem-solving, exercise, sleep, and relapse prevention. The sleep module is a new addition we have made to the platform; it is aimed at older adults, as insomnia and other sleep-related problems are strongly associated with the persistence of depressive symptoms in older adults [1,36-38]. Texts and videos lead the user through the modules, during which exercises are performed and homework assignments are given.

The online guided treatment for older adults from the general population includes the support of an online coach [39]. Participants receive online CBT over a period of 7 to 8 weeks. The participants are instructed to complete 1 module each week. The psychoeducation module is obligatory. We advise the participants to start with the behavioral activation and cognitive therapy modules. The problem-solving, exercise, sleep, and relapse-prevention modules are optional and are used according to the preferences of the participant. Online support for the guide consists of actively giving the participants feedback for the assignments (at the least after every completed module) using the secure messaging system included in the Moodbuster platform. Furthermore, the guide can answer any questions the participants might have.

The blended CBT treatment that will be offered to participants with moderate to severe depressive symptoms is based on evidence-based CBT protocols implemented in routine practice [40]. The blended format provides individuals face-to-face sessions and online sessions. Participants receive treatment over a period of 16 to 20 weeks, depending on the intensity of the treatment. The therapist and patient decide together the best way to organize face-to-face sessions and online sessions. For example, they can schedule an online session after each face-to-face session or an online session after 2 face-to-face sessions. The practitioner should provide feedback for the online sessions within the face-to-face sessions.

Study Procedure

The participants will be recruited from the 2 target groups and settings simultaneously. Participants with mild to moderate depressive symptoms (as assessed with the GDS-15) [41] will be recruited from the general population via advertisements in digital media and an online recruitment platform, Link2Trials (Link2Trials BV). For this group the following steps will be

taken: potential participants can express their interest by filling out a web form, after which they will receive an information letter and a printed informed consent form via postal mail. When the signed informed consent form is received, it will be scanned and safely stored at the department. Participants who sign the consent form will receive a link to the online screening questionnaires (T–1) through a secure electronic data capture (EDC) system and, once found eligible for participation, they will receive a link to the baseline questionnaires (T0) through Castor EDC (Castor Research Inc). Once the baseline questionnaires are completed, another email will be sent with login credentials for accessing the Moodbuster 2.0 platform. Participants are strongly advised to change their password upon the first login. Participants are advised to work through the intervention in 7 to 8 weeks (ie, 1 module per week). After a maximum of 8 weeks of participation, participants will receive another email with a link to another set of questionnaires to acquire posttreatment assessments (T1). After completing the posttreatment assessments, participants will receive an email to thank them for their participation and ask them if they wish to be informed about the study's results. After filling in the last questionnaire, participants will be reimbursed for their participation with €30 (US $29.41). After the treatment has ended, the participants are invited to fill in an open-field questionnaire to evaluate their experience with Moodbuster.

Patients with moderate to severe depressive symptoms will be recruited from the patient population of the specialized mental health care outpatient clinic. For this group, the following steps will be taken: patients who express interest during intake with their therapist will receive an information letter and an informed consent form at the end of the session. Patients who sign the consent form will be assessed by their therapist to confirm they have moderate to severe depressive symptoms (as assessed with the GDS-15 [41]). Once found eligible for participation, they will receive a link to the baseline questionnaires (T0) through Castor EDC. Once the baseline questionnaires are completed, another email will be sent with the login credentials for accessing the platform. The GGZ inGeest therapists will aid participants with logging in on the platform the first time they use it. Participants are strongly advised to change their password upon the first login. Also in this step, the practitioners will assist the participants with becoming familiar with the platform and answer any questions they might have. It will also be communicated that participants should contact their therapist if they feel their symptoms are suddenly deteriorating. Participants will use the platform in a blended format. The therapists will be trained on how to use the platform before the participants start the treatment. After 16 to 20 weeks of participation (depending on the duration of the treatment), the participants will receive another email with a link to another set of questionnaires to acquire posttreatment assessments (T1). After completing the posttreatment assessments, the participants will receive an email to thank them for their participation and ask them if they wish to be informed of the study's results. After the treatment ends, 5 participants will be invited to participate in individual interviews, which will be conducted face-to-face, through videoconferencing, or by telephone, to evaluate their experience with Moodbuster.

Assessments

Questionnaires will be completed online for both groups. Data will be collected and managed using Castor EDC. Table 1 provides an overview of the measures employed at specific time points.

Table 1. Measures at each assessment interval.

Questionnaires	Aim	Screening (T-1)	Baseline (T0)	Posttreatment (T1)
Screening				
Geriatric Depression Scale-15	Depressive symptoms	✓		
Item 9 of Patient Health Questionnaire-9	Suicidal ideation	✓		
Feasibility				
Client Satisfaction Questionnaire-8	Acceptability/ satisfaction			✓
System Usability Scale[a]	Usability			✓
Twente Engagement with eHealth Platforms Scale	Engagement		✓	✓
Secondary outcome measures				
Patient Health Questionnaire-8	Depressive symptoms		✓	✓
Working Alliance Inventory—Short Form[a]	Working alliance			✓
Working Alliance Inventory Technical—Short Form	Technical alliance			✓
Uptake	Continued use			✓
Digital experiences	General experiences		✓	
Digital Health Literacy Instrument	Digital literacy		✓	

[a]Measure taken from from participants and practitioners.

Screening

Depression Severity

The GDS-15 [41] will be used as a screener to assess depression severity, with a cutoff between 5 and 10 for the group with mild to moderate depressive symptoms and a cutoff of 11 or higher for the group with moderate to severe depressive symptoms. The GDS-15 has 15 items with the option to respond with yes or no. Total scores range from 0 to 15, with higher scores indicating higher severity of depression. The GDS-15 has been found to be a reliable and valid instrument [42].

Suicidal Ideation

Participants will be screened for suicidal ideation using item 9 from the PHQ-9 [32] and excluded. Item 9 of the PHQ-9 asks about thoughts of being better off dead or hurting oneself in some way over the previous 2 weeks. Response options include 0 (“not at all”), 1 (“several days”), 2 (“more than half the days”), or 3 (“nearly every day”). A higher score indicates higher suicidal ideation. Item 9 on the PHQ-9 is a robust predictor of suicide attempts and deaths regardless of age [43].

Primary Outcome Measures

Acceptance and Satisfaction

Acceptance and user satisfaction will be measured with the Client Satisfaction Questionnaire-8 (CSQ-8) for internet-based interventions [44]. The CSQ-8 is composed of eight 4-point Likert-scale items with response options ranging from 1 (“does not apply to me”) to 4 (“applies to me”). Total scores range from 8 to 32, with higher scores indicating higher levels of client satisfaction. Scores between 8 and 13 indicate poor satisfaction, scores between 14 and 19 indicate fair satisfaction, scores between 20 and 25 indicate good satisfaction, and scores between 26 and 32 indicate excellent satisfaction [45]. The CSQ-8 has been found to be a reliable instrument (Cronbach α=.87) [46].

Usability

Usability will be measured with the System Usability Scale (SUS), which was developed by Brooke [47], and with logfile analysis. The SUS has ten 5-point Likert-scale items with response options ranging from 0 (“strongly disagree”) to 4 (“strongly agree”). Total scores are converted (by multiplying the total score by 2.5) to a scale ranging from 0 to 100, where higher scores are indicative of higher platform usability. The SUS is considered a reliable instrument (Cronbach α=.90), with scores higher than 70 indicating “good” usability [48,49].

Engagement

Engagement with the platform will be measured with the Twente Engagement with eHealth Technologies Scale (TWEETS), developed by Kelder and Kip [50]. The TWEETS is a 9-item self-reported scale that can be used to measure expectations of engagement, current engagement, or past engagement with digital interventions. In the current studies, expected and past engagement will be assessed. The questions are answered on a 5-point Likert scale in which higher scores indicate higher levels of treatment engagement. The total score is derived by summing the scores for each of the 9 items on a 0 to 4 scale and can range from 0 to 40. The TWEETS has shown to be a valid tool that possesses good psychometric qualities to assess engagement with eHealth technologies (Cronbach α=.87) [51].

Secondary Outcome Measures

Depression Severity

Depression severity will be assessed with the Patient Health Questionnaire-8 (PHQ-8) [52]. The PHQ-8 is composed of 8 items with response options ranging from 0 (“not at all”) to 3 (“nearly every day”). Total scores range from 0 to 24, with higher scores indicating higher severity of depression. Scores between 5 and 9 indicate mild depression, scores between 10 and 14 indicate moderate depression, scores between 15 and 19 indicate moderately severe depression, and scores between 20 and 24 indicate severe depression. The PHQ-8 has been found to be a reliable and valid instrument (Cronbach α= 0.82) [52,53].

Working Alliance

Working alliance will be measured using the short version of the Working Alliance Inventory–Short Form (WAI-SF) [54] which assesses the therapeutic alliance between the practitioner and participant. The questionnaire covers three dimensions of working alliance: (1) therapeutic goals, (2) tasks, and (3) bond. The WAI-SF for patients has 12 items with responses on a 5-point Likert scale, ranging from 1 (“never or rarely”) to 5 (“very often”). The WAI-SF for therapists has 10 items with responses on a 5-point Likert scale ranging from 1 (“never”) to 5 (“always”). The WAI-SF has been found to be a reliable and valid instrument for both patients and therapists (Cronbach α=.86 and α=.88, respectively) [54,55].

Technical Alliance

Technical alliance will be measured with the Dutch Working Alliance Inventory for Online Interventions-Short Form (WAI-TECH-SF) [56]. This questionnaire assesses the therapeutic alliance between participant and online platform. The questionnaire was designed to cover three dimensions: (1) therapeutic goals, (2) tasks, and (3) bond. The WAI-TECH-SF has 12 items with responses rated on a 7-point Likert scale, ranging from 1 (“never”) to 7 (“always”). The total score ranges from 12 to 84, with higher scores indicating a better technical alliance. The WAI-TECH-SF has been found to be a reliable instrument (Cronbach α=.97) [56].

Uptake

Uptake refers to the degree to which a participant engages with the content of the intervention by using or not using [57] the intervention, in this case the Moodbuster 2.0 iCBT or blended CBT. This will be measured with a logfile analysis. This analysis measures logins, time spent on the platform, and number of modules attempted and completed [58]. Additionally, for the blended CBT intervention this will be measured with feedback from the therapist on the number of face-to-face sessions attended and the number of messages sent to the participants.

Participant Experiences

Participants’ experiences with the platform will also be explored by means of semistructured interviews. This is to gain a better understanding of participants’ satisfaction with the use of

Moodbuster. Qualitative interviews allow the participants more freedom in how to respond [59]. These interviews will focus on issues such as personal experiences with the platform, self-management strategies used by the participants, and contacts between participants and practitioners or guides. For the group with mild to moderate depressive symptoms (ie, the guided group) this will be done by means of an open-ended questionnaire after the last session. For the group with moderate to severe depressive symptoms (ie, the blended therapy group) this will be done by means of a number of individual interviews. The interviews will be conducted by telephone, by video conferencing, or be face-to-face, depending on the preferences of the participant.

Other Measures

Demographic Information

Demographic information will include age, sex (as assigned at birth), living situation, educational level, relationship status, daytime activities, and whether a participant has children.

Digital Literacy

Digital literacy is operationalized as the degree of a person's knowledge, comfort, and perceived skills on a digital instrument such as a computer. Digital literacy will be measured using 2 subscales of the Digital Health Literacy Instrument (DHLI), developed by van der Vaart and Drossaert [60]. The 2 subscales of the DHLI that will be used are "operational skills" and "adding content." The operational skills subscale is composed of 3 items, with response options ranging from 1 ("very easy") to 4 ("very hard"). Total scores range from 3 to 9, with higher scores indicating a lower degree of operational skills with digital technology. The operational skills subscale has been found to be reliable (Cronbach α=.77) [60]. The adding content subscale is composed of 3 items, with response options ranging from 1 ("very easy") to 4 ("very hard"). Total scores range from 3 to 9, with higher scores indicating a lower degree of ability to add content on a digital tool. The adding content subscale has been found to be reliable (Cronbach α=.89) [60].

Sample Size

Calculating the sample size for a pilot study is not standardized. Sample size can range from 15 to 100 participants and depends on the aim of the study [61]. Some studies recommend at least 12 participants [62] and other studies recommend 30 or more participants [63]. The target group from the general population is characterized by variation in both age and the nature of depressive symptoms. We will therefore recruit 30 participants from the general population. We will recruit patients receiving specialized mental health care from a smaller pool (only patients at GGZ inGeest); this population is also characterized by more severe depressive symptoms, and it will require more time to complete recruitment. Given the time frame for recruitment, we will therefore recruit 15 participants.

Statistical Analysis

When the data collection is completed, the data will be cleaned and assessed for accuracy. The data from participants from the general population will be analyzed separately from the data from the participants that are recruited from the specialized mental health care outpatient clinic.

Feasibility Parameters

Quantitative analysis will be conducted using SPSS (version 25; IBM Corp). The primary outcomes will only be assessed after the completion of the interventions (T1). Descriptive statistics (reported as means and SDs) will be calculated to examine and summarize the acceptance and satisfaction of the participants, system usability, and participant engagement with the platform.

Secondary and Other Study Parameters

Descriptive statistics will be also used to assess the working alliance, technical alliance, and the participants' use of the intervention (ie, uptake). To investigate baseline differences between participants who complete the studies and those who drop out, a 2-tailed, independent-sample *t* test or a Mann-Whitney *U* test will be used. The within-group secondary outcome of depressive severity at posttreatment will be inspected for outliers and a normal distribution. For each group, the change in depression severity pre- and postintervention will be analyzed using a 2-tailed, paired-sample *t* test with a significance level of α<.05. Effect size will be measured using Hedges *g*, and will be interpreted as follows: small (0.2), medium (0.5), and high (0.8) [64].

Qualitative Interviews

The interviews and questionnaires will be analyzed using thematic analysis [65]. Thematic analysis is an accessible and flexible method of qualitative data analysis. It identifies and categorizes themes captured in a study. These themes are then coded and organized into meaningful themes. Lastly, interpretative analyses are conducted.

Data Management

All raw data will be collected and managed using Castor EDC. Paper-based documents (such as signed informed consent forms) will be stored in a keycard-secured archive at the Department of Clinical, Neuro- and Developmental Psychology, Vrije Universiteit Amsterdam. All participants will receive a random study participant code. In the studies, participants will be referred to exclusively by that participant code, and the document linking the numbers will be destroyed once the studies are completed and the results have been disseminated. FAIR (Findability, Accessibility, Interoperability and Reusability) principles of data management will be applied. After data collection is completed, data will be kept in a repository (DarkStor) that serves as an offline archive for storing sensitive information and data.

Ethics Approval

Ethics approval was granted by the University Medical Centre, Amsterdam (2021.0435).

Results

Study enrollment started in September 2022. The studies were funded in October 2019 by ZorgOnderzoek Nederland–Medische Wetenschappen (ZonMw). Few studies

have studied the acceptability, satisfaction, usability, and engagement of iCBT in a guided and blended format for older adults. In our pilot studies, we expect that iCBT in a guided and blended format will prove acceptable and usable by older adults with depressive symptoms. Furthermore, we expect that symptoms of depression will decrease after following the online (guided or blended) treatment. According to the CONSORT (Consolidated Standards of Reporting Trials) guidelines [66] for reporting of feasibility studies, each objective result will be outlined, including expressions of uncertainty and estimations. Furthermore, the results of any other analysis we perform that could be of use for a future definitive trial will be reported. The manuscript will be submitted to the appropriate journals for dissemination after the final data are analyzed.

Discussion

Principal Findings

The results of these pilot studies will show whether Moodbuster, an online depression treatment platform, is feasible for use by older adults in 2 study settings. We will measure (1) acceptance and satisfaction with the platform, (2) usability of the platform, and (3) engagement with the platform. The treatment will be evaluated in 2 target groups with 2 formats: (1) participants with mild to moderate depressive symptoms in the general population, who will use a guided format, and (2) participants with moderate to severe depressive symptoms at a specialized mental health care outpatient clinic, who will use a blended format. In these pilot studies, a possible main finding could be that older adults will find that online treatment and the use of technology are acceptable. Furthermore, we expect that the platform will be usable by the participants, as well as by the therapists and guides. Lastly, we expect that the participants will be engaged with the platform. iCBT interventions have been widely studied and have been proven effective for a variety of common mental health disorders, including depression [27,28]. Little is yet known as to whether older adults are more or less likely to benefit from internet-based interventions compared to their younger counterparts, as there are very few interventions and RCTs specifically aimed at studying iCBT interventions for older adults. This underlines the need for more research to be able to assess the feasibility and effectiveness of these interventions for this specific group.

Strengths and Limitations

This pilot study is a first step in the development and evaluation of a digital intervention for older adults. This approach avoids wasting resources and placing unnecessary burdens on participants, because feasibility issues will be identified and addressed prior to the main RCT. Furthermore, this study will be the first empirical study of older adults in 2 settings and in 2 different groups. We have assessed the power of our sample size according to the recommendations and guidelines for conducting pilot studies found in the existing literature. However, it might prove to be the case that our sample size is too limited, which might influence the results we obtain.

Future Directions

Given the limited number of studies on this topic, more research is needed to demonstrate the possibilities of online mental health care for older adults with depression in unguided, guided, and blended settings. The results of this study may provide valuable information on next steps, such as an RCT for testing the clinical effectiveness and cost-effectiveness of iCBT for depressed older adults, and may potentially lead the way to its future implementation in routine care.

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Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions

KA is the principal investigator and pilot coordinator. KA adjusted the intervention. KA, MHJS, AK, and HR designed the study.

Conflicts of Interest

None declared.

References

1. Cuijpers RC, Reynolds CF. Increasing the impact of prevention of depression-new opportunities. JAMA Psychiatry 2022 Jan 01;79(1):11-12. [doi: 10.1001/jamapsychiatry.2021.3153] [Medline: 34817565]
2. Guajardo VD, Souza BP, Henriques SG, Lucia MC, Menezes PR, Martins MA, et al. Loss of interest, depressed mood and impact on the quality of life: cross-sectional survey. BMC Public Health 2011 Oct 25;11:826 [FREE Full text] [doi: 10.1186/1471-2458-11-826] [Medline: 22026632]

3. Volkert J, Schulz H, Härter M, Wlodarczyk O, Andreas S. The prevalence of mental disorders in older people in Western countries - a meta-analysis. Ageing Res Rev 2013 Jan;12(1):339-353. [doi: 10.1016/j.arr.2012.09.004] [Medline: 23000171]
4. Snowden M, Steinman L, Frederick J. Treating depression in older adults: challenges to implementing the recommendations of an expert panel. Prev Chronic Dis 2008 Jan;5(1):A26 [FREE Full text] [Medline: 18082015]
5. Clignet F, van Meijel B, van Straten A, Cuijpers P. A qualitative evaluation of an inpatient nursing intervention for depressed elderly: the systematic activation method. Perspect Psychiatr Care 2017 Oct;53(4):280-288. [doi: 10.1111/ppc.12177] [Medline: 27629821]
6. Aldrich N. CDC promotes public health approach to address depression among older adults. Centers for Disease Control and Prevention. URL: https://www.cdc.gov/aging/pdf/cib_mental_health.pdf [accessed 2022-06-18]
7. Wright PP, Thorpe CW. Triple threat among the elderly: depression, suicide risk, and handguns. J Emerg Nurs 2016 Jan;42(1):14-18. [doi: 10.1016/j.jen.2015.01.010] [Medline: 25937053]
8. Widera EW, Block SD. Managing grief and depression at the end of life. Am Fam Physician 2012 Aug 01;86(3):259-264 [FREE Full text] [Medline: 22962989]
9. Lin EHB, Katon W, Von Korff M, Tang L, Williams JW, Kroenke K, IMPACT Investigators. Effect of improving depression care on pain and functional outcomes among older adults with arthritis: a randomized controlled trial. JAMA 2003 Nov 12;290(18):2428-2429. [doi: 10.1001/jama.290.18.2428] [Medline: 14612479]
10. Frederick JT, Steinman LE, Prohaska T, Satariano WA, Bruce M, Bryant L, Late Life Depression Special Interest Project Panelists. Community-based treatment of late life depression an expert panel-informed literature review. Am J Prev Med 2007 Sep;33(3):222-249. [doi: 10.1016/j.amepre.2007.04.035] [Medline: 17826584]
11. Espinoza R, Kaufman AH. Diagnosis and treatment of late life depression. Psychiatr Times 2014;31(10):18 [FREE Full text]
12. Haigh EAP, Bogucki OE, Sigmon ST, Blazer DG. Depression among older adults: a 20-year update on five common myths and misconceptions. Am J Geriatr Psychiatry 2018 Jan;26(1):107-122. [doi: 10.1016/j.jagp.2017.06.011] [Medline: 28735658]
13. Kok RM, Reynolds CF. Management of depression in older adults: a review. JAMA 2017 May 23;317(20):2114-2122. [doi: 10.1001/jama.2017.5706] [Medline: 28535241]
14. Cuijpers P, Berking M, Andersson G, Quigley L, Kleiboer A, Dobson KS. A meta-analysis of cognitive-behavioural therapy for adult depression, alone and in comparison with other treatments. Can J Psychiatry 2013 Jul;58(7):376-385. [doi: 10.1177/070674371305800702] [Medline: 23870719]
15. Dafsari FS, Bewernick B, Biewer M, Christ H, Domschke K, Froelich L, et al. Cognitive behavioural therapy for the treatment of late life depression: study protocol of a multicentre, randomized, observer-blinded, controlled trial (CBTlate). BMC Psychiatry 2019 Dec 27;19(1):423 [FREE Full text] [doi: 10.1186/s12888-019-2412-0] [Medline: 31881995]
16. Cuijpers P, van Straten A, Smit F. Psychological treatment of late-life depression: a meta-analysis of randomized controlled trials. Int J Geriatr Psychiatry 2006 Dec;21(12):1139-1149. [doi: 10.1002/gps.1620] [Medline: 16955421]
17. Byers AL, Arean PA, Yaffe K. Low use of mental health services among older Americans with mood and anxiety disorders. Psychiatr Serv 2012 Jan;63(1):66-72 [FREE Full text] [doi: 10.1176/appi.ps.201100121] [Medline: 22227762]
18. Dworschak C, Heim E, Maercker A. Efficacy of internet-based interventions for common mental disorder symptoms and psychosocial problems in older adults: A systematic review and meta-analysis. Internet Interv 2022 Mar;27:100498 [FREE Full text] [doi: 10.1016/j.invent.2022.100498] [Medline: 35141136]
19. Karyotaki E, Efthimiou O, Miguel C, Bermpohl FMG, Furukawa TA, Cuijpers P, Individual Patient Data Meta-Analyses for Depression (IPDMA-DE) Collaboration, et al. Internet-based cognitive behavioral therapy for depression: a systematic review and individual patient data network meta-analysis. JAMA Psychiatry 2021 Apr 01;78(4):361-371 [FREE Full text] [doi: 10.1001/jamapsychiatry.2020.4364] [Medline: 33471111]
20. Webb CA, Rosso IM, Rauch SL. Internet-based cognitive-behavioral therapy for depression: current progress and future directions. Harv Rev Psychiatry 2017;25(3):114-122 [FREE Full text] [doi: 10.1097/HRP.0000000000000139] [Medline: 28475503]
21. Spek V, Nyklícek I, Smits N, Cuijpers P, Riper H, Keyzer J, et al. Internet-based cognitive behavioural therapy for subthreshold depression in people over 50 years old: a randomized controlled clinical trial. Psychol Med 2007 Dec;37(12):1797-1806. [doi: 10.1017/S0033291707000542] [Medline: 17466110]
22. Riper H, Andersson G, Christensen H, Cuijpers P, Lange A, Eysenbach G. Theme issue on e-mental health: a growing field in internet research. J Med Internet Res 2010 Dec 19;12(5):e74 [FREE Full text] [doi: 10.2196/jmir.1713] [Medline: 21169177]
23. Cuijpers P, Kleiboer A, Karyotaki E, Riper H. Internet and mobile interventions for depression: opportunities and challenges. Depress Anxiety 2017 Jul;34(7):596-602. [doi: 10.1002/da.22641] [Medline: 28471479]
24. Rasing SPA, Stikkelbroek YAJ, Bodden DHM. Is digital treatment the holy grail? literature review on computerized and blended treatment for depressive disorders in youth. Int J Environ Res Public Health 2019 Dec 24;17(1):153 [FREE Full text] [doi: 10.3390/ijerph17010153] [Medline: 31878249]
25. Romijn G, Batelaan N, Koning J, van Balkom A, de Leeuw A, Benning F, et al. Acceptability, effectiveness and cost-effectiveness of blended cognitive-behavioural therapy (bCBT) versus face-to-face CBT (ftfCBT) for anxiety disorders

in specialised mental health care: A 15-week randomised controlled trial with 1-year follow-up. PLoS One 2021;16(11):e0259493 [FREE Full text] [doi: 10.1371/journal.pone.0259493] [Medline: 34767575]
26. Riper H, Cuijpers P. Telepsychology and eHealth. In: Norcross JC, Van den Bos GR, Freedheim DK, Jrishnamurthy R, editors. APA Handbook of Clinical Psychology: Applications and Methods. Washington, DC: American Psychological Association; 2016:451-463.
27. Karyotaki E, Ebert DD, Donkin L, Riper H, Twisk J, Burger S, et al. Do guided internet-based interventions result in clinically relevant changes for patients with depression? An individual participant data meta-analysis. Clin Psychol Rev 2018 Jul;63:80-92. [doi: 10.1016/j.cpr.2018.06.007] [Medline: 29940401]
28. Carlbring P, Andersson G, Cuijpers P, Riper H, Hedman-Lagerlöf E. Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: an updated systematic review and meta-analysis. Cogn Behav Ther 2018 Jan;47(1):1-18. [doi: 10.1080/16506073.2017.1401115] [Medline: 29215315]
29. Titov N, Dear BF, Ali S, Zou JB, Lorian CN, Johnston L, et al. Clinical and cost-effectiveness of therapist-guided internet-delivered cognitive behavior therapy for older adults with symptoms of depression: a randomized controlled trial. Behav Ther 2015 Mar;46(2):193-205. [doi: 10.1016/j.beth.2014.09.008] [Medline: 25645168]
30. McMurchie W, Macleod F, Power K, Laidlaw K, Prentice N. Computerised cognitive behavioural therapy for depression and anxiety with older people: a pilot study to examine patient acceptability and treatment outcome. Int J Geriatr Psychiatry 2013 Nov;28(11):1147-1156. [doi: 10.1002/gps.3935] [Medline: 23495124]
31. Andreas S, Schulz H, Volkert J, Dehoust M, Sehner S, Suling A, et al. Prevalence of mental disorders in elderly people: the European MentDis_ICF65+ study. Br J Psychiatry 2017 Feb;210(2):125-131. [doi: 10.1192/bjp.bp.115.180463] [Medline: 27609811]
32. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001 Sep;16(9):606-613 [FREE Full text] [doi: 10.1046/j.1525-1497.2001.016009606.x] [Medline: 11556941]
33. Warmerdam L, Riper H, Klein M, van den Ven P, Rocha A, Ricardo Henriques M, et al. Innovative ICT solutions to improve treatment outcomes for depression: the ICT4Depression project. Stud Health Technol Inform 2012;181:339-343. [Medline: 22954884]
34. Kleiboer A, Smit J, Bosmans J, Ruwaard J, Andersson G, Topooco N, et al. European comparative effectiveness research on blended depression treatment versus treatment-as-usual (E-COMPARED): study protocol for a randomized controlled, non-inferiority trial in eight European countries. Trials 2016 Aug 03;17(1):387 [FREE Full text] [doi: 10.1186/s13063-016-1511-1] [Medline: 27488181]
35. Riper H. Digital Framework for E-health Research. Differ Foundation. URL: https://differ.science [accessed 2022-10-09]
36. Peng Y, Hsu Y, Chou M, Chu C, Su C, Liang C, et al. Factors associated with insomnia in older adult outpatients vary by gender: a cross-sectional study. BMC Geriatr 2021 Dec 07;21(1):681 [FREE Full text] [doi: 10.1186/s12877-021-02643-7] [Medline: 34876057]
37. Irwin MR, Carrillo C, Sadeghi N, Bjurstrom MF, Breen EC, Olmstead R. Prevention of incident and recurrent major depression in older adults with insomnia: a randomized clinical trial. JAMA Psychiatry 2022 Jan 01;79(1):33-41 [FREE Full text] [doi: 10.1001/jamapsychiatry.2021.3422] [Medline: 34817561]
38. van Straten A, Lancee J. Digital cognitive behavioural therapy for insomnia: the answer to a major public health issue? Lancet Digit Health 2020 Aug;2(8):e381-e382 [FREE Full text] [doi: 10.1016/S2589-7500(20)30167-9] [Medline: 33328041]
39. Kleiboer A, Donker T, Seekles W, van Straten A, Riper H, Cuijpers P. A randomized controlled trial on the role of support in internet-based problem solving therapy for depression and anxiety. Behav Res Ther 2015 Sep;72:63-71. [doi: 10.1016/j.brat.2015.06.013] [Medline: 26188373]
40. Kooistra LC, Wiersma JE, Ruwaard J, Neijenhuijs K, Lokkerbol J, van Oppen P, et al. Cost and effectiveness of blended versus standard cognitive behavioral therapy for outpatients with depression in routine specialized mental health care: pilot randomized controlled trial. J Med Internet Res 2019 Oct 29;21(10):e14261 [FREE Full text] [doi: 10.2196/14261] [Medline: 31663855]
41. van Marwijk HW, Wallace P, de Bock GH, Hermans J, Kaptein AA, Mulder JD. Evaluation of the feasibility, reliability and diagnostic value of shortened versions of the geriatric depression scale. Br J Gen Pract 1995 Apr;45(393):195-199 [FREE Full text] [Medline: 7612321]
42. Pocklington C, Gilbody S, Manea L, McMillan D. The diagnostic accuracy of brief versions of the Geriatric Depression Scale: a systematic review and meta-analysis. Int J Geriatr Psychiatry 2016 Aug;31(8):837-857. [doi: 10.1002/gps.4407] [Medline: 26890937]
43. Rossom RC, Coleman KJ, Ahmedani BK, Beck A, Johnson E, Oliver M, et al. Suicidal ideation reported on the PHQ9 and risk of suicidal behavior across age groups. J Affect Disord 2017 Jun;215:77-84 [FREE Full text] [doi: 10.1016/j.jad.2017.03.037] [Medline: 28319695]
44. Larsen DL, Attkisson CC, Hargreaves WA, Nguyen TD. Assessment of client/patient satisfaction: development of a general scale. Eval Program Plann 1979;2(3):197-207. [doi: 10.1016/0149-7189(79)90094-6] [Medline: 10245370]
45. Smith D, Roche E, O'Loughlin K, Brennan D, Madigan K, Lyne J, et al. Satisfaction with services following voluntary and involuntary admission. J Ment Health 2014 Feb 31;23(1):38-45. [doi: 10.3109/09638237.2013.841864] [Medline: 24484191]

46. Boß L, Lehr D, Reis D, Vis C, Riper H, Berking M, et al. Reliability and validity of assessing user satisfaction with web-based health interventions. J Med Internet Res 2016 Aug 31;18(8):e234 [FREE Full text] [doi: 10.2196/jmir.5952] [Medline: 27582341]
47. Brooke J. SUS: A 'Quick and Dirty' Usability Scale. In: Usability Evaluation In Industry. Boca Raton, FL: CRC Press; 1996:4.
48. Bangor A, Kortum PT, Miller JT. An empirical evaluation of the System Usability Scale. Int J Hum Comput Interact 2008 Jul 30;24(6):574-594. [doi: 10.1080/10447310802205776]
49. Lewis JR, Brown J, Mayes DK. Psychometric evaluation of the EMO and the SUS in the context of a large-sample unmoderated usability study. Int J Hum Comput Interact 2015 Jun 25;31(8):545-553. [doi: 10.1080/10447318.2015.1064665]
50. Kelders S, Kip H. Development and initial validation of a scale to measure engagement with eHealth technologies. In: CHI EA '19: Extended Abstracts of the 2019 CHI Conference on Human Factors in Computing Systems. 2019 Presented at: Conference on Human Factors in Computing Systems; May 4-9, 2019; Glasgow, Scotland p. 1-6. [doi: 10.1145/3290607.3312917]
51. Kelders SM, Kip H, Greeff J. Psychometric evaluation of the TWente Engagement with Ehealth Technologies Scale (TWEETS): evaluation study. J Med Internet Res 2020 Oct 09;22(10):e17757 [FREE Full text] [doi: 10.2196/17757] [Medline: 33021487]
52. Kroenke K, Strine TW, Spitzer RL, Williams JBW, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. J Affect Disord 2009 Apr;114(1-3):163-173. [doi: 10.1016/j.jad.2008.06.026] [Medline: 18752852]
53. Pressler SJ, Subramanian U, Perkins SM, Gradus-Pizlo I, Kareken D, Kim J, et al. Measuring depressive symptoms in heart failure: validity and reliability of the patient health questionnaire-8. Am J Crit Care 2011 Mar;20(2):146-152. [doi: 10.4037/ajcc2010931] [Medline: 20378777]
54. Hatcher RL, Gillaspy JA. Development and validation of a revised short version of the Working Alliance Inventory. Psychother Res 2006 Jan;16(1):12-25. [doi: 10.1080/10503300500352500]
55. Kooistra L, Ruwaard J, Wiersma J, van Oppen P, Riper H. Working alliance in blended versus face-to-face cognitive behavioral treatment for patients with depression in specialized mental health care. J Clin Med 2020 Jan 27;9(2):347 [FREE Full text] [doi: 10.3390/jcm9020347] [Medline: 32012722]
56. Herrero R, Vara MD, Miragall M, Botella C, García-Palacios A, Riper H, et al. Working Alliance Inventory for Online Interventions-Short Form (WAI-TECH-SF): the role of the therapeutic alliance between patient and online program in therapeutic outcomes. Int J Environ Res Public Health 2020 Aug 25;17(17):6169 [FREE Full text] [doi: 10.3390/ijerph17176169] [Medline: 32854381]
57. Lillevoll KR, Vangberg HCB, Griffiths KM, Waterloo K, Eisemann MR. Uptake and adherence of a self-directed internet-based mental health intervention with tailored e-mail reminders in senior high schools in Norway. BMC Psychiatry 2014 Jan 21;14:14 [FREE Full text] [doi: 10.1186/1471-244X-14-14] [Medline: 24443820]
58. Christensen H, Griffiths KM, Farrer L. Adherence in internet interventions for anxiety and depression. J Med Internet Res 2009 Apr 24;11(2):e13 [FREE Full text] [doi: 10.2196/jmir.1194] [Medline: 19403466]
59. Edwards R, Holland J. What is Qualitative Interviewing?. London, UK: Bloomsbury Academic; 2013.
60. van der Vaart R, Drossaert C. Development of the Digital Health Literacy Instrument: measuring a broad spectrum of health 1.0 and health 2.0 skills. J Med Internet Res 2017 Jan 24;19(1):e27 [FREE Full text] [doi: 10.2196/jmir.6709] [Medline: 28119275]
61. Hertzog MA. Considerations in determining sample size for pilot studies. Res Nurs Health 2008 Apr;31(2):180-191. [doi: 10.1002/nur.20247] [Medline: 18183564]
62. Julious SA. Sample size of 12 per group rule of thumb for a pilot study. Pharmaceut Statist 2005 Oct;4(4):287-291. [doi: 10.1002/pst.185]
63. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. J Eval Clin Pract 2004 May;10(2):307-312. [doi: 10.1111/j..2002.384.doc.x] [Medline: 15189396]
64. Cohen J. Statistical Power Analysis for the Behavioral Sciences, 2nd ed. New York, NY: Lawrence Erlbaum Associates; 1988.
65. Clarke V, Braun V. Thematic analysis. J Posit Psychol 2016 Dec 09;12(3):297-298. [doi: 10.1080/17439760.2016.1262613]
66. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Med 2010 Mar 24;8:18 [FREE Full text] [doi: 10.1186/1741-7015-8-18] [Medline: 20334633]

Abbreviations

CBT: cognitive behavioral therapy
CSQ-8: Client Satisfaction Questionnaire-8
DHLI: Digital Health Literacy Inventory
EDC: electronic data capture
GDS: Geriatric Depression Scale
GGZ inGeest: Geestelijk Gezondheidszorg inGeest

iCBT: internet cognitive behavioral therapy
PHQ-8: Patient Health Questionnaire-8
PHQ-9: Patient Health Questionnaire-9
RCT: randomized controlled trial
SUS: System Usability Scale
TWEETS: Twente Engagement with eHealth Technologies Scale
WAI-SF: Working Alliance Inventory–Short Form
WAI-TECH-SF: Working Alliance Inventory for Online Interventions–Short Form
ZonMw: ZorgOnderzoek Nederland–Medische Wetenschappen

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Protocol

A Medical-Grade Polycaprolactone and Tricalcium Phosphate Scaffold System With Corticoperiosteal Tissue Transfer for the Reconstruction of Acquired Calvarial Defects in Adults: Protocol for a Single-Arm Feasibility Trial

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Abstract

Background: Large skull defects present a reconstructive challenge. Conventional cranioplasty options include autologous bone grafts, vascularized bone, metals, synthetic ceramics, and polymers. Autologous options are affected by resorption and residual contour deformities. Synthetic materials may be customized via digital planning and 3D printing, but they all carry a risk of implant exposure, failure, and infection, which increases when the defect is large. These complications can be a threat to life. Without reconstruction, patients with cranial defects may experience headaches and stigmatization. The protection of the brain necessitates lifelong helmet use, which is also stigmatizing.

Objective: Our clinical trial will formally study a hybridized technique's capacity to reconstruct large calvarial defects.

Methods: A hybridized technique that draws on the benefits of autologous and synthetic materials has been developed by the research team. This involves wrapping a biodegradable, ultrastructured, 3D-printed scaffold made of medical-grade polycaprolactone and tricalcium phosphate in a vascularized, autotransplanted periosteum to exploit the capacity of vascularized periostea to regenerate bone. In vitro, the scaffold system supports cell attachment, migration, and proliferation with slow but sustained degradation to permit host tissue regeneration and the replacement of the scaffold. The in vivo compatibility of this scaffold system is robust—the base material has been used clinically as a resorbable suture material for decades. The importance of scaffold vascularization, which is inextricably linked to bone regeneration, is underappreciated. A variety of methods have been described to address this, including scaffold prelamination and axial vascularization via arteriovenous loops and autotransplanted flaps. However, none of these directly promote bone regeneration.

Results: We expect to have results before the end of 2023. As of December 2020, we have enrolled 3 participants for the study.

Conclusions: The regenerative matching axial vascularization technique may be an alternative method of reconstruction for large calvarial defects. It involves performing a vascularized free tissue transfer and using a bioresorbable, 3D-printed scaffold to promote and support bone regeneration (termed the *regenerative matching axial vascularization* technique). This technique

may be used to reconstruct skull bone defects that were previously thought to be unreconstructable, reduce the risk of implant-related complications, and achieve consistent outcomes in cranioplasty. This must now be tested in prospective clinical trials.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12620001171909; https://tinyurl.com/4rakccb3

International Registered Report Identifier (IRRID): DERR1-10.2196/36111

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KEYWORDS

3D printing; reconstruction; cranioplasty; free flap; craniofacial; surgery; bone; skull

Introduction

Background

Cranioplasty, as a procedure for reconstructing cranial defects, has been around for thousands of years. Despite significant advances in technology and extensive research into bone biology, the reconstruction of the calvarium still poses a significant challenge for surgeons [1,2]. Since the early 1900s, autologous bone grafts have been considered the gold standard, acting as readily available donor materials with marked strength, elasticity, assured biocompatibility, and the ability to provide adequate cosmesis [3]. Despite this, autologous bone grafts are not without complications, including bone flap resorption, and graft failure rates of up to 35% have been reported [4-7]. Other autologous bone grafts (eg, those in the form of banked allografts or those made of bone harvested from other anatomical locations) have also been shown to result in increased donor site morbidity and higher rates of graft failure.

These issues with autologous bone grafts have prompted research into suitable synthetic alternatives; metals, synthetic ceramics, and polymers are all advantageous in different ways but have significant fallbacks that relate to infection, malleability, and in situ inflammatory or exothermic reactions [8,9]. A bioresorbable composite scaffold comprised of polycaprolactone and tricalcium phosphate (PCL-TCP) has already been shown to be effective in various bone engineering platforms [7,10-13]. Further, 3D computed tomography (CT) modeling has revolutionized the customization of these osteoconductive scaffolds, enabling their seamless integration into skull defects, with aesthetic cranial contouring. Osteoinduction is a process whereby osteoprogenitor cells differentiate into osteoblasts and therefore is crucial in osteogenesis. Within PCL-TCP scaffolds, osteoinduction can be enhanced through the addition of biological additives (eg, bone morphogenetic protein-7) or cellular approaches (eg, the use of mesenchymal osteoprogenitor stem cells) that have been shown to augment bone growth [14-18].

The success of these cellular impregnation techniques for promoting acceptable osteogenesis has been shown to be directly linked with the vascularity of the constructs used [13,18]. The utilization of flap-based tissue with dependable axial vascularization (eg, based on a known arteriovenous system) not only enhances angiogenesis but also provides a specific tissue type that matches the intended regeneration along with corresponding progenitor cells [19]. Axial vascularization via a corticoperiosteal flap to stimulate bone regeneration is an example of regenerative matching axial vascularization (RMAV) [20]. The experimental application of this theory with corticoperiosteal flaps has been implemented in cases of critical long bone defects, with the results indicating enhanced bone regeneration and scaffold integration [21-23].

Throughout the literature, there is a clear consensus that an ideal cranioplasty graft should have the following: (1) long-term mechanical protection for the brain and meninges until the host bone regenerates, (2) acceptable cosmetic contouring, and (3) graft materials that promote bone growth through osteoconductive and osteoinductive mechanisms that are governed by degradation kinetics and biological interactions. Moreover, if the prosthesis remains, it should not cause undue complications or patient inconveniences.

The composite PCL-TCP scaffold acts as a synthetic analogue of two major bone constituents—hydroxyapatite and collagen. As cranioplasty materials, PCL-TCP fulfill the above criteria by retaining strength and promoting osteoconduction over extended remodeling periods via consistent degradation mechanics and with minimal adverse effects. As a consequence of advancements in tissue engineering, the demand for customizable implants is understandably intensifying. This case highlights the potential of harnessing emerging biomedical technologies and 3D tailoring to meet individual and specific clinical needs.

In a case report published by Yogishwarappa et al [24] in 2016, the authors utilized a 3D-printed PCL-TCP scaffold with iliac crest stem cells to reconstruct a craniotomy defect. The authors described good bone growth at 18 months but did not quantify this result via CT imaging, which has traditionally been the case in preceding animal studies. This case went further by incorporating axial vascularization techniques with strategies for the targeted regenerative matching of tissue types and progenitor cells.

Osteoinduction and, as a consequence, osteogenesis are intricately linked to angiogenesis in normal fracture healing [25]. Corticoperiosteal tissue from the medial femoral condyle can provide a vascularized source of tissue rich in osteogenic progenitor cells. Studies have shown that specific osteoprogenitor cells, such as those in periosteal tissue, are stimulated by growth factors to differentiate and form bone [26]. As a result, scaffolds are subject to the uniform delivery of host-derived growth factors, mesenchymal stem cells, and an optimal extra-cellular environment, of which all are essential for bone regeneration.

Investigations into periosteal flaps as sources of axial vascularization are well documented in animal models. Nau et

al [22] compared periosteal flaps with a tricalcium phosphate scaffold that did or did not have bone marrow–derived mononuclear cells to a periosteal flap alone. These were used in rat femurs with critical size defects. The periosteal flap with tricalcium phosphate and marrow cells had a significant increase in new bone formation, vascularization and strength radiographic, histological, and biomechanical outcomes at 4 weeks. More recently, Sparks et al [20] combined a pedicled corticoperiosteal flap, which was based on the anterior tibial vessels, with a PCL-TCP scaffold to bridge 3- and 6-cm tibial segmentectomies. The radiological and histological outcomes demonstrated new bone regeneration and excellent scaffold integration, with the complete bridging of both defects at 12 months.

The research by our group at the Centre for Regenerative Medicine (Queensland University of Technology, Brisbane, Australia) has focused on the reconstruction of critical-sized bone defects for more than 1 decade [13,17,27]. In particular, our work has focused on the bench-to-bedside translation of tissue-engineered bone replacements that are biodegradable, ultrastructured composite scaffolds made of medical-grade PCL-TCP (mPCL-TCP) [28]. In vitro, this scaffold system supports cell attachment, migration, and proliferation with slow but sustained degradation to permit host tissue regeneration and the replacement of the scaffold [29]. The in vivo compatibility of this scaffold system is robust [30,31], and this system may be used alongside the use of growth factors, such as recombinant human bone morphogenic protein-7 (rhBMP-7), that are known to promote the regeneration of bone. Importantly, the mPCL-TCP scaffold has been extensively evaluated in preclinical studies with a validated model of a large animal with a critical-sized bone defect that was developed by our group [13]. Our research using this model has shown that this scaffold system, when used alongside rhBMP-7 for a 3-cm, critical-sized long bone defect, is highly regenerative with respect to bones [13].

Although osteoinductive scaffolds have been trialed clinically by a number of authors [32-35], limitations in preclinical work that prevent the mainstream application of this approach remain. Scaffold vascularization, which is inextricably linked to bone regeneration, remains key, and its importance is generally underappreciated [18]. A variety of methods have been investigated to address this issue, including the prevascularization of scaffold prior to transplantation, vessel-based approaches for axial vascularization (arteriovenous loops and associated variations), and flap-based approaches for axial vascularization (muscle flaps, periosteal flaps, etc). Clearly, the ideal method for vascularizing a scaffold would also promote bone regeneration.

The regenerative capacity of vascularized corticoperiosteal tissue is well recognized [36,37]. It has a robust blood supply, and potential donor sites for distant transfer are plentiful [19]. For uniform scaffold vascularization, an intrinsic approach is considered key [38]. However, to date, a combined intrinsic and flap-based approach to scaffold vascularization that also exploits the innate autologous regenerative capacity of corticoperiosteal tissue for bone regeneration has not been explored. We define the coalescence of these concepts as RMAV, whereby a corticoperiosteal flap is used to vascularize scaffold intrinsically and also produce bone.

Between 2016 and 2018, we undertook a preclinical study that evaluated the concept of RMAV by using a corticoperiosteal flap from a sheep's hind limb and a 3D-printed mPCL-TCP scaffold to reconstruct 6- and 3-cm intercalary defects of the tibia [20]. This technique was compared against existing control data sets for this animal model. Control groups were reconstructed with autologous bone grafts alone, were reconstructed with mPCL-TCP scaffolds alone, or were left unreconstructed [20]. The regenerative matching approach resulted in the enhanced volume of regenerate bone, as shown on plain x-ray and micro-CT images [20], and equivalent biomechanical torsional stiffness when compared to the approach using bone grafts alone. In December 2019, we performed a first-in-human case study of applied RMAV, wherein a 3D-printed mPCL-TCP scaffold with rhBMP-7 and vascularized corticoperiosteal flaps was used to successfully perform a reconstruction of a large calvarial defect that had failed to heal after conventional cranioplasty [39]. This work builds on our experiences with bone defect reconstructive research, and it will involve the regenerative matching technique.

Given these successes in preclinical research and our first-in-human case, we feel that the logical next step for the emerging RMAV technique should be a robust feasibility clinical trial examining the behavior of the mPCL-TCP implant and postimplantation bone healing. Once appropriate outcome measures are clearly defined, it may then be appropriate to proceed to a randomized clinical trial in which RMAV is compared to other clinical techniques for a given bone defect.

Objectives

Hypothesis

The use of an mPCL-TCP scaffold, in conjunction with a corticoperiosteal tissue transfer, is a safe and effective approach to reconstructing critical-sized bone defects in the calvarium.

Primary and Secondary Objectives

The primary objectives of our trial are to (1) determine the feasibility and efficacy of using an mPCL-TCP scaffold, in conjunction with a vascularized corticoperiosteal tissue transfer, for the reconstruction of calvarial bone and (2) determine the clinically relevant functional outcomes that follow the reconstruction of an acquired calvarial defect by using an mPCL-TCP scaffold in conjunction with a vascularized corticoperiosteal tissue transfer.

The secondary objective is to collect data to allow for the later evaluation of the cost-effectiveness of this approach and a view of its applications across a broader range of clinical situations.

Methods

Study Design

Our study will be a single-arm feasibility trial that evaluates the outcomes of using an mPCL-TCP scaffold, in conjunction with a vascularized corticoperiosteal tissue, in participants with

acquired defects of the calvarial bones of the skull resulting from trauma, malignancy, or infection. The study will capture data that will be used to inform the design of future clinical trials in this area.

The mPCL-TCP scaffold that will be used in the study will be manufactured by the trial sponsor—Osteopore International Pte Ltd (Singapore). Osteopore products are made of a US Food and Drug Administration–approved polymer (K051093) called *polycaprolactone*, which is bioabsorbable, is malleable, is slow to degrade, and possesses mechanical strength that is similar to that of trabecular bone. The product will be manufactured by using 3D printing technology that is precise and allows for the customization of shape and geometry. The unique, 3D-printed, biomimetic microarchitecture of the 3D scaffolding, which is contained within Osteopore products, allows for the infiltration of cells and blood vessels, of which both play a key role in wound healing and tissue repair.

Study Setting

The study will be an open-label, single-arm feasibility trial that will be jointly coordinated by the investigators at the Princess Alexandra Hospital (PAH) in Woolloongabba (Queensland, Australia), the Herston Biofabrication Institute, the Australian Centre for Complex Integrated Surgical Solutions at the Translational Research Institute (Queensland, Australia), and the Centre for Regenerative Medicine at the Institute of Health and Biomedical Innovation in Kelvin Grove (Queensland, Australia). With the aim of calvarial reconstruction, the study population will include any patient with a calvarial defect that is amenable to reconstructive approaches that involve using the Osteopore implant, following discussions by the multidisciplinary team (MDT) of investigators.

Eligibility Criteria

Inclusion Criteria

Our inclusion criteria are as follows:

- Acquired defect of the calvarium that is suitable for reconstruction by using a PCL-TCP scaffold system and performing a corticoperiosteal tissue transfer
- Patients aged >18 years and <55 years
- Patients aged >55 years may still be eligible for the trial after an assessment by and at the discretion of the investigators, and documentation to this effect will be provided by the clinic for the trial documents pertaining to such patients
- Patients who are willing and able to comply with the study requirements
- Patients who are eligible for undergoing magnetic resonance imaging (MRI; ie, no implanted metal or metal devices and no history of severe claustrophobia)
- Patients or their guardians are capable of providing valid informed consent

Exclusion Criteria

Our exclusion criteria are as follows:

- Active infection at the time of study inclusion (in chronic infection cases, active infections may manifest as the result of a failed trial of being taken off antibiotics)
- Patients or their guardians are unwilling or unable to provide fully informed consent
- Patients with a known history of immunodeficiency, including a history of HIV, concomitant systemic corticosteroid therapy, chemotherapy, synchronous hematological malignancy, or other causes of a secondary or primary immunodeficiency
- Patients with a known severe concurrent or intercurrent illness (eg, a cardiovascular, respiratory, or immunological illness; psychiatric disorders; alcohol or chemical dependence; or possible allergies [including allergy to polycaprolactone]) that would, in the opinion of the primary investigator, compromise their safety or compliance or interfere with the interpretation of study results
- Women who are currently pregnant, are breastfeeding, or are planning to become pregnant within 2 years after the reconstruction surgery
- Women of childbearing potential who are not using an appropriate contraceptive method
- Patients who are ineligible for undergoing MRI
- Patients with a life expectancy of <36 months.
- Patients who are unable or unwilling to comply with the study requirements

Sample Size

This feasibility trial will recruit a total of 10 patients.

Recruitment

As a part of their clinical management, patients with acquired calvarial defects from the neurosurgery clinic or the skull base/head and neck clinic at the PAH will be reviewed as candidates for cranial reconstruction via the Osteopore implant by the MDT. Referrals to this process will be accepted from throughout Queensland via standard pathways, and national out-of-catchment referrals will be considered for special circumstances in which the PAH has unique expertise. The specific conditions assessed may include acute and subacute pathologies (major acute fractures with bone loss, bone malignancy, etc) or chronic pathologies (osteomyelitis, osteoradionecrosis, etc).

The relevant specialties that will be involved in the MDT review and decision-making process include infectious diseases, plastic and reconstructive surgery, neurosurgery, infectious diseases, and engineering. The MDT will determine the best treatment option for each patient. Should cranial reconstruction by using an Osteopore implant be recommended by the MDT, the patient's treating specialist will discuss the case with the coordinating principal investigator, and the extent to which the potential participant satisfies the trial's inclusion and exclusion criteria will be determined collaboratively. Written informed consent will be obtained following the MDT's decision and prior to the conduct of the cranioplasty. Informed consent must be completed prior to any study-related activities.

Patients will be followed up for at least 24 months from the time of initial reconstruction. Given that the PAH collectively

sees around 5 patients per year with significant bone defects, the recruitment phase will take place over 2 to 3 years to recruit a total of 10 patients for the feasibility analysis.

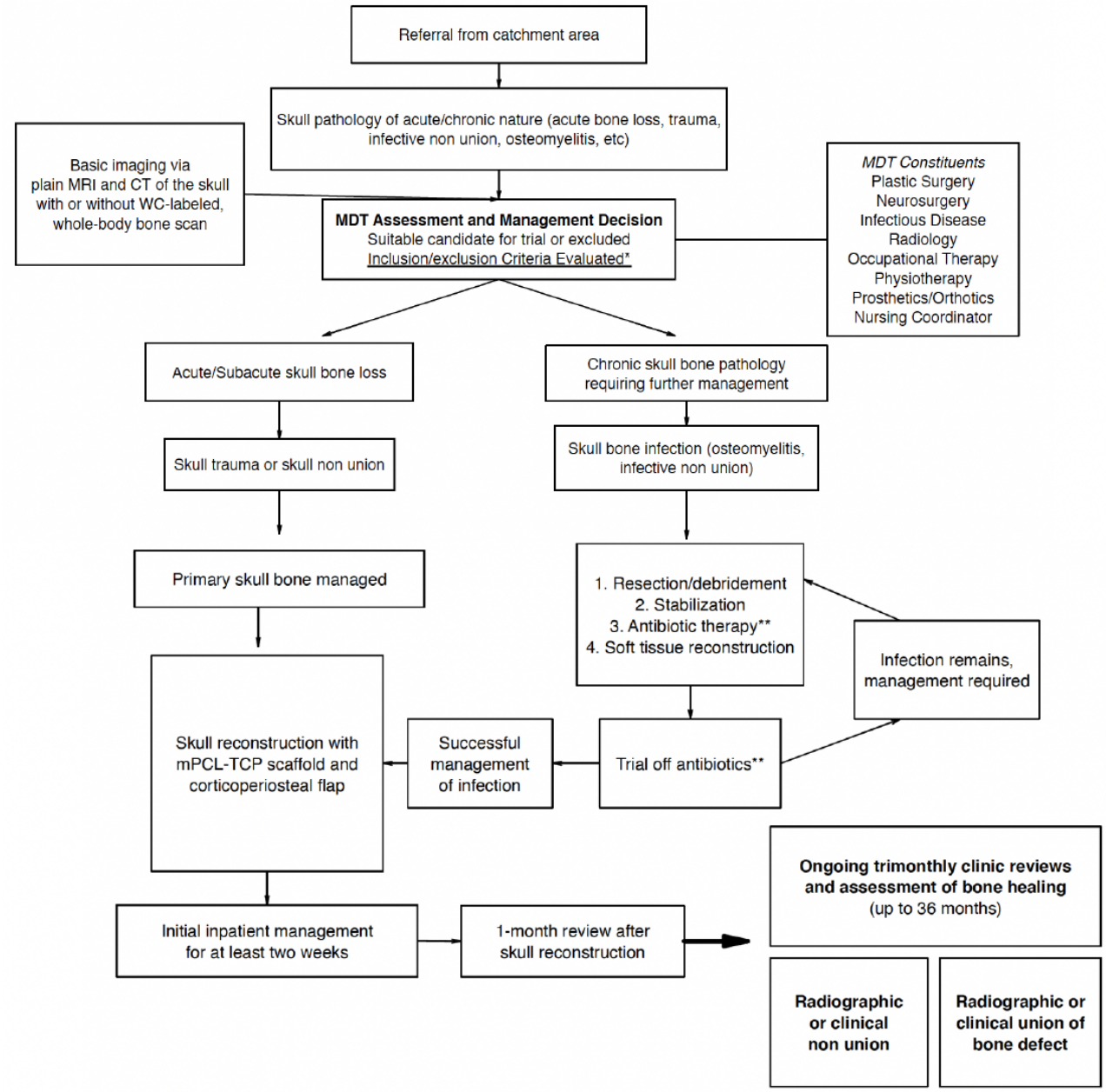
In addition to the prospective recruitment pathway detailed above, patients who have undergone cranioplasty via the Osteopore implant may also be recruited into the study at the discretion of the sponsor and coordinating principal investigator.

Intervention

Prior to deciding on a treatment pathway, medical imaging will be conducted as a part of each patient's standard clinical management, which may include CT and/or MRI scans of the head and neck, as well as white cell–labeled, whole-body bone scans. The imaging results will inform the clinical assessment performed by the neurosurgeon or the skull base/head and neck surgeon involved in the care of the patients and inform the MDT review. Clinical notes, including medical histories, will also be generated as a part of the clinical care process of patients during their clinical management. Imaging data and clinical notes that relate to the defects among patients and are collected prior to informed consent will be made available to the study participants as a part of the informed consent process.

A description of the patient journey is summarized in Figure 1. The clinical care reconstruction will be performed at time 0. A standard clinical protocol for wound care and rehabilitation will follow. Patients may undergo a review for routine clinical assessments every 3 months following the cranioplasty until they are clinically stable, with more or less frequent follow-up visits arranged according to their clinical needs.

Figure 1. Flowchart of patient journey. CT: computed tomography; MDT: multidisciplinary team; mPCL-TCP: medical-grade polycaprolactone and tricalcium phosphate; MRI: magnetic resonance imaging; WC: white cell. *see "Eligibility Criteria" section; **antibiotic therapy, as indicated by infectious disease physician consultation.



The trial-related interventions will focus on capturing defined functional outcomes and, consequently, will require the collection of data at specific time points. CT and/or MRI scans of the head and neck will be used to identify complications and establish clinical and radiological evidence of union at 1, 12, and 24 months after surgery. As performing 2 CT scans in the first year during the postoperative follow-up period is standard clinical practice, the amount of ionizing radiation to which the participants are exposed will not exceed the amount of radiation that patients typically receive during standard clinical care. Additional CT and MRI scans may be performed during the follow-up period in accordance with patients' clinical needs.

The other research-related functional assessments will include the administration of the Quality of Life After Brain Injury (QOLIBRI) and 36-item Short Form Quality of Life (SF-36) questionnaires at prereconstruction and at 1, 12, and 24 months after surgery.

End Points

The key primary end points for evaluation in our single-arm study are the time to the formation of stable, regenerated bone that is sufficient for protecting the brain (ie, radiographic or clinical evidence of bony union) and patient-reported outcomes. These primary end points serve as surrogate markers for satisfactory bone healing but, more importantly, are clinically useful for and relevant to the study goal and overarching purpose of the intervention. Functional outcomes are more difficult to measure reliably and are therefore secondary outcomes, which will be measured with the QOLIBRI and the SF-36 questionnaires [40]. The schedule of assessments is presented in Table 1.

Table 1. Schedule of assessments.

	Multidisciplinary team review	Enrollment	Reconstruction	Follow-up period	
				1-month review	3-, 6-, 9-, 12-, 15-, 18-, 21-, and 24-month review
Time point[a]	$-t_2$	$-t_1$	0	T_1	$T_{2\text{-}9}$
Enrollment					
Informed consent		✓[b]			
Eligibility screen		✓			
Demographics		✓			
Medical history and medical review	✓	✓		✓	✓
Interventions					
Infection management		✓			
Reconstruction			✓		
Assessments					
Computed tomography of head	✓			✓	✓[c]
Magnetic resonance imaging	✓			✓	✓
White cell–labeled, whole-body bone scan	✓			✓	✓
Quality of Life After Brain Injury questionnaire		✓		✓	✓[c]
36-item Short Form Quality of Life questionnaire		✓		✓	✓[c]

[a]"t" represents a time point prior to the intervention, and "T" represents a time point after the intervention.

[b]Denotes a clinical activity from which data may be utilized for the trial analysis.

[c]Trial-related assessment at 12 and 24 months only.

Statistical Methods

The statistical analysis of the data will be undertaken by the Queensland Facility of Advanced Bioinformatics (QFAB). QFAB personnel will use REDCap (Research Electronic Data Capture) software (Vanderbilt University) to design and validate an electronic data capture system for use in the trial. Deidentified data will be entered into the REDCap-based electronic data capture system by a member of the research team after the coordinating principal investigator or delegate has certified each case report form (CRF). The database will contain validation ranges for each variable to minimize the chance of data entry errors. An audit trail will be created to maintain a record of the initial entries and changes made, the reasons for changes, the times and dates of entries, and the usernames of the people who made the changes. Data queries will be raised, and missing data or suspected errors will be resolved prior to locking the database and performing the analysis.

Analysis

All patients who are registered for the trial will be accounted for in the (intention-to-treat) analysis. For retrospectively recruited patients, all data points may not be available for all assessments, or data collection may have occurred outside of the trial-specific window (eg, CT data are available for the 9-month follow-up but are not available for the 12-month follow-up). In such cases, these subjects will not be evaluated for a particular analysis unless the number of data points required for the analysis is enough, or a trend can be extrapolated from the data that were collected outside of the trial-specified window.

A quantitative analysis that relates to the evaluation of the cost-effectiveness of this approach will not be undertaken as a part of this study, as the data set will most likely be too small to achieve statistical significance. Instead, the outcome measures that have an impact on the financial burden for treating patients will be combined with data from other similar trials that are conducted in the future, and the analysis of health economics data will be undertaken at that point.

Statistical analyses of descriptive statistics for the demographic, primary, and secondary outcomes at each time point will be conducted. A comparison analysis of the questionnaire results at each time point and a univariate Cox regression analysis of the time to weight-bearing for the affected limbs will be performed due to the small sample size. Statistical significance will be defined as $P<.05$. Data will be analyzed by using SPSS for Windows version 22 (IBM Corporation).

Measures for Avoiding and Limiting Bias

The study represents a high-quality clinical study in which bias will be kept to an absolute minimum. The study will be heavily controlled with the well-defined inclusion and exclusion criteria that will ensure that the number of patients with confounding features will be reduced, thereby effectively minimizing sources of selection bias and increasing the homogeneity of the cohort under investigation.

The follow-up period is 24 months. Generally, we would expect to see sufficient bone regeneration for most extensive defects by this time. Ongoing care will be provided in accordance with the recommendations of the treating surgeons and other members with relevant specialties, as appropriate.

Ethics Approval

The trial will be conducted in accordance with the principles of the Declaration of Helsinki, Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95), as adopted by the Australian Therapeutic Goods Administration in 2000, and in accordance with the National Health and Medical Research Council's National Statement on Ethical Conduct in Research Involving Humans [41]. A copy of the signed and dated letter of approval will be provided to the clinical trial site and the sponsor prior to study commencement. Any written information and advertisements that are to be used for subject recruitment will be approved by the Human Research Ethics Committee prior to their use.

It is the responsibility of the investigator to obtain written informed consent from each individual who participates in the study after an adequate explanation (in lay terms) of the aims; methods; objectives; and potential discomforts, risks, and benefits of the study is given. The investigator must also explain to the subjects that they are completely free to refuse to enter the study or withdraw, without prejudice, from the study at any time. Before enrollment into the study, each prospective candidate will be given a full explanation of the study. Individuals who are eligible and wish to participate will be provided the trial's participant information and consent form (PICF) prior to participation. The PICF details all of the relevant aspects of the trial procedures. Potential participants will be given time to read through the information and ask any questions. The formal consent process will be undertaken by the principal investigator or the associate investigator and will be documented by the trial coordinator. The PICF will be submitted for approval to the Human Research Ethics Committee of the PAH. Participants will be provided with a copy of their signed PICF.

Results

As of December 2020, we have enrolled 3 participants for the study. We expect to have results before the end of 2023.

Discussion

Study Overview

We aim to evaluate the potential of tissue engineering with a bioresorbable, 3D-printed scaffold and autologous vascularized tissue transfer in the reconstruction of acquired calvarial defects. It is essential to undertake a prospective feasibility trial that formally explores this technique to establish its safety and efficacy. This trial will offer critical baseline data against which current and future implants can be compared. Tissue regeneration could be enhanced via scaffold refinements, including additives such as growth factors, osteoprogenitor cells, and vascular networks [35-39]. However, RMAV may always be necessary to optimize tissue regeneration.

The project, as a whole, has a number of benefits for both individuals and society at large. It is expected that the results of our open-label feasibility trial will provide additional evidence on the effectiveness of the RMAV treatment approach for patients with calvarial defects for which contemporary surgical management may have a greater risk of failure or complications [42,43].

Conclusion

The RMAV technique may be an alternative method of reconstruction for large calvarial defects. It involves performing a vascularized free tissue transfer and using a bioresorbable, 3D-printed scaffold to promote and support bone regeneration (termed the *regenerative matching axial vascularization* technique). This technique may be used to reconstruct skull bone defects that were previously thought to be unreconstructable, reduce the risk of implant-related complications, and achieve consistent outcomes in cranioplasty. This must now be tested in prospective clinical trials.

Acknowledgments

MW and DWH conceived the study. IGM, MW, DWH, SO, and MR contributed to the development of the protocol, in conjunction with Osteopore Limited. Osteopore Limited approved the final protocol. The trial sponsor—Osteopore Limited—will provide funding to support the non–standard-of-care components of this trial, including the design, manufacturing, and transport of the scaffold device from Osteopore Limited (Singapore). The practical costs associated with organizing the treatment of patients and the coordination of their care (ie, costs for both routine clinical care and the care provided as a part of the trial protocol) will be the responsibility of the investigators and will therefore be funded in kind by Metro South Health. Similarly, the costs for conducting the cranioplasty procedure, including the costs for conducting clinical follow-ups, will be funded by Metro South Health. Part of this work was funded by the National Health and Medical Research Council (investigator grant 2008018).

Conflicts of Interest

The mPCL-TCP scaffold that will be used in the study is manufactured by Osteopore Limited (Singapore) and will be provided free of charge by the company during the trial investigative phase. A senior coinvestigator (DWH) was a cofounder of the company that will manufacture the scaffolds that will be used in the trial. DWH has since left the company, has no ongoing financial involvement with Osteopore Limited, and is not currently receiving any financial benefits or other benefits from Osteopore Limited. Otherwise, no other types of financial involvement are anticipated or are apparent at the time of writing this protocol, for any and all investigators involved, that would lead to a conflict of interest.

References

1. Uygur S, Eryilmaz T, Cukurluoglu O, Ozmen S, Yavuzer R. Management of cranial bone defects: a reconstructive algorithm according to defect size. J Craniofac Surg 2013 Sep;24(5):1606-1609. [doi: 10.1097/SCS.0b013e3182a2101c] [Medline: 24036736]
2. Sahoo NK, N MR, Tomar K, Bhat S. Classification of the residual cranial defects and selection of reconstruction materials. J Craniofac Surg 2017 Oct;28(7):1694-1701. [doi: 10.1097/SCS.0000000000003752] [Medline: 28806376]
3. De Long WGJ, Einhorn TA, Koval K, McKee M, Smith W, Sanders R, et al. Bone grafts and bone graft substitutes in orthopaedic trauma surgery. A critical analysis. J Bone Joint Surg Am 2007 Mar;89(3):649-658. [doi: 10.2106/JBJS.F.00465] [Medline: 17332116]
4. Oliver JD, Banuelos J, Abu-Ghname A, Vyas KS, Sharaf B. Alloplastic cranioplasty reconstruction: A systematic review comparing outcomes with titanium mesh, polymethyl methacrylate, polyether ether ketone, and Norian implants in 3591 adult patients. Ann Plast Surg 2019 May;82(5S Suppl 4):S289-S294. [doi: 10.1097/SAP.0000000000001801] [Medline: 30973834]
5. Eufinger H, Weihe S, Scherer P, Rasche C, Wehmöller M. Management of cranial and craniofacial bone defects with prefabricated individual titanium implants: follow-up and evaluation of 166 patients with 169 titanium implants from 1994 to 2000. Int J Comput Assist Radiol Surg 2006 Nov 14;1:197-203. [doi: 10.1007/s11548-006-0054-4]
6. De Bonis P, Frassanito P, Mangiola A, Nucci CG, Anile C, Pompucci A. Cranial repair: how complicated is filling a "hole"? J Neurotrauma 2012 Apr 10;29(6):1071-1076. [doi: 10.1089/neu.2011.2116] [Medline: 22059899]
7. Williams LR, Fan KF, Bentley RP. Custom-made titanium cranioplasty: early and late complications of 151 cranioplasties and review of the literature. Int J Oral Maxillofac Surg 2015 May;44(5):599-608. [doi: 10.1016/j.ijom.2014.09.006] [Medline: 25482456]
8. Khader BA, Towler MR. Materials and techniques used in cranioplasty fixation: A review. Mater Sci Eng C Mater Biol Appl 2016 Sep 01;66:315-322. [doi: 10.1016/j.msec.2016.04.101] [Medline: 27207068]
9. Aydin S, Kucukyuruk B, Abuzayed B, Aydin S, Sanus GZ. Cranioplasty: Review of materials and techniques. J Neurosci Rural Pract 2011 Jul;2(2):162-167 [FREE Full text] [doi: 10.4103/0976-3147.83584] [Medline: 21897681]
10. Yeo A, Wong WJ, Khoo HH, Teoh SH. Surface modification of PCL-TCP scaffolds improve interfacial mechanical interlock and enhance early bone formation: an in vitro and in vivo characterization. J Biomed Mater Res A 2010 Jan;92(1):311-321. [doi: 10.1002/jbm.a.32366] [Medline: 19189386]
11. Rai B, Ho KH, Lei Y, Si-Hoe KM, Teo CMJ, Yacob KB, et al. Polycaprolactone-20% tricalcium phosphate scaffolds in combination with platelet-rich plasma for the treatment of critical-sized defects of the mandible: a pilot study. J Oral Maxillofac Surg 2007 Nov;65(11):2195-2205. [doi: 10.1016/j.joms.2006.11.026] [Medline: 17954314]
12. Le BQ, Rai B, Lim ZXH, Tan TC, Lin T, Lee JJL, et al. A polycaprolactone-β-tricalcium phosphate-heparan sulphate device for cranioplasty. J Craniomaxillofac Surg 2019 Feb;47(2):341-348. [doi: 10.1016/j.jcms.2018.11.013] [Medline: 30579746]
13. Reichert JC, Cipitria A, Epari DR, Saifzadeh S, Krishnakanth P, Berner A, et al. A tissue engineering solution for segmental defect regeneration in load-bearing long bones. Sci Transl Med 2012 Jul 04;4(141):141ra93. [doi: 10.1126/scitranslmed.3003720] [Medline: 22764209]

14. Berner A, Boerckel JD, Saifzadeh S, Steck R, Ren J, Vaquette C, et al. Biomimetic tubular nanofiber mesh and platelet rich plasma-mediated delivery of BMP-7 for large bone defect regeneration. Cell Tissue Res 2012 Mar;347(3):603-612. [doi: 10.1007/s00441-011-1298-z] [Medline: 22277992]
15. Cipitria A, Wagermaier W, Zaslansky P, Schell H, Reichert JC, Fratzl P, et al. BMP delivery complements the guiding effect of scaffold architecture without altering bone microstructure in critical-sized long bone defects: A multiscale analysis. Acta Biomater 2015 Sep;23:282-294. [doi: 10.1016/j.actbio.2015.05.015] [Medline: 26004222]
16. Berner A, Henkel J, Woodruff MA, Saifzadeh S, Kirby G, Zaiss S, et al. Scaffold-cell bone engineering in a validated preclinical animal model: precursors vs differentiated cell source. J Tissue Eng Regen Med 2017 Jul;11(7):2081-2089. [doi: 10.1002/term.2104] [Medline: 26648044]
17. Berner A, Reichert JC, Woodruff MA, Saifzadeh S, Morris AJ, Epari DR, et al. Autologous vs. allogenic mesenchymal progenitor cells for the reconstruction of critical sized segmental tibial bone defects in aged sheep. Acta Biomater 2013 Aug;9(8):7874-7884. [doi: 10.1016/j.actbio.2013.04.035] [Medline: 23628773]
18. Das A, Botchwey E. Evaluation of angiogenesis and osteogenesis. Tissue Eng Part B Rev 2011 Dec;17(6):403-414. [doi: 10.1089/ten.TEB.2011.0190] [Medline: 21902609]
19. Sparks DS, Saleh DB, Rozen WM, Hutmacher DW, Schuetz MA, Wagels M. Vascularised bone transfer: History, blood supply and contemporary problems. J Plast Reconstr Aesthet Surg 2017 Jan;70(1):1-11. [doi: 10.1016/j.bjps.2016.07.012] [Medline: 27843061]
20. Sparks DS, Savi FM, Saifzadeh S, Schuetz MA, Wagels M, Hutmacher DW. Convergence of scaffold-guided bone reconstruction and surgical vascularization strategies-A quest for Regenerative Matching axial vascularization. Front Bioeng Biotechnol 2020 Jan 10;7:448 [FREE Full text] [doi: 10.3389/fbioe.2019.00448] [Medline: 31998712]
21. Brey EM, Cheng MH, Allori A, Satterfield W, Chang DW, Patrick CWJ, et al. Comparison of guided bone formation from periosteum and muscle fascia. Plast Reconstr Surg 2007 Apr 01;119(4):1216-1222. [doi: 10.1097/01.prs.0000254361.74614.bb] [Medline: 17496593]
22. Nau C, Henrich D, Seebach C, Schröder K, Fitzsimmons SJ, Hankel S, et al. Treatment of large bone defects with a vascularized periosteal flap in combination with biodegradable scaffold seeded with bone marrow-derived mononuclear cells: An experimental study in rats. Tissue Eng Part A 2016 Jan;22(1-2):133-141. [doi: 10.1089/ten.TEA.2015.0030] [Medline: 26486307]
23. Ersoy B, Bayramiçli M, Ercan F, Şirinoğlu H, Turan P, Numanoğlu A. Comparison of bone prefabrication with vascularized periosteal flaps, hydroxyapatite, and bioactive glass in rats. J Reconstr Microsurg 2015 May;31(4):291-299. [doi: 10.1055/s-0034-1396770] [Medline: 25785651]
24. Yogishwarappa CN, Srinivasan S, Teoh SH, Vijayakumar A, Ishwar M. Customized osteomesh cranioplasty. Journal of Advanced Plastic Surgery Research 2016;2:25-32 [FREE Full text] [doi: 10.31907/2414-2093.2016.02.05]
25. Sparks DS, Wagels M, Taylor GI. Bone reconstruction: A history of vascularized bone transfer. Microsurgery 2018 Jan;38(1):7-13. [doi: 10.1002/micr.30260] [Medline: 29134687]
26. Wagels M, Rowe D, Senewiratne S, Theile DR. History of lower limb reconstruction after trauma. ANZ J Surg 2013 May;83(5):348-353. [doi: 10.1111/j.1445-2197.2012.06271.x] [Medline: 22989362]
27. Hutmacher DW, Schantz JT, Lam CXF, Tan KC, Lim TC. State of the art and future directions of scaffold-based bone engineering from a biomaterials perspective. J Tissue Eng Regen Med 2007;1(4):245-260. [doi: 10.1002/term.24] [Medline: 18038415]
28. Henkel J, Woodruff MA, Epari DR, Steck R, Glatt V, Dickinson IC, et al. Bone regeneration based on tissue engineering conceptions - A 21st century perspective. Bone Res 2013 Sep 25;1(3):216-248 [FREE Full text] [doi: 10.4248/BR201303002] [Medline: 26273505]
29. Lam CXF, Savalani MM, Teoh SH, Hutmacher DW. Dynamics of in vitro polymer degradation of polycaprolactone-based scaffolds: accelerated versus simulated physiological conditions. Biomed Mater 2008 Sep;3(3):034108. [doi: 10.1088/1748-6041/3/3/034108] [Medline: 18689929]
30. Rai B, Lin JL, Lim ZXH, Guldberg RE, Hutmacher DW, Cool SM. Differences between in vitro viability and differentiation and in vivo bone-forming efficacy of human mesenchymal stem cells cultured on PCL-TCP scaffolds. Biomaterials 2010 Nov;31(31):7960-7970. [doi: 10.1016/j.biomaterials.2010.07.001] [Medline: 20688388]
31. Zhou Y, Chen F, Ho ST, Woodruff MA, Lim TM, Hutmacher DW. Combined marrow stromal cell-sheet techniques and high-strength biodegradable composite scaffolds for engineered functional bone grafts. Biomaterials 2007 Feb;28(5):814-824. [doi: 10.1016/j.biomaterials.2006.09.032] [Medline: 17045643]
32. Warnke PH, Springer ING, Wiltfang J, Acil Y, Eufinger H, Wehmöller M, et al. Growth and transplantation of a custom vascularised bone graft in a man. Lancet 2004;364(9436):766-770. [doi: 10.1016/S0140-6736(04)16935-3] [Medline: 15337402]
33. Mesimäki K, Lindroos B, Törnwall J, Mauno J, Lindqvist C, Kontio R, et al. Novel maxillary reconstruction with ectopic bone formation by GMP adipose stem cells. Int J Oral Maxillofac Surg 2009 Mar;38(3):201-209. [doi: 10.1016/j.ijom.2009.01.001] [Medline: 19168327]
34. Horch RE, Beier JP, Kneser U, Arkudas A. Successful human long-term application of in situ bone tissue engineering. J Cell Mol Med 2014 Jul;18(7):1478-1485 [FREE Full text] [doi: 10.1111/jcmm.12296] [Medline: 24801710]

35. Kokemueller H, Spalthoff S, Nolff M, Tavassol F, Essig H, Stuehmer C, et al. Prefabrication of vascularized bioartificial bone grafts in vivo for segmental mandibular reconstruction: experimental pilot study in sheep and first clinical application. Int J Oral Maxillofac Surg 2010 Apr;39(4):379-387. [doi: 10.1016/j.ijom.2010.01.010] [Medline: 20167453]
36. Hertel R, Gerber A, Schlegel U, Cordey J, Rüegsegger P, Rahn BA. Cancellous bone graft for skeletal reconstruction. Muscular versus periosteal bed--preliminary report. Injury 1994;25 Suppl 1:A59-A70. [doi: 10.1016/0020-1383(94)90263-1] [Medline: 7927661]
37. Axhausen W. The osteogenetic phases of regeneration of bone; a historial and experimental study. J Bone Joint Surg Am 1956 Jun;38-A(3):593-600. [doi: 10.2106/00004623-195638030-00009] [Medline: 13319414]
38. Leibig N, Wietbrock JO, Bigdeli AK, Horch RE, Kremer T, Kneser U, et al. Flow-induced axial vascularization: The arteriovenous loop in angiogenesis and tissue engineering. Plast Reconstr Surg 2016 Oct;138(4):825-835. [doi: 10.1097/PRS.0000000000002554] [Medline: 27673517]
39. Castrisos G, Matheus IG, Sparks D, Lowe M, Ward N, Sehu M, et al. Regenerative matching axial vascularisation of absorbable 3D-printed scaffold for large bone defects: A first in human series. J Plast Reconstr Aesthet Surg 2022 Jul;75(7):2108-2118. [doi: 10.1016/j.bjps.2022.02.057] [Medline: 35370116]
40. Burton M, Walters SJ, Saleh M, Brazier JE. An evaluation of patient-reported outcome measures in lower limb reconstruction surgery. Qual Life Res 2012 Dec;21(10):1731-1743. [doi: 10.1007/s11136-011-0090-6] [Medline: 22179990]
41. National Health and Medical Research Council. National Statement on Ethical Conduct in Human Research (2007) - Updated 2018. National Health and Medical Research Council. 2018. URL: https://www.nhmrc.gov.au/about-us/publications/national-statement-ethical-conduct-human-research-2007-updated-2018 [accessed 2022-08-29]
42. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004 Aug;240(2):205-213. [doi: 10.1097/01.sla.0000133083.54934.ae] [Medline: 15273542]
43. Higgins TF, Klatt JB, Beals TC. Lower Extremity Assessment Project (LEAP)--the best available evidence on limb-threatening lower extremity trauma. Orthop Clin North Am 2010 Apr;41(2):233-239. [doi: 10.1016/j.ocl.2009.12.006] [Medline: 20399362]

Abbreviations

CT: computed tomography
CRF: case report form
MDT: multidisciplinary team
MRI: magnetic resonance imaging
mPCL-TCP: medical-grade polycaprolactone and tricalcium phosphate
PAH: Princess Alexandra Hospital
PCL-TCP: polycaprolactone and tricalcium phosphate
PICF: participant information and consent form
QFAB: Queensland Facility of Advanced Bioinformatics
QOLIBRI: Quality of Life After Brain Injury
REDCap: Research Electronic Data Capture
rhBMP-7: recombinant human bone morphogenic protein-7
RMAV: regenerative matching axial vascularization
SF-36: 36-item Short Form Quality of Life

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Protocol

A Living Database of HIV Implementation Research (LIVE Project): Protocol for Rapid Living Reviews

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Abstract

Background: HIV implementation research evolves rapidly and is often complex and poorly characterized, which makes the synthesis of data on HIV implementation strategies inherently difficult. This is further compromised by prolonged data abstraction processes due to variable interventions, outcomes, and context, and delays in the publication of review findings; this can all result in outdated and irrelevant systematic reviews.

Objective: The LIVE project (A Living Database of HIV Implementation Research) aims to overcome these challenges by applying an implementation science lens to the conduct of rapid living systematic reviews and meta-analyses to inform HIV service delivery priorities and guideline development.

Methods: The LIVE project will generate a series of living systematic reviews exploring implementation strategies for improving HIV cascade outcomes (HIV infection, HIV diagnosis, linkage and retention in HIV care, viral suppression, and mortality). We will search Embase and MEDLINE as well databases specific to review questions for studies conducted after 2004 using predefined search terms to identify studies conducted in any age group or setting, and using implementation strategies that target policy makers, society, health organizations, health workers, and beneficiaries of care and their families. Both randomized controlled trials and observational studies will be included to ensure reviews include pragmatic data. In addition to assessments of methodological quality, features of the implementation strategies, relevance for implementation, and evidence quality will be determined using recognized frameworks. After initial publication, knowledge gaps will be identified, and review questions and search strategies revised to address ongoing critical areas of inquiry. Updated searches will be conducted every 6 months, with subsequent ongoing screening, data abstraction, and revision of meta-analyses.

Results: As of July 2022, five reviews are at various stages of development within the LIVE project. Three systematic reviews are underway and living review processes are in development for two reviews with estimated completion over the next 12 months.

Conclusions: This project and resulting systematic reviews will provide critical insights for HIV service delivery to inform international guideline development.

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KEYWORDS

living review; HIV; systematic review; rapid review; implementation; HIV infection

Introduction

Systematic reviews addressing HIV implementation research questions are challenged by difficulties in synthesizing heterogenous pragmatic research and can become outdated rapidly. As HIV prevention strategies, testing methods, and treatments become increasingly effective, current primary HIV research and evidence synthesis questions are refocusing on how best to implement effective interventions to ensure long-term sustained engagement in HIV care [1,2]. This continuous emergence of new implementation research means that traditional methods for generating "static" systematic reviews that may take months or years to produce can quickly become obsolete [3,4]. With each new guideline development cycle, new review teams, searches, protocols, and reviews are undertaken, resulting in substantial duplication of efforts, delays in the generation of synthesized evidence and inability for guideline developers to quickly update recommendations.

Living and rapid review methods have been developed in recent years (now catalyzed by the COVID-19 pandemic) to address these inefficiencies and increase the utility of review evidence; these methods have however been infrequently applied to HIV implementation research [5]. The field of HIV implementation science is a rapidly evolving field, with frequent changes to HIV service delivery approaches (eg, multi-month prescribing), drug delivery systems for HIV treatment (eg, long-acting antivirals), and HIV prevention (eg, vaginal rings) and testing modalities (eg, HIV self-testing). Living methods offer an approach for systematic review updating, where new evidence is incorporated into a review as it emerges, generating a continual updating process that maintains the relevance of synthesized findings and builds on previous work. Living reviews require an explicitly stated commitment to a predetermined frequency of searches and review updating [6]. Rapid reviews aim to accelerate the review process through the elimination or attenuation of some systematic review requirements, including searches in fewer databases, applying language or publication year restrictions, limiting gray literature searches, applying data mining processes, and altering duplicate screening, data extraction, and quality appraisal processes [7,8]. Rapid reviews are being conducted with increased frequency to respond to policy-making needs [9,10]. Rapid and living processes are ideal for incorporation into "living guidelines"—a dynamic guideline development process that, instead of conducting mechanistic guideline updates with a predetermined frequency, uses the results of continuous literature surveillance, rapid updating of prioritized reviews, and frequent virtual consultations with guideline panels to create a continuous guideline development and revision process; this helps to ensure that policy makers and health workers can make up-to-date, evidence-based public health decisions [11-14]. Accelerating the pace of evidence synthesis and dissemination can facilitate the early and effective adoption of new strategies for improving health and reduce the evidence-practice gap [15,16].

Heterogeneity, a frequent and desirable property of implementation research, further complicates evidence synthesis for HIV service delivery. The application of systematic review and meta-analytic methods—originally designed for homogenous efficacy data—to complex implementation research questions can result in systematic review findings that are of limited relevance to policy makers [17-19]. Establishing the effectiveness of strategies to increase HIV testing or antiretroviral therapy uptake and adherence requires detailed characterization of strategy features (eg, where, how, and who delivered the intervention) as well as incorporation of pragmatic data that establishes effectiveness under real-world conditions. Tools are available for characterization of implementation strategies, assessment of real-world relevance of primary research, and reporting of implementation research methods and results, but to date such tools have had limited application in HIV implementation research evidence synthesis [20-23]. Heterogeneity does not preclude evidence synthesis; it is important to develop approaches to accommodate varied study designs and implementation strategies and still draw conclusions from the evidence.

The Living Database of HIV Implementation Research (LIVE) project aims to generate a series of methodologically robust rapid and living reviews characterizing and evaluating the effects of HIV implementation strategies on HIV cascade outcomes through an ongoing process of data abstraction and frequent review updates to produce valid and relevant synthesized evidence that contributes to a rapid public health response to HIV. In addition, this work will identify evidence gaps and put forward new approaches for reviewing and meta-analyzing complex implementation research specific to HIV but with relevance to evidence synthesis in the implementation science field more broadly.

Methods

This project protocol was designed according to PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines, living review guidelines, and World Health Organization (WHO) and Cochrane rapid review guidelines [6,8,10,24].

Identification of Review Questions

Relevant HIV implementation science questions will be developed in consultation with HIV guideline development groups. This will include questions regarding effectiveness of HIV implementation strategies. Individual review protocols will be published on PROSPERO, the international prospective register of systematic reviews.

Eligibility Criteria

Studies eligible for inclusion in living rapid reviews include those conducted in any population group or age category from any setting. Randomized controlled trials (RCTs), cohort studies (with or without a comparison arm), cross-sectional studies, and natural experiments are eligible for inclusion. Incorporation of a broad range of study designs including both randomized controlled trials and observational studies will facilitate exploration of the broad spectrum of implementation research assessing the performance of implementation strategies under trial and real-world conditions.

Studies must evaluate the implementation of evidence-based HIV interventions (strategies aimed at implementing a change

to the way HIV testing, antiretroviral treatment [ART], or prevention is delivered to modify patient behavior and improve outcomes) and report on at least one HIV cascade outcome (HIV incidence, HIV testing uptake, ART initiation, ART adherence, viral suppression, retention in care) (Table 1). Eligible studies will be restricted to English language publications.

Table 1. Eligibility criteria for inclusion in LIVE rapid living reviews.

	Eligibility criteria
Population	All settings, all ages
Implementation strategy	Implementation strategy aimed at (1) implementing a change to the way HIV care and preventions strategies are delivered or (2) modifying patient behavior
Comparison	Other intervention, standard of care, or no comparison
Outcome	HIV incidence, HIV testing uptake, antiretroviral therapy initiation, antiretroviral therapy adherence, viral suppression, retention in care

Database Searches

An information specialist will conduct searches of a minimum of two databases—MEDLINE and Embase—and will include CINAHL and other databases depending on the considered added value for the specified review question as determined in consultation with an information specialist. Search outputs will be refined through an iterative process of cross-checking against known studies in the field. Once finalized, automated searches running at a predetermined frequency (initially every 6 months) will generate updated lists of studies for screening and eligibility assessment and abstraction. Searches will include studies published between 2004 to the day of the search, but may be restricted to more recent studies depending on the specified review question.

Gray Literature Searches

At minimum, conference abstracts of the International AIDS Society and the Conference on Retroviruses and Opportunistic Infections will be searched for the previous two years. Additional conference searches will depend on their relevance to review questions. Clinical trial registries including ClinicalTrials.gov and WHO International Clinical Trials Registry Platform registries will be searched routinely; depending on the specific review, further trial registries may be considered.

Screening

Several team members may be involved in screening processes. Abstract and full-text screening will be conducted using Covidence software [25]. For abstract screening, 2 team members will screen the first 20% of abstracts with conflict resolution; once approaches to screening are calibrated and consistency developed, ongoing abstract screening will be conducted by one team member. Full-text screening will be conducted by one team member and excluded full texts will be screened by a second. Conference and clinical trial registry searches will be conducted by one team member with confirmation of eligibility of included abstracts by a second.

Data Abstraction

Study data will be abstracted into the LIVE database hosted on the Airtable platform (a relational database designed to be easily modified by end users and widely used commercially [26]. Extracted study outcomes will include numerators and denominators as well as adjusted and unadjusted effect estimates. Data abstraction and methodological quality assessments will be conducted by one team member and reviewed by a second team member. Descriptive information will be extracted from each study (including details on publication, study design, setting, context, and demographic characteristics) and additional data regarding the critical characteristics and components of implementation strategies will be recorded using existing frameworks for evaluating characteristics of implementation strategies, reporting of implementation outcomes, assessments of real-world relevance of primary research, and implementation characteristics of trial design (Table 2). By applying these implementation science tools and frameworks, the LIVE project will employ evidence synthesis methods that accommodate complexity, recognizing that heterogeneity is an inherent feature of the current HIV response and is essential [1].

Table 2. Tools used to assess study quality and characterize intervention strategies for living rapid reviews.

Assessment tool	Purpose
Cochrane risk of bias tools [27,28]	Assess the methodological quality of randomized controlled trials
Newcastle Ottawa scale [29]	Assess the methodological quality of cohort and cross-sectional studies
Proctor implementation strategy framework [20]	Characterize implementation strategies
Proctor implementation outcome classification system [21]	Characterize and assess reporting implementation outcomes
Pragmatic explanatory continuum indicator summary (PRE-CIS)-2 tool [22]	Evaluate explanatory vs pragmatic approaches of studies
Curran effectiveness-implementation hybrid trial designs [30]	Characterize trial types based on focus: clinical effectiveness versus implementation

Analyses

We will characterize individual study populations, implementation interventions, comparisons, and HIV cascade outcomes and other outcomes relevant to the review questions including harms and unintended consequences. We will use funnel plots to explore publication bias. If there is sufficient quantitative data, these data will be meta-analyzed in R, Stata, or SAS programs, depending on the type of data available for analysis (eg, continuous, binary, incidence, adjusted effect estimates, single means, or proportions). Pooled results and forest plots for random effects will be generated using Mantel-Hansel, Peto, generalized linear models, or generic inverse variance [31]. Inconsistency will be reviewed qualitatively to detect clinical diversity (population, context, implementation strategy) or methodological diversity (risk of bias, study design), and quantitatively using I^2, Kendall τ statistics, and subgroup analysis. Decisions regarding the appropriateness of pooling data, subgrouping, and sensitivity analyses will be conducted by study teams and will follow guidelines as set out by the Cochrane Handbook. Given the inherently heterogenous nature of HIV implementation research, we anticipate substantial explained and unexplained heterogeneity; as a result, pooled estimates may in many cases not reflect one true population effect estimate relevant to all contexts but rather a broader assessment of overall benefit or harm across various contexts [32]. Where sufficient data are available, we will use meta-regression to explore heterogeneity.

In addition, where multiple strategies are presented, network meta-analyses (NMA) may be conducted and will follow guidelines for conduct and reporting of NMA. The frequentist or Bayesian NMA approaches will be used to generate networks, evaluate inconsistency, and rank interventions. Although the inherent nature of implementation strategies may in some cases violate the assumption of transitivity due to variability in context and strategy heterogeneity—in terms of design and fidelity to intervention delivery—this analytic technique allows for the comparison of multiple interventions that have not been compared directly due to public health urgency and resource constraints [33].

Where data are insufficient for meta-analysis, we will summarize data narratively. The overall confidence in the review findings will be evaluated using recognized methodologies for rating evidence certainty such as the Grading of Recommendations Assessment, Development, and Evaluation system [34].

Living Processes

Once a review is completed and published, a continuous living process will be adopted to keep the review findings up to date as required [6,35]. First, the systematic review question will be examined in the light of the primary review findings and in consultation with key stakeholders (eg, WHO guideline developers) to determine if the question remains relevant in its current format, whether the review question should be altered to address different population groups, and whether additional strategies or specific implementation or HIV cascade outcomes should be focused on. Search strategies will be examined and refined to ensure that all relevant new terms and databases are included in updated search strategies. A comprehensive systematic search will be conducted every 6 months. If no new studies are detected, review records will be updated with the most recent search date and specify that no new relevant studies have been identified. If new studies are identified but appear unlikely to change the review findings or are insufficient for new meta-analyses, study data will be extracted but no meta-analyses will be performed. If new findings are deemed critical for revised or updated guidelines, new meta-analyses of all studies identified to date will be conducted and published in a peer reviewed journal. With each 6-month cycle, considerations for retirement of reviews will be revised, as the importance of research questions will be expected to change over time [36]. Such reviews may contribute to living guidelines, an emerging methodological area where guidelines are continuously assessed to determine whether they are sufficiently up to date and whether new studies or information is available that may change the guideline, leading to cycles of refinement and revision or retirement [14].

Results

As of July 2022, five reviews are at various stages of development within the LIVE project. Data extraction is underway for 3 systematic reviews with the aim of completion by the end of December 2022; living review processes are under development for 2 reviews.

Discussion

The LIVE project seeks to enhance the use of implementation research to inform guideline development and ultimately policy making. The project proposes to produce “living” systematic reviews by applying an ongoing updating and data extraction process to support guideline developers, including but not limited to questions on HIV service delivery at the WHO. In this project protocol, we outline a plan to support ongoing guideline development processes in HIV testing and use of antiretrovirals, but also identify how through the maintenance of living reviews this work can contribute to the future conceptualization and development of “living guideline” processes.

The additional application of implementation research tools and taxonomies further position this work to contribute to guidelines that directly impact global implementation efforts, particularly for questions in HIV service delivery. By broadly exploring how, where, and for whom HIV implementation strategies are most effective, the LIVE project will advance the implementation science field by directly addressing inherent heterogeneity and intervention complexity in implementation science evidence synthesis and support future HIV service delivery guideline development.

This work may be limited by difficulties in maintaining reviewers over the long term and ensuring continuous updates; the project will work to overcome this by involving a broad review team to ensure the ongoing longevity of individual systematic reviews. A further challenge may be decisions regarding when to publish an updated version of a review, retire a review, or alter review questions. To address this, decisions

regarding review updates will be determined in close collaboration with experts and policy makers to ensure ongoing relevance.

Synthesizing implementation research evidence is complex. This protocol and review portfolio propose new directions for implementation science evidence synthesis that also have relevance for other implementation questions beyond HIV service delivery.

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Conflicts of Interest

None declared.

References

1. Geng EH, Holmes CB, Moshabela M, Sikazwe I, Petersen ML. Personalized public health: An implementation research agenda for the HIV response and beyond. PLoS Med 2019 Dec;16(12):e1003020 [FREE Full text] [doi: 10.1371/journal.pmed.1003020] [Medline: 31891581]
2. Ford N, Geng E, Ellman T, Orrell C, Ehrenkranz P, Sikazwe I, et al. Emerging priorities for HIV service delivery. PLoS Med 2020 Feb;17(2):e1003028 [FREE Full text] [doi: 10.1371/journal.pmed.1003028] [Medline: 32059023]
3. Eshun-Wilson I, Jaffer S, Smith R, Johnson S, Hine P, Mateo A, et al. Maintaining relevance in HIV systematic reviews: an evaluation of Cochrane reviews. Syst Rev 2019 Feb 07;8(1):46 [FREE Full text] [doi: 10.1186/s13643-019-0960-5] [Medline: 30732644]
4. Elliott JH, Turner T, Clavisi O, Thomas J, Higgins JPT, Mavergames C, et al. Living systematic reviews: an emerging opportunity to narrow the evidence-practice gap. PLoS Med 2014 Feb;11(2):e1001603 [FREE Full text] [doi: 10.1371/journal.pmed.1001603] [Medline: 24558353]
5. Elliott J, Lawrence R, Minx JC, Oladapo OT, Ravaud P, Tendal Jeppesen B, et al. Decision makers need constantly updated evidence synthesis. Nature 2021 Dec;600(7889):383-385. [doi: 10.1038/d41586-021-03690-1] [Medline: 34912079]
6. Elliott JH, Synnot A, Turner T, Simmonds M, Akl EA, McDonald S, Living Systematic Review Network. Living systematic review: 1. Introduction-the why, what, when, and how. J Clin Epidemiol 2017 Nov;91:23-30. [doi: 10.1016/j.jclinepi.2017.08.010] [Medline: 28912002]
7. Tricco AC, Antony J, Zarin W, Strifler L, Ghassemi M, Ivory J, et al. A scoping review of rapid review methods. BMC Med 2015 Sep 16;13:224 [FREE Full text] [doi: 10.1186/s12916-015-0465-6] [Medline: 26377409]
8. Cochrane Rapid Reviews. Interim Guidance from the Cochrane Rapid Reviews Methods Group. URL: https://methods.cochrane.org/rapidreviews/cochrane-rr-methods [accessed 2022-08-19]
9. Kuchukhidze S, Long L, Pascoe S, Huber A, Nichols B, Fox M. Differentiated models of service delivery (DSD) for antiretroviral treatment of HIV in subSaharan Africa: A review of the gray literature. 2019. URL: https://sites.bu.edu/ambit/files/2019/11/AMBIT-report-03-gray-literature-review-2019-11-08.pdf [accessed 2022-08-23]
10. Tricco A, Langlois E, Straus S. Rapid reviews to strengthen health policy and systems: a practical guide. Rapid reviews to strengthen health policy and systems: a practical guide. Geneva: World Health Organization. 2017. URL: https://apps.who.int/iris/bitstream/handle/10665/258698/9789241512763-eng.pdf [accessed 2022-08-23]
11. Keeping global recommendations up-to-date: A 'living guidelines' approach to maternal and perinatal health. World Health Organization. URL: https://www.who.int/news/item/19-08-2019-keeping-global-recommendations-up-to-date-a-living-guidelines-approach-to-maternal-and-perinatal-health [accessed 2022-08-23]
12. Akl EA, Meerpohl JJ, Elliott J, Kahale LA, Schünemann HJ, Living Systematic Review Network. Living systematic reviews: 4. Living guideline recommendations. J Clin Epidemiol 2017 Nov;91:47-53. [doi: 10.1016/j.jclinepi.2017.08.009] [Medline: 28911999]
13. Living guidance for clinical management of COVID-19 2021. World Health Organization. URL: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-2 [accessed 2022-08-23]
14. Vogel JP, Dowswell T, Lewin S, Bonet M, Hampson L, Kellie F, et al. Developing and applying a 'living guidelines' approach to WHO recommendations on maternal and perinatal health. BMJ Glob Health 2019;4(4):e001683 [FREE Full text] [doi: 10.1136/bmjgh-2019-001683] [Medline: 31478014]
15. Grimshaw JM, Eccles MP, Lavis JN, Hill SJ, Squires JE. Knowledge translation of research findings. Implement Sci 2012;7:50 [FREE Full text] [doi: 10.1186/1748-5908-7-50] [Medline: 22651257]

16. Morris ZS, Wooding S, Grant J. The answer is 17 years, what is the question: understanding time lags in translational research. J R Soc Med 2011 Dec;104(12):510-520 [FREE Full text] [doi: 10.1258/jrsm.2011.110180] [Medline: 22179294]
17. Lie RK, Miller FG. What counts as reliable evidence for public health policy: the case of circumcision for preventing HIV infection. BMC Med Res Methodol 2011 Mar 31;11:34 [FREE Full text] [doi: 10.1186/1471-2288-11-34] [Medline: 21453535]
18. Deaton A, Cartwright N. Understanding and misunderstanding randomized controlled trials. Soc Sci Med 2018 Aug;210:2-21 [FREE Full text] [doi: 10.1016/j.socscimed.2017.12.005] [Medline: 29331519]
19. Edwards N, Barker PM. The importance of context in implementation research. J Acquir Immune Defic Syndr 2014 Nov 01;67 Suppl 2:S157-S162. [doi: 10.1097/QAI.0000000000000322] [Medline: 25310123]
20. Proctor EK, Powell BJ, McMillen JC. Implementation strategies: recommendations for specifying and reporting. Implement Sci 2013 Dec 01;8:139 [FREE Full text] [doi: 10.1186/1748-5908-8-139] [Medline: 24289295]
21. Proctor E, Silmere H, Raghavan R, Hovmand P, Aarons G, Bunger A, et al. Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. Adm Policy Ment Health 2011 Mar;38(2):65-76 [FREE Full text] [doi: 10.1007/s10488-010-0319-7] [Medline: 20957426]
22. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. BMJ 2015 May 08;350:h2147. [doi: 10.1136/bmj.h2147] [Medline: 25956159]
23. Pinnock H, Barwick M, Carpenter CR, Eldridge S, Grandes G, Griffiths CJ, StaRI Group. Standards for Reporting Implementation Studies (StaRI) Statement. BMJ 2017 Mar 06;356:i6795 [FREE Full text] [doi: 10.1136/bmj.i6795] [Medline: 28264797]
24. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021 Mar 29;372:n71 [FREE Full text] [doi: 10.1136/bmj.n71] [Medline: 33782057]
25. Covidence. URL: https://www.covidence.org/ [accessed 2022-08-22]
26. Garcia de Cortazar AR, Cabrera Leon A, Hernan Garcia M, Jimenez Nunez JM. Attitudes of adolescent Spanish Roma toward noninjection drug use and risky sexual behavior. Qual Health Res 2009 May;19(5):605-620. [doi: 10.1177/1049732309333813] [Medline: 19299254]
27. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Cochrane Bias Methods Group, Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011 Oct 18;343:d5928 [FREE Full text] [doi: 10.1136/bmj.d5928] [Medline: 22008217]
28. RoB 2: A revised Cochrane risk-of-bias tool for randomized trials 2019. Cochrane. URL: https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials [accessed 2022-08-22]
29. Wells GA, O'Connell D, Peterson J, Welch V, Losos M. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. Ottawa Hospital Research Institute. URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [accessed 2022-08-22]
30. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. Med Care 2012 Mar;50(3):217-226 [FREE Full text] [doi: 10.1097/MLR.0b013e3182408812] [Medline: 22310560]
31. R: A language and environment for statistical computing. R Foundation for Statistical Computing: Vienna, Austraia; 2013. URL: http://www.R-project.org/ [accessed 2022-08-22]
32. Deeks J, Higgins J, Altman D. Chapter 10: Analysing data and undertaking meta-analyses (version 6.2). Cochrane Handbook for Systematic Reviews of Interventions. URL: https://training.cochrane.org/handbook [accessed 2022-08-22]
33. Geng EH, Petersen ML. Network meta-analyses: powerful but not without perils. Lancet HIV 2014 Dec;1(3):e95-e96. [doi: 10.1016/S2352-3018(14)00010-1] [Medline: 26424122]
34. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011 Apr;64(4):383-394. [doi: 10.1016/j.jclinepi.2010.04.026] [Medline: 21195583]
35. Counotte MJ, Kim CR, Wang J, Bernstein K, Deal CD, Broutet NJN, et al. Sexual transmission of Zika virus and other flaviviruses: A living systematic review. PLoS Med 2018 Jul;15(7):e1002611 [FREE Full text] [doi: 10.1371/journal.pmed.1002611] [Medline: 30040845]
36. Garner P, Hopewell S, Chandler J, MacLehose H, Schünemann HJ, Akl EA, Panel for updating guidance for systematic reviews (PUGs). When and how to update systematic reviews: consensus and checklist. BMJ 2016 Jul 20;354:i3507 [FREE Full text] [doi: 10.1136/bmj.i3507] [Medline: 27443385]

Abbreviations

ART: antiretroviral therapy
LIVE: Living Database of HIV Implementation Research
NMA: network meta-analysis
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

RCT: randomized controlled trial
WHO: World Health Organization

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Protocol

Exponential Growth Bias of Infectious Diseases: Protocol for a Systematic Review

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Abstract

Background: Humans struggle to grasp the extent of exponential growth, which is essential to comprehend the spread of an infectious disease. Exponential growth bias is the tendency to linearize exponential functions when assessing them intuitively. Effective public health communication about the nonlinear nature of infectious diseases has strong implications for the public's compliance with strict restrictions. However, there is a lack of synthesized knowledge on the communication of the exponential growth of infectious diseases and on the outcomes of exponential growth bias.

Objective: This systematic review identifies, evaluates, and synthesizes the findings of empirical studies on exponential growth bias of infectious diseases.

Methods: A systematic review will be conducted using the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 statement. Eligibility criteria include empirical studies of exponential growth bias of infectious diseases regardless of methodology. We include studies both with and without interventions/strategies. For information sources, we include the following five bibliographic databases: MEDLINE, Embase, Cochrane Library, PsychINFO, and Web of Science Core Collection. The risk of bias will be assessed using RoB 2 (Risk of Bias 2) and STROBE (Strengthening the Reporting of Observational Studies in Epidemiology). Data synthesis will be achieved through a narrative synthesis.

Results: By February 2022, we included 11 experimental studies and 1 cross-sectional survey study. Preliminary themes identified are the presence of exponential growth bias, the effect of exponential growth bias, and communication strategies to mitigate exponential growth bias. Data extraction, narrative synthesis, and the risk of bias assessment are to be completed by February 2023.

Conclusions: We anticipate that this systematic review will draw some lines related to how people comprehend and misperceive exponential growth and its consequences for infectious disease mitigation and communication. Furthermore, the study will conclude with the limitations of the research and suggestions for future research.

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KEYWORDS

exponential growth bias; pandemic; infectious diseases; COVID-19; health communication; risk communication

Introduction

The COVID-19 pandemic has unfortunately demonstrated the power of exponential growth and the need to understand why humans struggle to grasp the extent of a spreading infectious disease. Exponential growth bias is defined by Stango and Zinman [1] as "the pervasive tendency to linearize exponential functions when assessing them intuitively." Exponential growth bias is a well-documented phenomenon that dates to the 1970s [2-4].

Exponential growth bias has been documented in numerous contexts and populations, using both experimental and observational methods [1]. Nonexperts underestimate exponential growth and trends, assuming that the growth is linear [2-4]. At the same time, many nonexperts overestimate their ability to estimate exponential growth [5]. The bias may seem robust, as the misconception of exponential growth is occurring even among people with an advanced education in mathematics [6,7]. Even heads of state either failed to respond or downplayed the spread of the virus in the early phases of the COVID-19 pandemic [8].

Prior epidemiological studies have documented how the spread of infectious diseases, especially in the initial stages, often follows an exponential function [9-11]. Early in the COVID-19 pandemic, Li et al [9] documented how the spread of COVID-19 was exponential. In West Africa, outbreaks of Ebola showed near-exponential growth in the districts of Margibi in Liberia and Bombali and Bo in Sierra Leone [12].

Effective public health communication of the nonlinear nature of infectious diseases has strong implications for public compliance with restrictions. However, there is little synthesized knowledge on the communication of exponential growth of infectious diseases and the outcomes of the exponential growth bias. This systematic review identifies, evaluates, and synthesizes the findings of empirical studies on the exponential growth bias of infectious diseases. The review questions are:

- What are the consequences of exponential growth bias of infectious diseases?
- What strategies can mitigate exponential growth bias of infectious diseases?

Methods

A systematic review will be conducted using the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 statement [13].

Eligibility Criteria

Consistent with the aim to identify findings of empirical studies, we include empirical studies regardless of applied methodology (eg, randomized controlled trials, nonrandomized studies [quasi-experimental trials], survey studies, and qualitative studies). Commentaries, reviews, opinion pieces, or other papers not reporting primary empirical research are excluded. Only English-language peer-reviewed studies are included. PICO (Problem, Intervention or Exposure, Comparison, Outcome) is used to define our rationale and eligibility criteria.

Problem

We include studies of exponential growth bias of infectious diseases. We define exponential growth bias as "the pervasive tendency to linearize exponential functions when assessing them intuitively" [1]. We exclude studies of exponential growth of infectious diseases that did not study the human perception of exponential growth (eg, statistical, prediction, or selection bias). Likewise, studies of cognitive biases not related to exponential growth are excluded (eg, anchoring bias). Infectious diseases include outbreaks, epidemics, and pandemics in real-life or fictional cases. Studies of exponential growth bias in other contexts (eg, economy) are excluded.

Intervention or Exposure

We included studies both with and without interventions/strategies to mitigate exponential growth bias.

Outcome

The studies have to report on the presence of exponential growth bias of infectious diseases to be included. Additional outcomes of interest, which are not necessary to be eligible for inclusion, are the outcomes of strategies to mitigate exponential growth bias of infectious diseases and the outcomes of exponential growth bias of infectious diseases.

Search Strategy and Information Sources

A presearch provided a limited number of hits. To increase the sensitivity of the search, we include five bibliographic databases: MEDLINE, Embase, Cochrane Library, PsychINFO, and Web of Science Core Collection. Based on initial literature searches, several papers were selected for further cited reference searches in Web of Science as a supplement to the traditional searches. In line with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [13], the selection of databases, search terms, and search methodology was determined in collaboration with a university library technician (Geir Strandenæs Larsen) who designed the final search. Author SH gave feedback on the search terms related to infectious diseases. The final search results were exported to EndNote, and Geir Strandenæs Larsen removed the duplicates. The main database search was conducted on January 5 and 7, 2022. We searched using the terms *exponential growth bias*, *exponential growth prediction bias forecast/misconception/misperception of exponential growth*, AND *infectious diseases*, *epidemic**, *pandemic**, *outbreak**, or *contagious/transmissible/communicable disease**. No filters or limits were added in our literature searches (eg, language, peer-review, or publication date range). No searches of gray literature were conducted. The full electronic search strategy for all databases is shown in Multimedia Appendix 1.

Selection of Sources of Evidence

As of February 2022, the search yielded 585 results. After removing duplicates, there were 365 unique results. The full text of 50 articles were read and assessed for eligibility; 39 were excluded, and 11 were included in the review.

One reviewer (SHB) undertook the screening and inclusion, in dialogue with author JR. All records were added to Rayyan

(software for intelligent systematic review). SHB assessed abstracts and full-text articles using the eligibility criteria.

Data-Charting Process

Data will be extracted by one researcher (SHB) and will be checked by a second researcher (DAL or JR). Data from included papers will be extracted to a matrix prior to synthesis: author, year of publication, aim, sample size, origin, methods, and results. Pilot-testing of the data extraction form has been conducted by extracting information from 3 studies. The extracted data will be displayed in a table, and the content of the table will be validated by JR and DAL.

Synthesis Methods

Due to the heterogeneity of the studies regarding methodology and outcome measures, a statistical meta-analysis was considered inappropriate [14]. A narrative synthesis is used when statistical meta-analysis is not feasible and refers to an approach for systematic reviews and synthesis of findings from multiple studies that relies primarily on the use of words and text to summarize and explain the findings of the synthesis [15]. When used in a systematic review, a narrative synthesis focuses on a wide range of questions, not only those relating to the effectiveness of a specific intervention [15]. Data synthesis will be achieved through a narrative synthesis using the four stages of data synthesis proposed by Whittemore and Knafl [16]. The results relevant to the review question will be summarized, coded inductively, and initially categorized in accordance with the review questions (first stage). Data displays of the categories will be made to visualize patterns and relationships among data (second stage). The themes will be verified by keeping track of the primary source data (fourth stage). The analysis will be conducted by SHB. JR and DAL will read the articles and validate the analysis.

Quality Appraisal

Risk of bias will be assessed using the ROBINS-I (Risk of Bias in Nonrandomized Studies of Interventions), the preferred tool to be used in Cochrane reviews for nonrandomized studies of interventions [17]. The randomized controlled trials will be assessed using Cochrane Collaboration's RoB 2 (Risk of Bias 2) tool for randomized trials [18]. The randomized and nonrandomized studies will be assessed as critical, serious, moderate, low, or no information (templates shown in Tables 1 and 2). The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement checklist will be used for quality assessment of observational (cohort and cross-sectional) studies [19]. The risk of bias assessment will be conducted by authors SHB, JR, DAL, and KB.

Table 1. Template for the risk of bias assessment in accordance to ROBINS-I (Risk of Bias in Nonrandomized Studies of Interventions) [17].

	Studies
Confounding	__[a]
Selection of participants	—
Classifications of interventions	—
Deviations from interventions	—
Missing data	—
Measurement of outcome	—
Selection of reported results	—
Overall risk of bias	—

[a]Reference numbers will be included here.

Table 2. Template for risk of bias assessment in accordance to RoB 2 (Risk of Bias 2) [18].

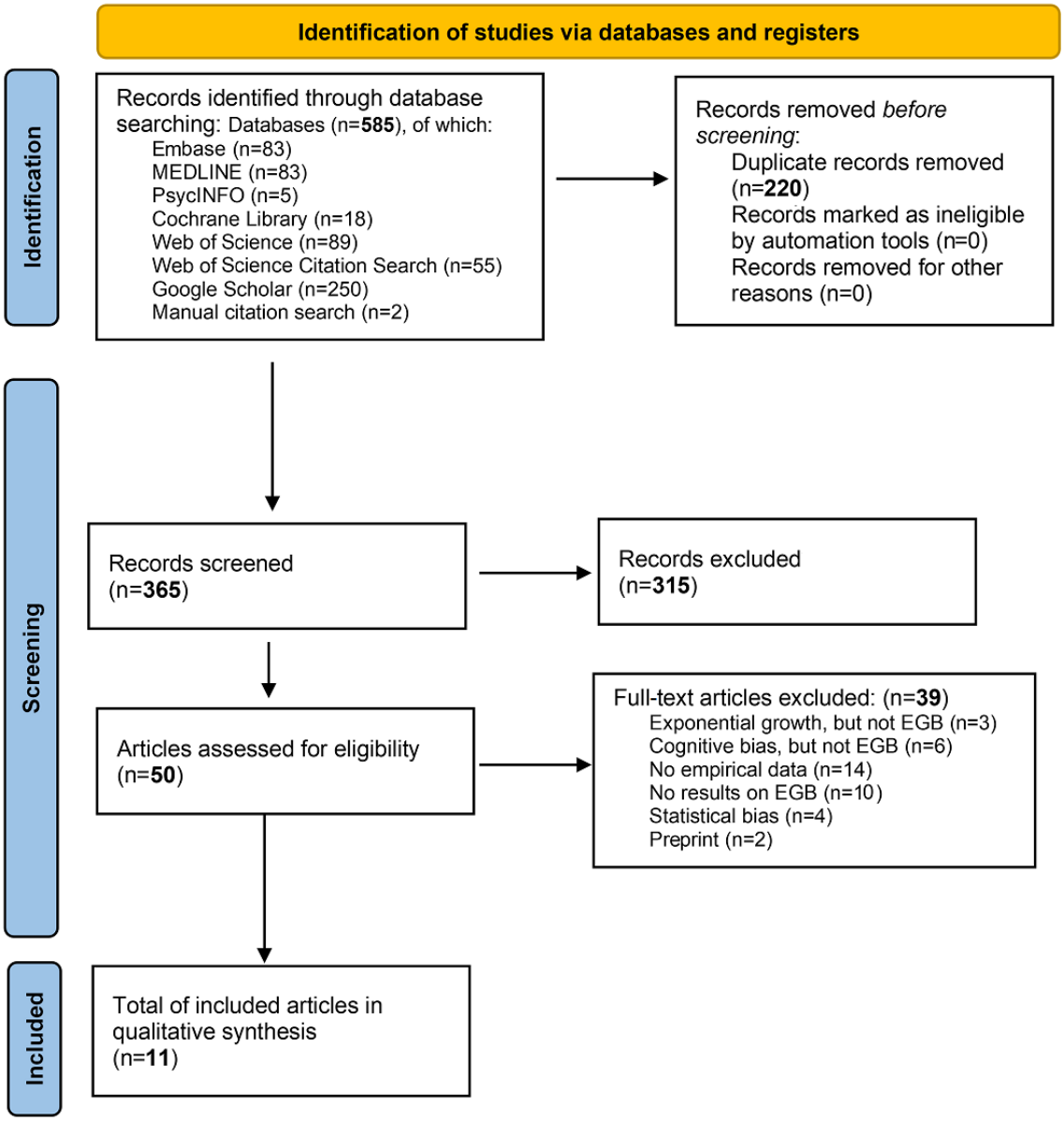
	Studies
Randomization process	__[a]
Deviations from interventions	—
Missing data	—
Measurement of outcome	—
Selection of reported results	—
Overall risk of bias	—

[a]Reference numbers will be included here.

Results

As of February 2022, we have included 11 studies (see the PRISMA flow diagram in Figure 1). This comprises 11 experimental studies and 1 cross-sectional survey study. The preliminary themes identified are the presence of exponential growth bias, the effect of exponential growth bias, and communication strategies to mitigate exponential growth bias. Data extraction, narrative synthesis, and the risk of bias assessment is expected to be completed by February 2023.

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for studies included in the present review of exponential growth bias (EGB).



Discussion

This review presents an unbiased summary and analysis of the evidence of the exponential growth bias of infectious diseases. We believe that the review will provide useful information to guide future research and public health communication strategies. The anticipated main findings of this study will document the presence of exponential growth bias of infectious diseases and its personal and societal consequences, and identify communication strategies that may mitigate the exponential growth bias of infectious diseases. However, since this research is in its early development, we expect to find few methodologically diverse studies. Although we cannot conduct a meta-analysis and statistical synthesis of the outcomes in this systematic overview, we expect this review to generate scholarly discussion and research. Thus, the discussion will focus on the limitations of the research and suggestions for future research in the fields of health communication, media studies, psychology, and mathematics. The review is expected to be submitted to the *Journal of Medical Internet Research* in June 2023.

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Authors' Contributions

SHB had the original idea for the study and designed the work. As of February 2022, SHB screened and extracted data. SH reviewed the search terminology. KB validated the procedure for the risk of bias assessment. JR and DAL validated the search strategy and inclusion of selected studies. All authors contributed substantially to the methodological design of the protocol and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 32 KB - resprot_v11i10e37441_app1.docx]

References

1. Stango V, Zinman J. Exponential growth bias and household finance. J Finance 2009 Nov 25;64:2807-2849. [doi: 10.1111/j.1540-6261.2009.01518.x]
2. Zamir E, Teichman D. Mathematics, psychology, and law: the legal ramifications of the exponential growth bias. SSRN J 2021:1-48. [doi: 10.2139/ssrn.3804329]
3. Wagenaar WA, Timmers H. The pond-and-duckweed problem; three experiments on the misperception of exponential growth. Acta Psychologica 1979;43(3):239-251. [doi: 10.1016/0001-6918(79)90028-3]
4. Wagenaar WA, Sagaria SD. Misperception of exponential growth. Perception Psychophysics 1975 Nov;18(6):416-422. [doi: 10.3758/bf03204114]
5. Levy MR, Tasoff J. Exponential-growth bias and overconfidence. J Econ Psychol 2017 Feb;58:1-14. [doi: 10.1016/j.joep.2016.11.001]
6. Christandl F, Fetchenhauer D. How laypeople and experts misperceive the effect of economic growth. J Econ Psychol 2009 Jun;30(3):381-392. [doi: 10.1016/j.joep.2009.01.002]
7. Levy M, Tasoff J. Exponential-growth bias and lifecycle consumption. J Eur Econ Assoc 2015 Aug 22;14(3):545-583. [doi: 10.1111/jeea.12149]
8. Lammers J, Crusius J, Gast A. Correcting misperceptions of exponential coronavirus growth increases support for social distancing. Proc Natl Acad Sci U S A 2020 Jul 14;117(28):16264-16266 [FREE Full text] [doi: 10.1073/pnas.2006048117] [Medline: 32581118]
9. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med 2020 Mar 26;382(13):1199-1207 [FREE Full text] [doi: 10.1056/NEJMoa2001316] [Medline: 31995857]
10. Thomas R. Modelling space-time HIV/AIDS dynamics: applications to disease control. Soc Sci Med 1996 Aug;43(3):353-366. [doi: 10.1016/0277-9536(95)00396-7] [Medline: 8844937]
11. Chowell G, Viboud C. Is it growing exponentially fast? -- Impact of assuming exponential growth for characterizing and forecasting epidemics with initial near-exponential growth dynamics. Infect Dis Model 2016 Oct;1(1):71-78 [FREE Full text] [doi: 10.1016/j.idm.2016.07.004] [Medline: 28367536]
12. Viboud C, Simonsen L, Chowell G. A generalized-growth model to characterize the early ascending phase of infectious disease outbreaks. Epidemics 2016 Jun;15:27-37 [FREE Full text] [doi: 10.1016/j.epidem.2016.01.002] [Medline: 27266847]
13. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015 Jan 01;4:1 [FREE Full text] [doi: 10.1186/2046-4053-4-1] [Medline: 25554246]
14. McKenzie JE, Brennan SE. Synthesizing and presenting findings using other methods. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editors. Cochrane Handbook for Systematic Reviews of Interventions, Second Edition. Hoboken, NJ: Wiley; 2019:321-347.
15. Popay J, Roberts H, Sowden A, Petticrew M, Arai L, Rodgers M, et al. Guidance on the conduct of narrative synthesis in systematic reviews. Lanchester University. URL: https://www.lancaster.ac.uk/media/lancaster-university/content-assets/documents/fhm/dhr/chir/NSsynthesisguidanceVersion1-April2006.pdf [accessed 2022-09-28]
16. Whittemore R, Knafl K. The integrative review: updated methodology. J Adv Nurs 2005 Dec;52(5):546-553. [doi: 10.1111/j.1365-2648.2005.03621.x] [Medline: 16268861]
17. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016 Oct 12;355:i4919 [FREE Full text] [doi: 10.1136/bmj.i4919] [Medline: 27733354]
18. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019 Aug 28;366:l4898. [doi: 10.1136/bmj.l4898] [Medline: 31462531]

19. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg 2014 Dec;12(12):1495-1499 [FREE Full text] [doi: 10.1016/j.ijsu.2014.07.013] [Medline: 25046131]

Abbreviations

PICO: Problem, Intervention or Exposure, Comparison, Outcome
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
RoB 2: Risk of Bias 2
ROBINS-I: Risk of Bias in Nonrandomized Studies of Interventions
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Protocol

The Use of Segmental and Suprasegmental Sequencing Skills to Differentiate Children With and Without Childhood Apraxia of Speech: Protocol for a Comparative Accuracy Study

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Abstract

Background: Childhood apraxia of speech (CAS) is a motor-based speech sound disorder (SSD) with a core impairment in the planning and programming of spatiotemporal parameters of speech movement sequences. CAS may cause deficits in both segmental and suprasegmental components of speech, and it can severely affect children's ability to speak intelligibly and communicate effectively and impact their quality of life. Assessment tasks, such as the maximum performance tasks (MPT) and Syllable Repetition Task (SRT), examine children's segmental sequencing skills to assist with the diagnosis of CAS. In Hong Kong, although the MPT and SRT have been used clinically to diagnose CAS in Cantonese-speaking children, their validity has not been reported. There is an urgent need for such investigations. Suprasegmentally, lexical stress errors have been reported as a consensual feature and to aid in the diagnosis of CAS. However, there are challenges in diagnosing CAS in children who speak tonal languages like Cantonese. A recent study has reported lexical tone errors in Cantonese-speaking children with CAS. Furthermore, deficits in pitch-variation skills were found in Cantonese-speaking children with CAS using a tone sequencing task (TST). It is hypothesized that there is a universal deficit in pitch-variation skills among tonal and nontonal language speakers with CAS. Further investigations of pitch-variation skills using the TST in Cantonese-speaking children with CAS may shed light on suprasegmental deficits in tonal languages and contribute to the development of a valid diagnostic tool for CAS in children who speak other tonal languages, such as Vietnamese, Thai, and Mandarin.

Objective: This study aims to examine the diagnostic potential of the MPT, SRT, and TST in diagnosing Cantonese-speaking children with CAS and to investigate pitch-variation skills in Cantonese-speaking children with and without CAS.

Methods: A total of 25 children with CAS and 3 groups of age- and gender-matched controls (non-CAS SSD only group, non-CAS SSD co-occurring with language impairment group, and typical development group) will be recruited. All participants will perform the MPT, SRT, and TST measures. Their performances on these tools will be perceptually judged and acoustically measured.

Results: Data collection will last from January 1, 2022, to October 30, 2023. As of August 2022, the project has recruited 4 children in the CAS group, 21 children in the non-CAS SSD group, 4 children in the speech and language impairment group, and 53 children in the typical development group.

Conclusions: It is anticipated that Cantonese-speaking children with CAS will have poorer pitch-variation skills than the control groups and that the MPT, SRT, and TST will be appropriate diagnostic tools for identifying CAS in Cantonese-speaking children. The project will benefit the field of speech-language pathology locally and internationally, with short- and long-term impacts.

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KEYWORDS

childhood apraxia of speech; diagnosis; pitch variation

Introduction

Background

Childhood apraxia of speech (CAS) is a motor-based speech sound disorder (SSD) with a core impairment in planning and programming of spatiotemporal parameters of speech movement sequences. It can occur as an idiopathic neurogenic SSD or as a result of known neurological impairment [1]. It can severely affect children's ability to speak intelligibly and communicate effectively. CAS onsets from childhood and may persist into adolescence and adulthood [2-4]. If left untreated, the quality of life of children with CAS will be affected because of the long-term consequences of CAS on articulation, speech intelligibility, expressive language [5], academic performance, and social functioning [2-4,6,7].

CAS in children is characterized by deficits in both segmental and suprasegmental components of speech. The American Speech-Language-Hearing Association [1] reported that there are three consensual features, including (1) inconsistent errors in sequential repetitions; (2) deficits in coarticulation or syllable segregation (ie, choppy speech); and (3) prosodic deficits, especially lexical stress errors. Lexical stress errors, as one of the consensual features of CAS, have been widely studied in English speakers because of their high value as a suprasegmental marker of CAS [8]. The errors reflect underlying deficits in speech motor planning and programming skills that control the intensity, frequency, and duration of suprasegmental parameters. Deficits in the temporal control of lexical stress production have been documented, but it has been difficult to separate other specific acoustic aspects of lexical stress, such as pitch [9].

CAS Diagnosis in English-Speaking Children

The gold standard for making a CAS diagnosis primarily relies on perceptual judgments of CAS experts. However, very recently, a pilot study reported only moderate agreement among 4 expert listeners [10]. Along with perceptual judgment, the maximum performance tasks (MPT) [11] and Syllable Repetition Task (SRT) [12] have been reported to provide valuable relevant information about segmental sequencing skills in children with CAS. Both MPT and SRT assess deficits in speech processing. The MPT aims to assess motor involvement in children with speech problems [11]. Specifically, the maximum repetition rate for trisyllabic stimuli (MRRtri) and maximum fricative duration (MFD) in MPT assess underlying deficits in the motor planning and programming of speech [13], while the maximum repetition rate for monosyllabic stimuli and maximum phonation duration assess deficits in speech motor execution. The SRT targets encoding, memory, and transcoding processes, which refer to mapping, prearticulatory or phonological planning, and transformation of the phonological plan into a motor plan, respectively [14]. Although the terminology is not identical, both the MPT and SRT address the same underlying deficits of CAS, speech motor planning and programming skills. Research has shown that the MPT has high sensitivity and specificity (ranging from 89% to 100%) in making a CAS diagnosis [11], whereas a cutoff transcoding score of 80 on the SRT is able to differentiate children with CAS from children with concomitant speech delay and language impairment (LI) [15].

CAS Diagnosis in Cantonese-Speaking Children

There are challenges in diagnosing CAS in children who speak tonal languages like Cantonese. In Hong Kong, speech-language pathologists may apply English-based research findings to assess, diagnose, and treat children with CAS among the local Cantonese-speaking population. Although MPT and SRT have been used clinically to diagnose CAS in Cantonese-speaking children, the validity of applying these objective measures and diagnostic criteria from English-speaking populations to Cantonese-speaking populations is unknown. Owing to the segmental and suprasegmental differences between English and Cantonese, such as the fact that English has lexical stress patterns while Cantonese has lexical tones, English-based findings cannot be fully applied to Cantonese speakers with CAS, especially as prosodic deficits are one of the consensual clinical features of CAS. The current gold standard relies on expert perceptual judgment of clinical features reported in the English literature. Therefore, it is possible that misdiagnoses or underdiagnoses are occurring in the current clinical practice in Hong Kong. As higher frequency treatment is suggested for children with CAS [16] owing to the need for speech motor learning, inaccurate diagnoses may impact children, families, and society in terms of allocation of resources. Therefore, a valid diagnostic tool is urgently needed for Cantonese speakers with CAS to correctly identify and provide appropriate treatment to children with CAS.

Previous Pilot Studies

A recent study [14] identified a new clinical feature, namely tone production errors, which has not been reported in English speakers with CAS. The authors proposed that the same underlying deficit of speech motor planning and programming skills manifests differently in Cantonese and English [14]. Both English and Cantonese speakers with CAS may have similar control challenges with the correct production of segments; however, they control suprasegmentals differently because of linguistic differences. Suprasegmentals are overlaid differently for lexical stress in English versus lexical tone in Cantonese. English speakers apply 3 stress features—simultaneous pitch, loudness, and duration variations—to syllables to express a grammatical or pragmatic meaning. Cantonese speakers vary the pitch of segments to indicate different lexical meanings. Owing to these differences, further investigations of lexical tone errors are vital to increase the understanding of tone production skills in children with CAS.

In an effort to further explore tone production skills in Cantonese-speaking children with CAS, tone sequencing tasks (TSTs) have been used in 2 studies to examine the accuracy,

consistency, and duration of tone production in Cantonese-speaking children with CAS [17,18]. The TST is considered to be a potential assessment task that reflects impairment in speech motor planning and programming in Cantonese-speaking children with CAS [17,18]. It requires children to produce 5 repetitions of each item that is formed of 3 early-acquired Cantonese tones, that is, tone 1 (high-level), tone 2 (high-rising), and tone 4 (low-falling). Wong et al [18] administered the initial version of the TST to 2 Cantonese-speaking children with CAS and 2 Cantonese-speaking children with non-CAS SSDs. The results showed that children with CAS performed significantly more poorly than children without CAS in sequencing tones. The effect sizes (Cohen *d*) for tone accuracy and consistency were 0.68 and 0.60, respectively. Both of them were considered to be medium-to-large effect sizes.

In a subsequent study, the research team examined the linguistic effects of syllable structure and lexical status on TSTs using the second version of the TST [18]. A total of 4 Cantonese-speaking children with CAS were matched with 3 children with non-CAS speech and LI (S&LI), 3 with LI alone, and 3 with typical development (TD). Tone accuracy was judged perceptually and calculated as the percentage of tones correct. The consistency strength procedure adopted from the study by Williams et al [19] was used to calculate consistency scores. In the study by Wong et al [20], the team added 2 acoustic measures (ie, fundamental frequency [F0] values and acoustic duration) to further examine the data. The results showed both syllable structure and lexical status effects. Cantonese-speaking children with and without CAS showed significant between-group differences in F0 values for both vowel and consonant-vowel structures, as well as tone accuracy, tone consistency, and acoustic duration of word stimuli. A small to medium effect size (Cohen *d* ranging from 0.22 to 0.61) was obtained for F0 values, whereas large effect sizes were obtained for tone accuracy (Cohen *d* ranging from 1.37 to 1.98), tone consistency (Cohen *d* ranging from 1.36 to 1.85), and acoustic duration (Cohen *d* ranging from 0.9 to 1.45). The results suggest that syllable structure and lexical status play some roles in tone sequencing skills in children with CAS. In summary, these pilot studies suggest that children with CAS have difficulty with pitch-variation skills, specifically tone sequencing skills, and perform more poorly than control groups. The findings also support the diagnostic potential of TST as it provides a platform to investigate pitch variation in children with CAS and should be further developed as a linguistically appropriate assessment tool for Cantonese-speaking children. However, the generalizability of these findings is limited because of the extremely small sample sizes.

Studying Pitch-Variation Skills Using the TST

Pitch-variation skills refer to the skills of varying F0 values within and between syllables in tonal languages. Pitch-variation skills present in English lexical stress patterns and Cantonese lexical tones. Although lexical stress errors have been empirically studied and it has been found that children with CAS have a deficit in the temporal control of lexical stress productions [9], the development and disorders of pitch-variation skills embedded in lexical stress errors remain unknown. Kopera and Grigos [9] attempted to examine the acoustic properties (ie, duration, peak F0, and average F0) of lexical stress errors using the pairwise variability index [21] between children with and without CAS. No significant between-group difference was found. The authors concluded that lexical stress errors in children with CAS can only be studied in a collective fashion, such as using the lexical stress ratio [8], which examines pitch, loudness, and duration simultaneously, instead of investigating acoustic parameters independently.

Nevertheless, new findings have shown significant between-group differences in both F0 values and acoustic duration between children with CAS and control groups [20]. This preliminary result suggests that Cantonese-speaking children with CAS have difficulty in varying pitch and that pitch-variation skills in Cantonese speakers with CAS can be studied independently via the TST in the context of this tonal language. This provides the basis for further investigations of pitch-variation skills in children with CAS who speak other tonal languages (eg, Mandarin, Vietnamese, and Thai) as well as children with CAS who speak nontonal languages (eg, English). TST can be used in English to assess pitch-variation skills in children with CAS in an out-of-stress context. This application may elucidate the role of pitch control in out-of-stress contexts and shed light on pitch control across languages in speakers with CAS.

The Goal of the Proposed Study

This study aims the following:

1. To show that the MPT and SRT can contribute to the diagnosis of CAS in Cantonese-speaking children.
2. To document differences in pitch-variation skills in Cantonese-speaking children with versus without CAS.
3. To prove that TSTs are effective in diagnosing CAS in Cantonese-speaking children.

We hypothesized the following:

1. The MPT and SRT would differentiate Cantonese-speaking children with CAS from those without CAS.
2. Cantonese-speaking children with CAS would have significantly poorer pitch-variation skills than the control groups.
3. TSTs would differentiate Cantonese-speaking children with CAS from those without CAS.

Methods

Protocol Version

The original version of the protocol was submitted to the Research Grants Council of the Hong Kong Special Administrative Region Government on October 30, 2020. This protocol is version 2, in which the sample size was changed from 120 to 100 children. This change was approved by the Research Grants Council on May 17, 2022.

Study Design

This is a comparative accuracy study that will compare the diagnostic accuracy of the MPT, SRT, and TST in children with and without CAS.

Participants

A total of 25 children with CAS will be recruited for the study. The inclusion criteria are as follows: (1) age between 3 years and 6 years 11 months, (2) diagnosed with or suspected of having CAS by a qualified speech-language pathologist, (3) no hearing impairment or structural abnormality that affects speech production, and (4) Cantonese as the main language for daily communication. The same number of age- and gender-matched children will be recruited for each of the following 3 control groups: non-CAS SSDs only, non-CAS SSDs co-occurring with S&LI, and TD. The non-CAS SSD group will be recruited because it will allow a direct comparison between children with and without CAS. Research has shown that LI is usually present in children with CAS [5]; therefore, an S&LI group will be included to compare the performance of children with and without CAS, while controlling for language skills. A total of 100 participants will be recruited. Originally, a sample size of 172 participants (ie, 43 for each group) was estimated from the effect size of tone accuracy in a pilot study [20] via power analysis. An actual power of 0.954 could be achieved from 172 participants with an error probability of 0.05 (F_{168}=2.658). There should be sufficient children with CAS in this population. However, taking into consideration the time and effort needed to screen and find suitable participants with and without CAS, SSD, and S&LI, it will be very challenging to recruit 172 participants within 2 years (the proposed study period). In addition, many reported studies [22,23] have only recruited 20 to 30 children with CAS for the investigations of assessment and diagnostic accuracy. Therefore, the total sample size was reduced to 100 participants.

Recruitment

A recent study estimated the population-based prevalence of CAS in children aged 4 to 8 years to be 1 child per 1000 [24]. Given that there were about 303,000 children between the ages of 5 and 9 years in Hong Kong in the mid-2020 [25], there may be 303 children in this age range in Hong Kong who are currently impacted by this severe motor speech disorder. Children were recruited through local advertising and invitations. Recruitment posters were posted in the university campus and on the web via social media platforms. The digital version of the posters was posted on the official Facebook page of the university speech-language therapy clinic, the Facebook page and Instagram accounts of Cantonese CAS, and the personal Facebook and Instagram accounts of the members of the research team. For the CAS group, recruitment information was also delivered to speech-language pathologists who attended local continuing education seminars on Cantonese CAS. Personal invitations were sent to the parents of children with CAS who have connections with the research team. The non-CAS groups were recruited from the general public by forwarding the digital posters to the parents of preschool children on WhatsApp chat groups, inviting parents of the children who were receiving speech-language therapy services in the university clinic, and sending invitation emails to kindergartens located in the same district as the university.

Procedure

Initial Assessment

An expert speech-language pathologist will conduct initial assessments to diagnose each participant, if appropriate. The expert speech-language pathologist will have at least 10 years of clinical experience in assessing and treating Cantonese-speaking children with and without CAS. The assessment tasks include case history, speech sample collection, standardized language tests (ie, Hong Kong Test of Preschool Oral Language [Cantonese] [26] and Hong Kong Cantonese Receptive Vocabulary Test [27]), standardized articulation test (ie, Hong Kong Cantonese Articulation Test [28]), imitation of polysyllabic words, a standardized tone identification test (ie, Cantonese Tone Identification Test [29]), an oral and speech motor control assessment [30], and the documentation of prosodic characteristics. If a child is suspected to have autism spectrum disorder (ASD), the expert speech-language pathologist will conduct further assessments. According to Tierney et al [31], there is high comorbidity between CAS and ASD. The diagnosis of CAS and ASD may be delayed or inaccurate when both conditions are present in a child; children with CAS may be wrongly diagnosed with ASD and vice versa. Therefore, the Autism Diagnostic Observation Schedule, Second Edition [32], a standardized tool with high specificity and sensitivity for diagnosing ASD [33], will be administered to obtain information about the appropriateness of an ASD diagnosis. The assessment session will be audio- and video recorded so that another expert speech-language pathologist can review the assessments and diagnose independently. The CAS diagnosis will be confirmed if both speech-language pathologists reach a consensus on the presence of CAS features.

The diagnosis of CAS will be confirmed based on international standards and the methods used in our previous pilot study [20]. A CAS diagnosis will be based on the presence of 3 consensual features [1] and 4 clinical features that have reported 91% diagnostic accuracy [22], with appropriate modifications for Cantonese-speaking children, and across different assessment tasks (eg, speech sample, imitation of polysyllabic words, standardized articulation test, and diadochokinetic tasks). Murray et al [22] suggest using (1) syllable segregation, (2) lexical stress matches, (3) percent phonemes correct from polysyllabic words, and (4) articulatory accuracy on repetitions of [p t k] for the differential diagnosis of CAS. Modification of some of these features is necessary for Cantonese. The second feature will be changed to *lexical tone errors* owing to the prosodic differences between English and Cantonese. The third feature will be changed from both segmental and suprasegmental correctness to only segmental correctness because of the constant duration of Cantonese syllables [34]. This set of criteria was used in our previous pilot study [20].

MPT and SRT

Every child will perform the MPT, SRT, and TST. The order of administration will be randomized. The administrative procedures and interpretation of MPT and SRT are described in the studies by Rvachew et al [35] and Rvachew and Matthews [15], respectively. There are four tasks in the MPT, including (1) maximum phonation duration, (2) MFD, (3) maximum

repetition rate for monosyllabic stimuli, and (4) MRRtri. A total of 6 scores can be obtained from these tasks [11]. A dyspraxia score of 0, 1, or 2 is obtained from the performances of MFD and MRRtri. A dyspraxia score of 2 indicates the presence of CAS in children.

The SRT includes 18 items [12]. The items are formed of early developing phones (eg, [m], [d], [n], and [a]), which are easier for younger or severely impaired children to produce. The items included eight 2-syllable stimuli (eg, [bada]), six 3-syllable stimuli (eg, [bamana]), and four 4-syllable stimuli (eg, [bamadana]). The SRT gives 4 scores, including a competency score, an encoding score, a memory score, and a transcoding score. The interpretation of these 4 scores is based on z-scores from the means and SDs reported in the study by Lohmeier and Shriberg [36]. Table 1 presents a comparison of MPT and SRT.

Most of the stimuli used in the MPT and SRT are shared between English and Cantonese. For example, the vowel [a] and initial consonants [m], [f], and [s] in the MPT and SRT are shared in Cantonese. Although the voiced consonants [b] and [d] and voiceless consonants [p], [t], and [k] in English cannot be found in Cantonese, these sounds can be replaced by voiceless unaspirated [p] and [t] and voiceless aspirated [p^h], [t^h], and [k^h] in Cantonese. This replacement is logical as, from a motor perspective, the contrastive aspiration feature in Cantonese consonants is similar to the voicing feature in English consonants [38]. With this logical replacement, it is anticipated that the SRT and MPT will be useful in differentiating between Cantonese speakers with and without CAS, as has been proven in English and Dutch speakers [11,15].

Table 1. Comparison of the maximum performance tasks (MPT) and Syllable Repetition Task (SRT).

	MPT [11]	SRT [12]
Area assessed	• Motor planning and programming of speech	• Encoding process (mapping) • Memory process (prearticulatory or phonological planning) • Transcoding process (transformation of the phonological plan into a motor plan)
Scores	• MPD[a]: mean duration of the longest prolongation of [a] and [mama] • MFD[b]: mean duration of the longest prolongation of [s], [f], and [z] • MRRmono[c] score: mean repetition rate for the fastest repetition of each [pa], [ta], and [ka] • MRRtri[d] score: number of syllables produced per second in the child's fastest repetition of [p t k] • Sequence score: 1 for correct sequence and 0 for unsuccessful production • Attempt score: number of attempts required to produce the correct sequence	• Competency: PCC[e] of 18 items • Encoding: percentage of consonants within-manner class substitution errors (excluding voicing errors) • Memory: ratio of PCC for 3-syllable items to PCC for 2-syllable items • Transcoding: percentage of items that are produced with ≥1 additions
Interpretation of the scores	• MFD and MRRtri scores are used to obtain a dyspraxia score (0, 1, or 2), while MPD and MRRmono scores are used to obtain a dysarthria score (0, 1, or 2)	• Interpretation of these 4 scores is made based on the z-scores from the means and SDs reported in the study by Lohmeier and Shriberg [36]

Criteria of CAS[f] diagnosis	• A dyspraxia score of 2 indicates the presence of CAS; it is obtained when
	  • MRRtri ≤3.4 or
	  • Sequence=0 or
	  • Dyspraxia score is not 0 or 1
		• Cutoff scores for CAS diagnosis [37]:
		  • Competency score=65
		  • Encoding score=46.9
		  • Memory score=67.5
		  • Transcoding score=80

[a]MPD: maximum phonation duration.

[b]MFD: maximum fricative duration.

[c]MRRmono: maximum repetition rate for monosyllabic stimuli.

[d]MRRtri: maximum repetition rate for trisyllabic stimuli.

[e]PCC: percentage of consonants correct.

[f]CAS: childhood apraxia of speech.

TST Procedure

The TST proposed in this study is a shorter version modified based on the findings in the study by Wong et al [18]. This new version of TST has 16 stimuli, derived from 2 vowel structures, 2 consonant-vowel structures with early acquired sounds, and 3 early acquired Cantonese tones. The details of the TST are listed in Table 2. There are twelve 1-syllable items and four 3-syllable items. Both word and nonword stimuli are included. The participants will repeat each item as fast as they can 5 times. Four outcome measures will be obtained from the TST:

1. Tone accuracy will be calculated from perceptual judgments of correctness.
2. Tone consistency will be calculated using the consistency strength formula described in the study by Williams et al [19]. The 5 repetitions of each stimulus will be compared with the children's own baseline one by one to determine the consistency strength of that production.
3. F0 values will be measured using Praat. F0 will be estimated at 5 evenly spaced time points (0%, 25%, 50%, 75%, and 100%) from the beginning to the end of the voiced segment of each syllable in the TST [39].
4. Acoustic durations will be measured in Praat from the onset of the first syllable to the end of the last syllable.

All assessment sessions will be conducted at a local university clinic or laboratory, and all data collection sessions will be conducted in the soundproof booth in the laboratory. Children's performances on the MPT, SRT, and TST will be audio- and video-recorded. Two speech-language pathologists with experience in childhood disordered speech will perceptually transcribe children's productions using narrow transcription and score their performance. Furthermore, 20% of the ratings will be rerated by the speech-language pathologists to determine intra- and interrater reliability.

Table 2. Stimuli of tone sequencing task (TST) for the proposed study.

TST type	Structure	
	Vowel	Consonant-vowel
TSTmono[a]		
	[a1[b]][c]×5	[pa1][c]×5
	[a2[d]][c]×5	[pa2][c]×5
	[a4[e]][c]×5	[pa4][c]×5
	[u1]×5	[hu1]×5
	[u2]×5	[hu2]×5
	[u4]×5	[hu4]×5
TSTtri[f]		
	[a1a2a4]×5	[pa1pa2pa4]×5
	[u1u2u4]×5	[hu1hu2hu4]×5

[a]TSTmono: tone sequencing task for monosyllabic stimuli.

[b]The number 1 indicates high-level tone in Cantonese.

[c]Indicates word stimuli (the others are nonword stimuli).

[d]The number 2 indicates high-rising tone in Cantonese.

[e]The number 4 indicates low-falling tone in Cantonese.

[f]TSTtri: tone sequencing task for trisyllabic stimuli.

Statistical Methods

For the statistical analysis, linear mixed-effects models will be used. Our models will include group (CAS vs SSD vs S&LI vs TD) as a fixed effect and participants and items as random effects.

The sensitivity and specificity of the MPT, SRT, and TST in making a diagnosis of CAS in Cantonese-speaking children will be determined using the receiver operating characteristics curve [40]. The new cutoff scores of the MPT and SRT to diagnose CAS in Cantonese-speaking children will be compared with the existing cutoff scores recommended for English-speaking children. The cutoff scores for the TST will also be determined from the receiver operating characteristics curve.

Ethics Approval

An information sheet and informed consent form will be given to the parents or guardians of the child participants before the initial assessment or data collection sessions. All parents or guardians will be asked to provide consent by signing the informed consent form given. The parents or guardians of the participants will be informed that their participation is voluntary and that they can withdraw their children at any time without giving a reason and without any negative consequences. All the information provided by the participants and their parents or guardians will be handled confidentially and anonymously, which means that all the data from which the participants can be identified will be removed. All the data will be encrypted and stored in a repository with restricted access. Only researchers working on this study will have access to personal and research data for the purposes of this study. This study has received ethical approval from the Hong Kong Polytechnic University Institutional Review Board (HSEARS 20210125011 and HSEARS 20210330007). Responsible members of Hong Kong Polytechnic University may be given access for monitoring and auditing the research. Any important changes in the protocol will be informed to the Hong Kong Polytechnic University Institutional Review Board.

Results

Data collection started in January 2022 but was soon disrupted by the fifth wave of the COVID-19 pandemic in Hong Kong. As of August 2022, the project has recruited 4 children in the CAS group, 21 children in the non-CAS SSD group, 4 children in the S&LI group, and 53 children in the TD group. Data collection is ongoing and will continue until October 2023.

Discussion

Principal Findings

The proposed study will address an important clinical research gap owing to which there is an urgent need for a valid diagnostic tool for Cantonese speakers with CAS. In particular, we aimed (1) to show that the MPT and SRT can contribute to the diagnosis of CAS in Cantonese-speaking children, (2) to document differences in pitch-variation skills in Cantonese-speaking children with versus without CAS, and (3) to prove that TSTs are effective for diagnosing CAS in Cantonese-speaking children.

Comparison With Prior Work

With reference to previous investigations of the TST [17,20], it is anticipated that Cantonese-speaking children with CAS will have significantly poorer pitch-variation skills than the control groups. Specifically, Cantonese speakers with CAS will show less variations in F0 values, longer acoustic repetition durations, lower percentages of tones correct, and lower consistency than those in the control groups. It is further anticipated that TST, like MPT and SRT, will be shown to be effective for diagnosing CAS in Cantonese speakers, with appropriate sensitivity and specificity.

Strengths and Limitations

On completion, this study will provide 2 objective measures (ie, MPT and TST) and 2 measures that convert perceptual judgments into quantitative data (ie, SRT and TST) for diagnosing CAS in Cantonese speakers. The results will promote the standard of CAS diagnosis in Cantonese speakers from reliance on expert perceptual judgment based on a list of clinical features [41] to a combination of perceptual judgment and quantitative data. In addition, the short administration time of the measures proposed in this study (ie, approximately 15-20 minutes per measure) will provide clinicians with quick and accurate methods for CAS diagnosis in Cantonese speakers than approximately 2 hours of comprehensive assessment [18,41,42] of speech motor skills reported in the literature. Moreover, the results of this study will provide the basis for further investigations of pitch-variation skills in children with CAS who speak other tonal languages (eg, Mandarin, Vietnamese, and Thai) as well as in children with CAS who speak nontonal languages (eg, English). Finally, investigations of the effects of linguistic elements (such as the lexical status, syllable structure, number of syllables, and syllable position) on children's pitch-variation skills or speech motor control will provide information on how the linguistic elements of Cantonese interact with speech motor planning and programming skills.

This study faces several challenges. First, data collection started in January 2022 but was disrupted owing to the fifth wave of the COVID-19 pandemic in Hong Kong. Restrictions on face-to-face interactions during the fifth wave forced the cessation of data collection for several months. Although the fifth wave is now over, the parents of participants are still concerned about mask-off activities during data collection, resulting in slow progress in data collection. Second, the study is recruiting either patients with CAS with an existing CAS diagnosis or individuals suspected of having CAS by a qualified speech-language pathologist. However, a recent study has shown that about half of the Hong Kong speech-language pathologist respondents to a questionnaire (36/77, 47%) had never worked with children with CAS or suspected CAS. Furthermore, a majority of the respondents (64/77, 83%) rated their understanding of Cantonese CAS as "a little" or "fair" [43]. This may be because of a possible low prevalence of CAS in Hong Kong or limited understanding of CAS among local clinicians. Both factors could have limited participant recruitment in this study. In an effort to solve these problems, the research team has provided continuing education opportunities for local speech-language pathologists to enhance their understanding of CAS among Cantonese speakers. In addition, the research team may extend participant recruitment to Macau, another special administrative region of China, because, as in Hong Kong, the people of Macau also use Cantonese as their primary language for oral communication. Third, coexisting developmental issues in the participants may limit the results of this study. Owing to the challenge of recruiting participants with CAS, the research team will not control for coexisting developmental conditions in the participants, such as intellectual disability and ASDs, which may affect the speech production skills of the participants. The research team is aware of this limitation and will balance the sample size and coexisting developmental conditions of the participants.

Dissemination Plan

This project will benefit the field of speech-language pathology locally and internationally. Locally, the results of this study will be shared with speech-language pathologists through continuing education seminars and conferences. Owing to the limited understanding of CAS in Cantonese speakers, the professional training of local speech-language pathologists currently does not adequately address this severe pediatric SSD. Postqualification continuing education is frequently requested. A study has shown that an understanding of CAS in Cantonese speakers is lacking. Even experienced speech-language pathologists are not confident in using criteria for making a differential diagnosis of CAS in Cantonese-speaking children [44]. The challenge of making such an accurate diagnosis will be ameliorated through the dissemination of these results. If this study finds that the 2 existing diagnostic tools (ie, MPT and SRT) and the potential tool (ie, TST) are effective in differentiating Cantonese-speaking children with CAS from those without CAS, local clinical practices will benefit directly from the study findings and the related assessment package. speech-language pathologists will be more confident in diagnosing children with CAS and providing appropriate

treatment, subsequently improving the quality of life of children with CAS and their families. In addition, the local professional training of speech-language pathologists will be enhanced with more data from the local population. The benefit will further extend to society as a medium-term impact, when the appropriate amount of speech-language therapy time is allocated according to valid CAS diagnoses.

Internationally, the results of this study will be shared with other academics through publications in international peer-reviewed journals with open-access and via international conferences. We anticipate that there will be an increased understanding of pitch-variation skills in Cantonese-speaking children with CAS. We also hope to provide a potential diagnostic tool for CAS. This will serve as the basis for further investigations of pitch-variation skills in children who speak other tonal languages, such as Mandarin, Vietnamese, and Thai, and may lead to the development of the TST as a diagnostic tool for CAS in children learning these languages. The results of this study may also provide insight into pitch-variation skills in children with CAS, regardless of their language background. Given that the same underlying deficits in speech motor planning and programming skills manifest differently among different languages [14], this project will have theoretical implications that will impact future international investigations. Ballard et al [21] stated that "exploring additional speaking contexts would be valuable in fully understanding how control of f0 develops over time in children." If the results show that degraded pitch-variation skills are one of the deficits in children with CAS, the TST can be applied to speakers of English (or other nontonal languages) in an out-of-stress context. This application may shed light on the role of pitch control in out-of-stress contexts and confirm the existence of deficits in pitch control in speakers with CAS across languages.

Future Investigations

The results of this study will also provide a basis for further investigations of pitch-variation skills in other disordered populations, such as ASDs, hearing impairment, developmental language disorders, acquired apraxia of speech, and aphasia. In the long term, theoretical knowledge about pitch-variation skills in disordered populations will be acquired and applied by frontline health care professionals. In addition to the MPT and SRT, the TST will become a vital component of the assessment process for children with communication disorders.

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Data Availability

The data sets generated and analyzed during this study are not publicly available but can be obtained from the corresponding author on reasonable request.

Authors' Contributions

MNW is the principal investigator of this grant application, while ECHW and SLV are coinvestigators. ECHW took the lead in designing the study and writing the protocol, while MNW and SLV provided supervision. All authors read and approved the final manuscript and contributed to the drafting and revision of the manuscript. ECHW will take the lead in the collection, management, analysis, and interpretation of the data, writing of the report, and publication of the report. MNW will oversee the whole project and provide support for data collection and analysis. MNW and SLV will provide supervision in the analysis and interpretation of the data and in the writing and publication of the report.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review reports from the General Research Fund and Early Career Scheme Research Grants Council of the Hong Kong Special Administration Region Government.
[PDF File (Adobe PDF File), 570 KB - resprot_v11i10e40465_app1.pdf]

References

1. Childhood apraxia of speech. American Speech Language Hearing Association. 2007. URL: https://www.asha.org/policy/tr2007-00278/ [accessed 2022-08-02]
2. Jakielski K. Persistent speech and language needs of children and teens with CAS. 2008 Presented at: National Conference on Childhood Apraxia of Speech; Jul, 2008; Williamsburg, VA. [doi: 10.1044/policy.tr2007-00278]

3. Miller GJ, Lewis B, Benchek P, Freebairn L, Tag J, Budge K, et al. Reading outcomes for individuals with histories of suspected childhood apraxia of speech. Am J Speech Lang Pathol 2019 Nov 19;28(4):1432-1447. [doi: 10.1044/2019_ajslp-18-0132]
4. Turner S, Vogel A, Parry-Fielder B, Campbell R, Scheffer I, Morgan A. Looking to the future: speech, language, and academic outcomes in an adolescent with childhood apraxia of speech. Folia Phoniatr Logop 2019 Jul 22;71(5-6):203-215 [FREE Full text] [doi: 10.1159/000500554] [Medline: 31330526]
5. Lewis BA, Freebairn LA, Hansen AJ, Iyengar SK, Taylor HG. School-age follow-up of children with childhood apraxia of speech. Lang Speech Hear Serv Sch 2004 Apr;35(2):122-140. [doi: 10.1044/0161-1461(2004/014)]
6. Hill N. Social functioning characteristics of a young adult with a history of childhood apraxia of speech. Duquesne University. 2016 Jan 1. URL: https://dsc.duq.edu/cgi/viewcontent.cgi?article=1096&context=etd [accessed 2022-08-02]
7. McCabe P, Murray E, Thomas D. Evidence summary - childhood apraxia of speech – January 2020. The University of Sydney. 2020. URL: https://www.apraxia-kids.org/wp-content/uploads/2020/07/CAS_evidence_brief_2020.pdf [accessed 2022-08-02]
8. Shriberg LD, Campbell TF, Karlsson HB, Brown RL, McSweeny JL, Nadler CJ. A diagnostic marker for childhood apraxia of speech: the lexical stress ratio. Clin Linguist Phon 2003 Jul 09;17(7):549-574. [doi: 10.1080/0269920031000138123] [Medline: 14608799]
9. Kopera HC, Grigos MI. Lexical stress in childhood apraxia of speech: acoustic and kinematic findings. Int J Speech Lang Pathol 2020 Feb 11;22(1):12-23 [FREE Full text] [doi: 10.1080/17549507.2019.1568571] [Medline: 30744428]
10. Murray E, Velleman S, Preston J, McCabe P, Heard R. Speaking the same language? Developing a rating form for diagnostic features of childhood apraxia of speech. 2020 Presented at: Motor Speech Conference; Feb 20-23, 2020; Santa Barbara, CA, USA.
11. Thoonen G, Maassen B, Gabreels F, Schreuder R. Validity of maximum performance tasks to diagnose motor speech disorders in children. Clin Linguist Phon 2009 Jul 09;13(1):1-23. [doi: 10.1080/026992099299211]
12. Shriberg LD, Lohmeier HL, Campbell TF, Dollaghan CA, Green JR, Moore CA. A nonword repetition task for speakers with misarticulations: the Syllable Repetition Task (SRT). J Speech Lang Hear Res 2009 Oct;52(5):1189-1212. [doi: 10.1044/1092-4388(2009/08-0047)]
13. Diepeveen S, van Haaften L, Terband H, de Swart B, Maassen B. A standardized protocol for maximum repetition rate assessment in children. Folia Phoniatr Logop 2019 Jun 28;71(5-6):238-250 [FREE Full text] [doi: 10.1159/000500305] [Medline: 31256159]
14. Wong EC, Lee KY, Tong MC. The applicability of the clinical features of English childhood apraxia of speech to Cantonese: a modified Delphi survey. Am J Speech Lang Pathol 2020 May 08;29(2):652-663. [doi: 10.1044/2019_ajslp-19-00118]
15. Rvachew S, Matthews T. Using the syllable repetition task to reveal underlying speech processes in childhood apraxia of speech: a tutorial. Can J Speech Lang Pathol Audiol 2017;41(1):106-126.
16. Kaipa R, Peterson AM. A systematic review of treatment intensity in speech disorders. Int J Speech Lang Pathol 2016 Dec 24;18(6):507-520. [doi: 10.3109/17549507.2015.1126640] [Medline: 27063688]
17. Wong E, Lee K, Tong M. Tone sequencing in childhood apraxia of speech: a pilot study. 2019 Presented at: 31st World Congress of IALP; Aug 18-22, 2019; Taipei, Taiwan.
18. Wong E, Lee K, Tong M. Sequencing lexical tone in children with childhood apraxia of speech: Preliminary results. 2020 Presented at: Motor Speech Conference 2020; Feb 20-23, 2020; Santa Barbara, CA.
19. Stackhouse PW. Rate, accuracy and consistency: diadochokinetic performance of young, normally developing children. Clin Linguist Phon 2009 Jul 09;14(4):267-293. [doi: 10.1080/02699200050023985]
20. Wong EC, Velleman SL, Tong MC, Lee KY. Pitch variation in children with childhood apraxia of speech: preliminary findings. 2021 Jun 18;30(3S):1511-1524. [doi: 10.1044/2021_ajslp-20-00150]
21. Ballard KJ, Djaja D, Arciuli J, James DG, van Doorn J. Developmental trajectory for production of prosody: lexical stress contrastivity in children ages 3 to 7 years and in adults. J Speech Lang Hear Res 2012 Dec;55(6):1822-1835. [doi: 10.1044/1092-4388(2012/11-0257)]
22. Murray E, McCabe P, Heard R, Ballard KJ. Differential diagnosis of children with suspected childhood apraxia of speech. J Speech Lang Hear Res 2015 Feb;58(1):43-60. [doi: 10.1044/2014_jslhr-s-12-0358]
23. Strand EA, McCauley RJ, Weigand SD, Stoeckel RE, Baas BS. A motor speech assessment for children with severe speech disorders: reliability and validity evidence. J Speech Lang Hear Res 2013 Apr;56(2):505-520. [doi: 10.1044/1092-4388(2012/12-0094)]
24. Shriberg LD, Kwiatkowski J, Mabie HL. Estimates of the prevalence of motor speech disorders in children with idiopathic speech delay. Clin Linguist Phon 2019 Apr 15;33(8):679-706 [FREE Full text] [doi: 10.1080/02699206.2019.1595731] [Medline: 30987467]
25. Table 1A : population by sex and age group. Census and Statistics Department The Government of the Hong Kong Special Administrative Region. URL: https://www.censtatd.gov.hk/hkstat/sub/sp150.jsp?tableID=002&ID=0&productType=8 [accessed 2022-08-02]
26. Child Assessment Services. The Hong Kong Test of Preschool Oral Language (Cantonese). Hong Kong SAR, China: Hong Kong SAR: Child Assessment Services; 2019.

27. Lee KY. The Hong Kong Cantonese Receptive Vocabulary Test. Hong Kong: The Hong Kong Society for Child Health and Development; 1996.
28. Cheung P, Ng A, To CK. Hong Kong Cantonese articulation test. Hong Kong SAR, China: Hong Kong Language Inform Sci Res Centre and City University of Hong Kong; 2006.
29. Lee K. Cantonese Tone Identification Test (CANTIT). Hong Kong SAR, China: Department of Otorhinolaryngology, Head and Neck Surgery, The Chinese University of Hong Kong; 2012.
30. Robbins J, Klee T. Clinical assessment of oropharyngeal motor development in young children. J Speech Hear Disord 1987 Aug;52(3):271-277. [doi: 10.1044/jshd.5203.271] [Medline: 3455449]
31. Tierney C, Mayes S, Lohs S, Black A, Gisin E, Veglia M. How valid is the checklist for autism spectrum disorder when a child has apraxia of speech? J Dev Behav Pediatr 2015 Oct;36(8):569-574. [doi: 10.1097/DBP.0000000000000189] [Medline: 26114615]
32. Lord C, Rutter M, DilLavore PC, Risi S. Autism Diagnostic Observation Schedule. Torrance, CA, US: Western Psychological Services; Jun 24, 2010.
33. Randall M, Egberts KJ, Samtani A, Scholten RJ, Hooft L, Livingstone N, et al. Diagnostic tests for autism spectrum disorder (ASD) in preschool children. Cochrane Database Syst Rev 2018 Jul 24;7:CD009044 [FREE Full text] [doi: 10.1002/14651858.CD009044.pub2] [Medline: 30075057]
34. Peng G. Temporal and tonal aspects of Chinese syllables: a corpus-based comparative study of Mandarin and Cantonese. J Chinese Linguistics 2006 Jan;34(1):134-154.
35. Rvachew S, Hodge M, Ohberg A. Obtaining and interpreting maximum performance tasks from children: a tutorial. J Speech Lang Pathol Audiol 2005;29(4):146 [FREE Full text]
36. Lohmeier H, Shriberg L. Reference data for the Syllable Repetition Task (SRT). University of Wisconsin-Madison. 2011 Nov. URL: https://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.720.832&rep=rep1&type=pdf [accessed 2022-08-02]
37. Shriberg LD, Lohmeier HL, Strand EA, Jakielski KJ. Encoding, memory, and transcoding deficits in childhood apraxia of speech. Clin Linguist Phon 2012 May 10;26(5):445-482 [FREE Full text] [doi: 10.3109/02699206.2012.655841] [Medline: 22489736]
38. Whitehill TL. Studies of Chinese speakers with dysarthria: informing theoretical models. Folia Phoniatr Logop 2010 Apr 29;62(3):92-96 [FREE Full text] [doi: 10.1159/000287206] [Medline: 20424463]
39. Ma JK, Ciocca V, Whitehill TL. Effect of intonation on Cantonese lexical tones. J Acoust Soc Am 2006 Dec;120(6):3978-3987. [doi: 10.1121/1.2363927] [Medline: 17225424]
40. Hajian-Tilaki K. Receiver operating characteristic (ROC) curve analysis for medical diagnostic test evaluation. Caspian J Intern Med 2013;4(2):627-635 [FREE Full text] [Medline: 24009950]
41. Wong E, Wong M, Velleman S. Assessment and diagnostic standards of apraxia of speech in Chinese-speaking adults and children: a scoping review. 2022:1 (forthcoming).
42. Wong EC, Wong MN, Velleman SL, Tong MC, Lee KY. Lexical tone perception and production in Cantonese-speaking children with childhood apraxia of speech: a pilot study. 2022 Jun 09:1-14. [doi: 10.1080/02699206.2022.2074310] [Medline: 35678458]
43. Wong E, Wong M, Velleman S. A survey study of clinical management of childhood apraxia of speech in Hong Kong. 2022 Presented at: Apraxia Kids Research Symposium 2022; Jul 7-9, 2022; Las Vegas, NV.
44. Wong E. Development of a treatment protocol for Cantonese-speaking children with childhood apraxia of speech : case study. 2017 Sep. URL: https://repository.lib.cuhk.edu.hk/tc/item/cuhk-1839387 [accessed 2022-08-02]

Abbreviations

ASD: autism spectrum disorder
CAS: childhood apraxia of speech
F0: fundamental frequency
LI: language impairment
MFD: maximum fricative duration
MPT: maximum performance tasks
MRRtri: maximum repetition rate for trisyllabic stimuli
S&LI: speech and language impairment
SRT: Syllable Repetition Task
SSD: speech sound disorder
TD: typical development
TST: tone sequencing task

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Protocol

Medication Adherence and Cardiometabolic Control Indicators Among American Indian Adults Receiving Tribal Health Services: Protocol for a Longitudinal Electronic Health Records Study

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Abstract

Background: American Indian adults have the highest prevalence of type 2 diabetes (T2D) in any racial or ethnic group and experience high rates of comorbidities. Uncontrolled cardiometabolic risk factors—insulin resistance, resulting in impaired glucose tolerance, dyslipidemia, and hypertension—increase the risk of mortality. Mortality is significantly reduced by glucose- and lipid-lowering and antihypertensive medication adherence. Medication adherence is low among American Indian adults living in non–Indian Health Service health care settings. Virtually nothing is known about the nature and extent of medication adherence among reservation-dwelling American Indian adults who primarily receive their medications without cost from Indian Health Service or tribal facilities. Electronic health records (EHRs) offer a rich but underused data source regarding medication adherence and its potential to predict cardiometabolic control indicators (C-MCIs). With the support of the Choctaw Nation of Oklahoma (CNO), we address this oversight by using EHR data generated by this large, state-of-the-art tribal health care system to investigate C-MCIs.

Objective: Our specific aims are to determine, using 2018 EHR data, the bivariate relationships between medication adherence and C-MCIs, demographics, and comorbidities and each C-MCI and demographics and comorbidities; develop machine learning models for predicting future C-MCIs from the previous year's medication adherence, demographics, comorbidities, and common laboratory tests; and identify facilitators of and barriers to medication adherence within the context of social determinants of health (SDOH), EHR-derived medication adherence, and C-MCIs.

Methods: Drawing on the tribe's EHR (2018-2021) data for CNO patients with T2D, we will characterize the relationships among medication adherence (to glucose- and lipid-lowering and antihypertensive drugs) and C-MCIs (hemoglobin A1c ≤7%, low-density lipoprotein cholesterol <100 mg/dL, and systolic blood pressure <130 mm Hg); patient demographics (eg, age, sex, SDOH, and residence location); and comorbidities (eg, BMI ≥30, cardiovascular disease, and chronic kidney disease). We will also characterize the association of each C-MCI with demographics and comorbidities. Prescription and pharmacy refill data will be used to calculate the proportion of days covered with medications, a typical measure of medication adherence. Using machine learning techniques, we will develop prediction models for future (2019-2021) C-MCIs based on medication adherence, patient demographics, comorbidities, and common laboratory tests (eg, lipid panel) from the previous year. Finally, key informant interviews (N=90) will explore facilitators of and barriers to medication adherence within the context of local SDOH.

Results: Funding was obtained in early 2022. The University of Florida and CNO approved the institutional review board protocols and executed the data use agreements. Data extraction is in process. We expect to obtain results from aims 1 and 2 in 2024.

Conclusions: Our findings will yield insights into improving medication adherence and C-MCIs among American Indian adults, consistent with CNO's State of the Nation's Health Report 2017 goal of reducing T2D and its complications.

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KEYWORDS

medication adherence; American Indian; type 2 diabetes

Introduction

Background

American Indian adults have the highest prevalence of type 2 diabetes (T2D) in any racial and ethnic group and have high rates of comorbidities [1]. Uncontrolled cardiometabolic risk factors—insulin resistance, resulting in impaired glucose tolerance, dyslipidemia, and hypertension (HTN)—increase the risk of mortality. Mortality is significantly reduced by glucose- and lipid-lowering and antihypertensive medication adherence [2,3]. Medication adherence is low among American Indian adults living in non–Indian Health Service (IHS) health care settings [4], whereas virtually nothing is known about the nature and extent of medication adherence among reservation-dwelling adults who primarily receive their medications without cost from IHS or tribal facilities. Electronic health record (EHR) systems at these facilities offer a rich but underused data source about medication adherence and its potential to predict cardiometabolic control indicators (C-MCIs), for example, hemoglobin A1c (HbA1c), low-density lipoprotein cholesterol (LDL-C), and systolic blood pressure (SBP). We will address this oversight by using EHR data from a large tribal health care system to investigate medication adherence and C-MCIs to inform future interventions.

Prior evidence of medication adherence among reservation-dwelling adults includes 2 small studies with extremely low medication adherence [5,6] and another study across 5 American Indian tribes (n=166), in which 72% had low to moderate medication adherence [7]. American Indian adults with T2D who received care in a non-IHS setting were significantly less likely to adhere to oral T2D medication than non-Hispanic White adults [4]. Among Medicare enrollees with T2D, *older age*, being *female*, and cost of copays were significant predictors of nonadherence [8,9]. Other knowledge about C-MCIs in the American Indian population is derived largely from the Strong Heart Study (SHS), the largest population-based cohort study of American Indian adults [10,11]. Its findings documented that cardiovascular complications are related to *sex, olderage, T2D, HTN,* obesity (*BMI*>30), and *hyperinsulinemia* [12,13]. However, the SHS did not assess medication adherence, focused only on older adults (45-74 years), and examined cardiovascular risk factors through cross-sectional interviews [11]. Our study builds on the SHS by considering the relationship between medication adherence and C-MCIs (*HbA1c, LDL-C, and SBP*), longitudinally estimating future C-MCIs across a broader age span, and describing facilitators of and barriers to medication adherence. Our preliminary findings suggest that from 43% to 65% of Choctaw Nation of Oklahoma (CNO) adults have above-target C-MCIs and 37% have medication adherence below the 0.8 target for metformin, an oral T2D medication (Scarton, L, unpublished data, September 2022). CNO patients receive most or all of their health care within one tribal system, allowing us to track medication adherence and C-MCIs over a 4-year longitudinal study. The prevalence of T2D and C-MCIs is increasing among young adults and is higher in rural communities such as CNO, whose citizens are affected by high rates of poverty, distant health care, and difficulty transiting tribal lands spread over 11,000 square miles [14-16]. Diabetes distress, depressive symptoms, forgetting to take medications, adverse effects, cost, and knowledge gaps are known barriers to medication adherence [5,17,18], but little is known about medication adherence facilitators, other barriers, and the role of social determinants of health (SDOH) among reservation-dwelling American Indian adults.

Drawing on the tribe's EHR (2018-2021) data for the (5970 in 2017) CNO patients with T2D, we will characterize the relationships among medication adherence (to glucose- and lipid-lowering and antihypertensive drugs) and *C-MCIs* (HbA1c ≤7%, LDL-C <100 mg/dL, and SBP <130 mm Hg); patient *demographics* (eg, age, sex, SDOH, and residence location); and *comorbidities* (eg, BMI ≥30, cardiovascular disease [CVD], and chronic kidney disease [CKD]). We will also characterize the association of each *C-MCI* with *demographics* and *comorbidities*. Prescription and pharmacy refill data will be used to calculate the proportion of days covered (PDC) with medications, a typical measure of medication adherence [19]. Using machine learning techniques, we will develop prediction models for future (2019-2021) C-MCIs based on *medication adherence, patient demographics, comorbidities, and common laboratory tests* (eg, lipid panel) from the previous year. Such techniques have advantages over traditional algorithms related to CVD outcomes [20-22] but none have been applied to American Indian populations. Finally, key informant interviews (N=90) will explore facilitators of and barriers to medication adherence within the context of local SDOH.

Study Aims

This study addresses the following 3 aims among American Indian adults with T2D.

Aim 1

Using the 2018 EHR data, we will determine the bivariate relationships between *medication adherence* and C-MCIs, demographics, and comorbidities (aim 1a). We expect that adherence will be positively associated with HbA1c ≤7%, LDL-C <100 mg/dL, SBP <130 mm Hg, younger age, male sex, nonrural residence, and BMI <30. We will also determine the relationship between each C-MCI and demographics and comorbidities (aim 1b). We expect decreased C-MCIs in older adults or those with BMI ≥30, higher HbA1c and LDL-C in females, and higher SBP in males.

Aim 2

We will develop machine learning models (eg, random forest and nearest neighbors) for predicting future (2019-2021) C-MCIs from the previous year's medication adherence, demographics, comorbidities, and common laboratory tests. We will compare the models and identify the ones that perform best in predicting at-risk patients. Interpretable models (eg, penalized logistic regression) for both medication adherence and C-MCIs will be developed to identify modifiable factors as potential intervention targets.

Aim 3

We will identify facilitators of and barriers to medication adherence within the context of SDOH, EHR-derived medication adherence (PDC), and C-MCIs (at target, above target, and uncontrolled HbA1c).

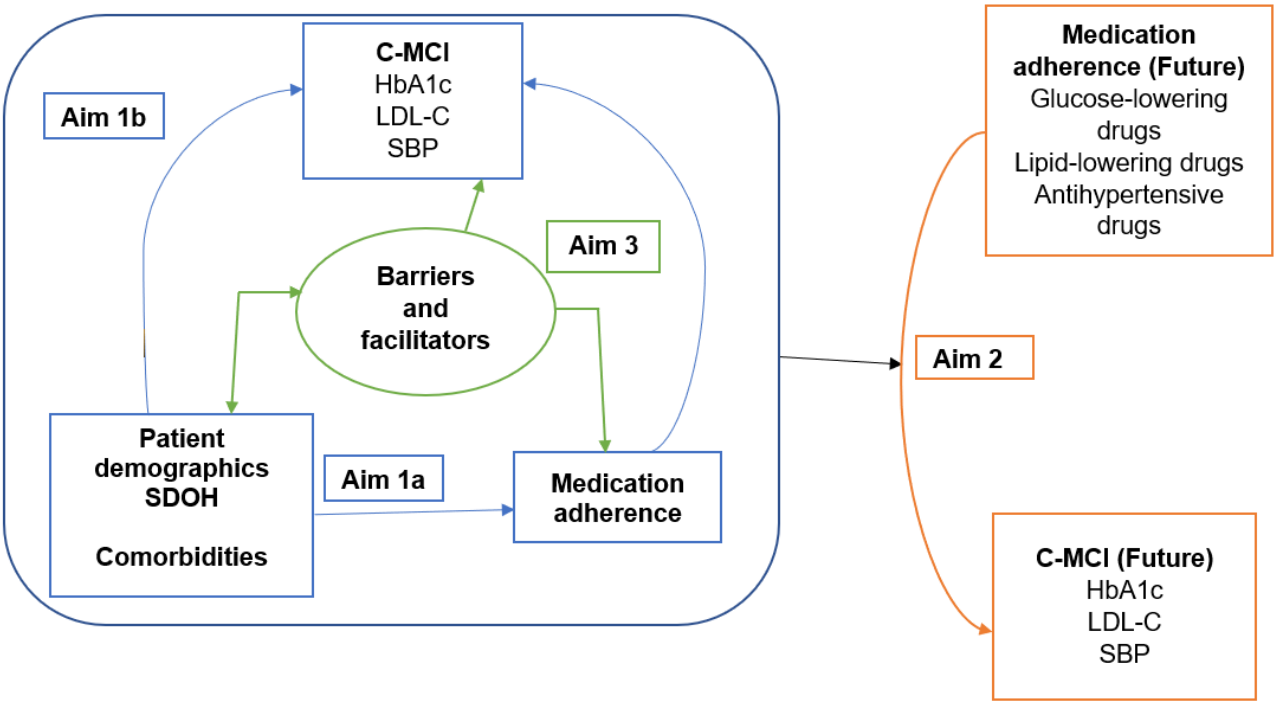
Research Strategy and Significance

American Indian adults are >2.5 times as likely to have T2D compared with other racial and ethnic groups [23]. Although African Americans and Hispanic adults have higher rates of T2D than non-Hispanic White adults (12%, 12.5%, and 7.5%, respectively), American Indian adults experience even greater rates between 15% and 50% [23]. Among CNO tribal patients living within CNO tribal boundaries in Oklahoma, approximately 16% have been diagnosed with T2D [24]. T2D can often be prevented or managed by monitoring HbA1c levels, lifestyle changes, and medications. American Indian adults with T2D have poorer glycemic control (higher HbA1c values) compared with their White counterparts, putting American Indian adults at increased risk for developing diabetes-related complications [25] and increased prevalence of above-target C-MCIs, which can lead to high rates of mortality. Targeting HbA1c levels alone will not eliminate these morbidities. Focus is also needed on other C-MCIs (eg, LDL-C and SBP) and adherence to medications that reduce them.

Conceptual Framework

Figure 1 illustrates the conceptual framework of this study. This framework is guided by SDOH, which are known to contribute to health disparities and impact T2D health outcomes [26]. SDOH include factors such as socioeconomic status, education, employment, and access to health care. In addition, there is strong scientific evidence regarding how medication adherence affects the control of cardiometabolic conditions, as evidenced by HbA1c, LDL-C, and SBP levels [2,3]. There is also some evidence that adverse SDOH are associated with lower overall medication adherence [27]. For example, long-distance commutes to receive health care and housing instability were associated with lower medication adherence [27]. As shown in Figure 1 and supported by evidence from other populations, the conceptual framework shows the expected relationships to be examined by each of the 3 study aims. Among American Indian adults receiving care from a tribal health care system that provides services and medications without copay, medication adherence is expected to be associated with C-MCIs, as well as the patient demographics, SDOH, and comorbidities (aim 1a) and patient demographics (including residence location); SDOH and comorbidities are expected to be associated with C-MCIs (aim 1b). Patient demographics, SDOH, comorbidities as indicated by common laboratory values and complications, and medication adherence of the previous year will predict C-MCIs of the future year (aim 2). Finally, insights gained from qualitative interviews with a large sample of patients with different levels of C-MCIs and medication adherence (aim 3) will inform future model development and the creation and testing of interventions focused on improving medication adherence and C-MCIs.

Figure 1. Conceptual framework. C-MCI: cardiometabolic control indicator; HbA1c: hemoglobin A1c; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; SDOH: social determinants of health.

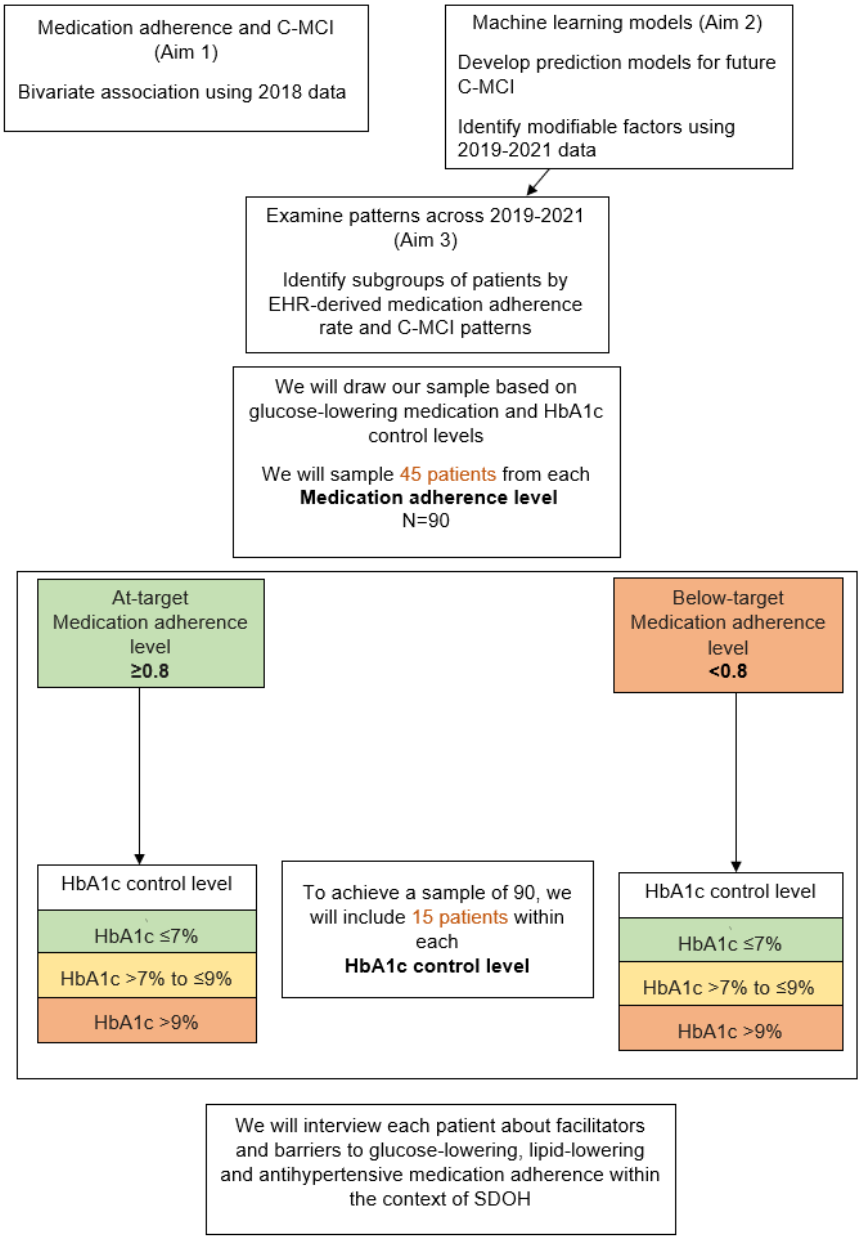


Methods

Overview

The Methods section, from research procedures to analysis, are described by aims 1 to 3. Owing to the differences in the samples, we first discuss aims 1 and 2 and then aim 3. The procedure flow diagram (Figure 2) shows the flow from aim 1 to aim 3 as well as the approach for drawing the aim 3 sample.

Figure 2. Flow diagram. C-MCI: cardiometabolic control indicator; EHR: electronic health record; HbA1c: hemoglobin A1c; SDOH: social determinants of health.



Aims 1 and 2

Research Procedures

Our study will draw upon existing CNO EHR data. The CNO has a robust, modern integrated EHR data system. These EHR data represent clinical measures as indicators of CNO program outcomes from 2018 to 2021.

The CNO uses an EHR system designed specifically for IHS and tribal health care facilities, the EHR Resource and Patient Management System, which provides CNO access to personal health information and epidemiological data. Information available through this system includes diagnosis of chronic and acute conditions in International Classification of Diseases, Tenth Revision (ICD-10) codes, prescription and dispensing data, information on processes of care procedures and monitoring (eg, blood pressure, screening, and annual health checks), and demographics (eg, age, sex, SDOH, and residence location). CNO pharmacy refill data are linked to EHR data and provide information such as dosage regimen (eg, dose, route of administration, and how to take the medication), date of new medication prescribed, date when picked up, and refill dates. This system is integrated across acute care hospitals, clinics, and other health care facilities (eg, diabetes wellness centers).

All encounters with CNO health system (internal or external) are captured within the EHR unless the patient seeks care outside CNO health system network and pays out of pocket for services. Any patient referred to a specialty clinic outside of CNO will still be captured in the EHR. There may be some patients without office visits or laboratory results within 4 years after the medication fill. The American Diabetes Association guidelines recommend that patients be seen at least every 3 to 6 months until their HbA1c levels are under control. Therefore, we anticipate only a few patients without any follow-up visits. In addition, CNO providers recommend that patients be seen

at least every 6 months for diabetes follow-up. Nonetheless, the frequency of patients who fill their medication and the number of patients who do not follow up with their primary care physician during the next 3 years will be very helpful information for designing interventions.

Setting

CNO was originally located in the southeastern United States (Alabama, Florida, Mississippi, and Louisiana) until the Choctaw Removal in the early 1830s. The removal, known as the Trail of Tears, split the tribe into what is now 3 federally recognized tribes: CNO, Jena Band of Choctaw Indians, and Mississippi Band of Choctaw Indians. The study will be conducted with CNO, which spreads over 11,000 square miles in 10.5 counties in rural southeastern Oklahoma. CNO, the third largest federally recognized American Indian tribe, has over 200,000 tribal members throughout the United States [28]. The 4 major health challenges associated with CNO have remained the same over the last several years: T2D, HTN, obesity, and CVD [24]. Although CNO has implemented many health promotion programs and is dedicated to the well-being of citizens, SDOH concerns such as poverty, long distance to health clinics, and discrimination continue to persist.

Sample Eligibility Criteria

Criteria for *inclusion* in the analysis are tribal members who (1) have at least one health system encounter between January 1, 2018, and December 31, 2021 (office visits, laboratory results, and medication fill), (2) are aged ≥18 years, and (3) have T2D based on ICD-10 codes. We will *exclude* patients who fill their prescriptions outside of CNO and those with end-stage renal disease (ESRD).

Sample Power

We estimated the power of the sample based on 5970 patients with T2D in 2017. In this population, 56% (3343/5970) had HbA1c >7%, 43.39% (2057/4741) had an LDL-C level of 100 mg/dL or higher, and 65.31% (3891/5958) had an SBP ≥130 mm Hg. To accommodate the multiple hypotheses to be tested in our aims, we will set the level of significance at a 2-sided α of .002. We assume conservatively that medication adherence, as measured by the PDC, has an SD of 0.2, based on the study by Borne et al [19] as well as our preliminary findings, where PDCs for various medications had an SD of 0.2 or lower. For each of the 3 classes of medications, over 67.82% (4049/5970) of our sample had prescriptions. The proposed sample had sufficient power (80%) to detect a 6.2% difference between the 2 balanced groups in the prevalence of HbA1c >7%, LDL-C ≥100 mg/dL, and SBP ≥130 mm Hg. The power is lower when the groups are unbalanced, but even for a very unbalanced 80/20 split, the proposed sample would have sufficient power (80%) to detect a 7.7% difference in the prevalence of these conditions. The sample will have sufficient power (80%) to detect a 2.5% difference in medication adherence between the 2 balanced groups and a 3.1% difference in an unbalanced 80/20 split.

We will extract the EHR variables listed in Table 1. We will examine medication by class: antihypertensive (eg, angiotensin-converting enzyme inhibitors), glucose-lowering (eg, metformin), and lipid-lowering (eg, statins) measured by PDC based on prescriptions and refills between January 2018 and December 2021.

Table 1. Data domain, measures, and clinic visit time points extracted from EHR[a].

Domain and measure (target value and description)[b]	Collection time points
Medications, prescriptions, and refills	
PDC[c] glucose-lowering agents	Date of first dispensing the medication in 2018 to the last dispensing in 2021
PDC lipid-lowering agents	Date of first dispensing the medication in 2018 to the last dispensing in 2021
PDC antihypertensive agents	Date of first dispensing the medication in 2018 to the last dispensing in 2021
C-MCI[d]	
HbA1c[e] (≤7%)	All visits in measurement period
LDL-C[f] (<100 mg/dL)	All visits in measurement period
SBP[g] (<130 mm Hg)	All visits in measurement period
Patient demographics	
Age (date of birth)	As of January 1, 2018
Sex (male or female)	As of January 1, 2018
Community of residence (coded)	As of January 1, 2018
Comorbid conditions	
CVD[h], CKD[i], and obesity with BMI (≥30)	As of January 1, 2018
Common laboratory tests	
eGFR[j], lipid panel, CMP[k], HbA1c, and CBC[l]	All visits in measurement period

[a]EHR: electronic health record.

[b]Values will be collected from patients aged ≥18 years with type 2 diabetes (based on the International Classification of Diseases, Tenth Revision code).

[c]PDC: proportion of days covered.

[d]C-MCI: cardiometabolic control indicators.

[e]HbA1c: hemoglobin A1c values defined according to the American College of Physicians guidelines for 2018.

[f]LDL-C: low-density lipoprotein cholesterol values defined according to the American College of Physicians guidelines for 2018.

[g]SBP: systolic blood pressure values defined according to the American College of Physicians guidelines for 2018.

[h]CVD: cardiovascular disease.

[i]CKD: chronic kidney disease.

[j]eGFR: estimated glomerular filtration rate.

[k]CMP: comprehensive metabolic panel.

[l]CBC: complete blood count.

Data Extraction Process

Qualified and experienced CNO program staff members agreed to extract data (January 1, 2018, to December 31, 2021) from CNO EHR database according to a list of variables in our data dictionary. The data will include medication prescriptions and pharmacy refill data from CNO EHR. We chose a 4-year timeframe to ensure adequate capture of pharmacy dispensing data, based on a similar study [29]. The data will be stored on a University of Florida (UF) password-protected file server in a secure environment. Only the research team members will have access to the raw data. Any paper data resulting from the study (such as a printout of part of the electronic file) will be stored in locked file cabinets in a locked office.

Measures

Control indicators (HbA1c, LDL-C, and SBP) were measured using labs collected at each visit within the measurement period. The data domains, measures, and clinic visit time points are listed in Table 1.

HbA1c and LDL-C levels were analyzed by 1 of the 9 CNO labs. HbA1c is a reliable test that measures the amount of glucose attached to hemoglobin over the past 3 months. This assay will determine the patient's metabolic control over a 3-month period [30]. The target HbA1c range is ≤7% for individuals with T2D [31]. LDL-C level is associated with an increased risk of developing heart disease. The target LDL-C range is <100 mg/dL [32]. SBP is obtained in the clinic environment by a licensed health professional or registered nurse and entered into the EHR system. The target SBP range is <130 mm Hg [33].

Medication adherence was measured for medications that were prescribed at least once. Each patient's adherence was assessed based on the methodology developed by the Pharmacy Quality Alliance (PQA), called PDC. The PDC is widely used by health plan accreditors and in Medicare Part D Drug Plan Star Ratings

as a proxy measure for adherence to medications used in the treatment of T2D, HTN, and high blood cholesterol [34]. The PDC is the proportion of calendar days in a period in which a patient had medication on hand to treat their chronic condition. PDC are commonly classified into 2 categories where ≥0.8 is considered adherent and <0.8 not adherent. The threshold of 0.8 for adherence is the level above which medication in these drug classes has a reasonable likelihood of achieving clinical benefit [35], although Lo-Ciganic et al [36] and Tuller et al [37] recommend that PDC be measured continuously among patients with diabetes on hypoglycemic agents. Given these considerations, adherence will be operationalized as a continuous measure of PDC within a range of 0 to 1. We will also report the percentage of samples that were adherent (PDC ≥0.8) and nonadherent (PDC <0.8).

Persons with ESRD are excluded from the PDC measure because adherence to glucose-lowering medications may not be accurately reflected in pharmacy claims data because of frequent dosage and medication adjustments. Patients undergoing peritoneal dialysis may also have glucose-containing dialysate that influence glycemic control, which leads to resultant adjustments to diabetes medications. Furthermore, the PQA recommends that patients on insulin be excluded from the PDC measure because insulin requires titration and frequent dosage adjustments, and despite directions to discard insulin vials after 30 days, many patients continue to use the insulin beyond 30 days [38]. However, as insulin is used by a significant percentage of the study sample and because insulin use is difficult for many individuals, we will calculate the PDC for patients who are dispensed insulin, noting that these data should be interpreted cautiously.

As we have access to the EHRs of enrolled patients, we will also determine primary medication nonadherence (PMN) events, which are recommended by the PQA to assess when a new medication is prescribed for a patient, but the patient does not obtain the medication, or an appropriate alternative, within an acceptable period after it was prescribed [39]. PMN will be reported at the individual patient level based on prescriptions for medications prescribed for the treatment of T2D, HTN, and high blood cholesterol. A PMN will be identified when there is no pharmacy dispensing event that matches the patient and the prescribed drug within 30 days following the prescribing event based on medication information documented by the medical provider in the EHR and within-pharmacy refill data. Medications that are not new will be excluded from the PMN calculation. Thus, prescriptions refilled in the preceding 180 days for the same drug will be excluded [39].

In the study analyses, we will calculate the PDC at the level of the medical condition (ie, T2D, HTN, and high blood cholesterol). For patients prescribed multiple medications for a medical condition, the PQA methodology for multiple medications will be used in the calculations of the PDC. For example, in T2D, where a patient has been prescribed multiple glucose-lowering drugs, participants need coverage with at least one medication for each day of the treatment period. Coverage can include different types of T2D medications throughout the treatment period, as long as all medications are on the target medication list [38].

Data Management

Deidentified data will be imported into statistical software R for cleaning and analysis. We will use custom scripts written for this project to rigorously audit the data for validity (ie, conformation to range, data type, set membership, and other constraints), consistency (between different variables and between values of the same variable across time), and completeness (missing data).

Data Analysis

Aim 1: To Determine the Bivariate Relationships Between (1) Medication Adherence and C-MCIs, Patient Demographics, and Comorbidities and (2) Each C-MCI and Patient Demographics and Comorbidities

We will use descriptive statistics to summarize demographic and clinical variables using the 2018 data. We will calculate medication adherence PDC for glucose- and lipid-lowering and antihypertensive drugs using the pharmacy data previously described. We define above-target C-MCIs as HbA1c >7%, LDL-C ≥100 mg/dL, and SBP ≥130 mm Hg and will use the latest values of these variables in 2018 in this analysis. Regression modeling and likelihood ratio test will be used to examine associations between medication adherence and C-MCI as well as between them and comorbidities and patient demographic variables including age, sex, and residence location.

Aim 2: To Develop Machine Learning Models (eg, Random Forest, Nearest Neighbors, and Others) for Predicting Future (2019-2021) C-MCIs from the Previous Year's Medication Adherence, Patient Demographics, Comorbid Conditions, and Common Laboratory Tests

Unlike traditional regression, machine learning focuses on the prediction performance of the overall model rather than the individual predictors. Through regulation and hyperparameter tuning, it automatically adjusts the model complexity, balancing bias and variance to achieve optimal prediction performance, and does not need to rely on an arbitrary threshold for statistical significance. In addition, machine learning methods such as random forest and nearest neighbor can implicitly accommodate nonlinearity and high-order interactions. In traditional regression analysis, they must be manually prespecified to be included in the model, which is an almost impossible task given the large number of possibilities. Traditional model selection approaches such as stepwise selection also lead to overfitting, resulting in inferior prediction performance.

We will construct machine learning classifiers (random forest, nearest neighbors, and others) to predict future C-MCIs based on the previous year's medication adherence, patient demographics (eg, age, sex, SDOH, and residence location), comorbidities (eg, CVD, BMI ≥30, and CKD), and common laboratory tests (eg, e-GFR and lipid panel). We will use a random 80/20 partition to reserve 20% (1194/5970) of the patient sample as the test set, with the remaining 80% (4776/5970) as the training and validation set. All modeling will be performed on the training and validation set, including coding of the predictors, model training, model validation, hyperparameter tuning, and model selection. We will use nested

cross-validation: the inner (10-fold) cross-validation will be used to choose hyperparameters for a machine learning algorithm, whereas the outer (leave-one-out) cross-validation will be used to evaluate the generalization performance of a model, enabling comparison of different modeling approaches to select the optimal model. The finalized model will be assessed using the reserved test data set to obtain an unbiased estimate of its performance when applied to new data. We will also construct LASSO (least absolute shrinkage and selection operator) regression models for medication adherence and C-MCIs. LASSO regression is a penalized regression method that produces interpretable parsimonious models. These models may provide insight into modifiable factors and tailoring factors that can be the target of future intervention studies.

Predictors for our machine learning models include patient demographics, SDOH, comorbid conditions, medication adherence, and common laboratory tests from the previous year. Some predictors, such as sex and race, have stable values. Other predictors could change substantially over the course of a year. For example, a patient may have several HbA1c measurements in a year, and there may be substantial variance between these measurements. To construct models with good prediction performance, the coding (representation) of predictors must be guided by scientific theory behind the disease mechanism. Our data analyst will work closely with subject matter experts during this process. For example, our tentative choice for representing HbA1c is to include 4 quarterly values in our model, reflecting the fact that each HbA1c measurement represents a weighted average of the blood glucose level in the previous 3 months. For patients missing some HbA1c measurements, we will consider a combination of within-participant (eg, last value carried forward and interpolation) and between-participant (eg, median, mean, and possibly adjusting for covariates) imputation. This process will be iterative and must be conducted carefully.

Rigor and Reproducibility

To ensure the reproducibility of data extraction, scripts for the data query will be documented. The high quality of the data set will be the foundation for the rigor of our study. All decisions made regarding data cleaning will be documented and executed via scripts in R statistical software (R Foundation for Statistical Computing), ensuring that the resulting data set for analysis will be of high quality and the entire process will be reproducible. We will use R Markdown in data analysis to ensure that all results are completely reproducible. Our analysis including sex and age as predictors will provide valuable insights into their impact on medication adherence and patient outcomes.

Aim 3

Research Procedures

Key informant interviews will be conducted to learn about the facilitators of and barriers to medication adherence within the context of local SDOH. This important knowledge cannot be discovered through EHR data alone and will provide vital information necessary to develop targeted and tailored interventions designed to improve medication adherence and manage T2D and other cardiometabolic conditions. We will draw a subsample of 90 patients from the larger sample to identify facilitators of and barriers to medication adherence. Our sample will be drawn based on glucose-lowering medication adherence (PDC <0.8 or PDC ≥0.8) and HbA1c control targets (at target, above target, or uncontrolled). To draw our purposeful sample of 90 patients, we will sample 45 patients from each of the two glucose-lowering target medication adherence levels: (1) at target (PDC ≥0.8) and (2) below target (PDC <0.8). Within each of the target medication adherence levels, we will include 15 patients from each of the three HbA1c target control levels: (1) HbA1c ≤7% (at target), (2) HbA1c from >7% to ≤9% (above target), and (3) HbA1c >9% (uncontrolled). These values were selected based on Medicare definitions [40] and American Diabetes Association guidelines [31]. Although we are drawing our sample based only on glucose-lowering medication adherence, we will interview the participants about facilitators and barriers to glucose- and lipid-lowering and antihypertensive medication adherence within the context of SDOH. We are not including all classes of medication (lipid-lowering and antihypertensive) or all C-MCIs (LDL-C and SBP) because it would be too complex. Although 90 patients are a large sample for a theory-generating or phenomenology qualitative study, selected purposefully based on their medication adherence and control, 90 patients responding to our open-ended questions is a reasonable approach. We expect to achieve response saturation for the facilitators of and barriers to medication adherence for the many types of medications used for C-MCIs and with consideration of the individual SDOH that may impact adherence within CNO health care system, which addresses some of the structural SDOH.

Design

A qualitative descriptive content analysis design using interviews with open-ended questions will be used to identify facilitators of and barriers to medication adherence within the context of SDOH among CNO patients with T2D.

Setting

This study will take place within CNO's 10.5 county service area to facilitate face-to-face interviews. Qualitative interviews will be conducted by a community health worker from the Choctaw Nation. Interviews will be conducted face-to-face at a convenient location.

Sample Eligibility Criteria

We will purposively select a subsample of American Indian patients (documented in CNO EHR) from our larger sample, all of whom have a diagnosis of T2D. The subsample *inclusion criteria* include (1) enrolled tribal member, (2) aged ≥18 years, (3) who have been diagnosed with T2D, (4) live within CNOs 10.5 county service area, (5) who use CNO Tribal Health Services, (6) for whom C-MCI levels and medication adherence level will have been generated from the aim 1 analysis of CNO data, and (7) willing and able to participate in a 60- to 90-minute interview focused on facilitators of and barriers to medication adherence. Although tribal patients who live throughout Oklahoma and the United States use CNO Tribal Health Services, we will *exclude* those residing outside CNO's 10.5 county service area for this qualitative study. We will exclude

tribal members with ESRD, consistent with aim 1 and aim 2 exclusion criteria.

Sample Size

We will recruit 90 CNO patients and conduct an open-ended interview per patient. Our sample will include 15 patients from each of the 6 groups, represented by the matrix shown in Figure 2. These interviews will provide a deeper understanding of the facilitators of and barriers to adherence for patients within each of the target medication adherence levels and HbA1c control levels. For example, we will learn from 15 patients who meet the target medication adherence and are at target for HbA1c control their perceptions of what factors make medication adherence difficult and easier. Their perceptions may be different from those within the group with below-target medication adherence and above-target HbA1c control. For these reasons, we divided the sample into 6 different groups. Using guidance from Morse [41], who found that at least 6 participants are needed to understand the essence of an experience, we estimate that 15 interviews per control level will be enough to gain insight and meaning around facilitators and barriers to medication adherence and to reach data saturation [41].

Data Collection

We will draw our subsamples as previously described. Once patients are identified, we will provide a coded list of eligible patients from our deidentified data set to CNO information management team. CNO information management team will provide the contact information for 135 individuals directly to CNO community health worker, who will then contact the patients. We expect that from the 135 total available samples in the 6 sampling groups based on medication adherence and C-MCIs, over 80% (108/135) will agree to participate, of which 83.3% (90/108) will follow through to complete the interviews based on our past experience with recruiting for a CNO focus group study [42].

CNO community health worker will contact by telephone the identified eligible patients within each of the sampling groups (labeled 1-6) to introduce the study. Patients who are eligible and interested in participating in the study will be given the option to participate in a face-to-face interview at a convenient site. A structured interview guide using semistructured and open-ended questions with probes will be used to collect in-depth information on facilitators and barriers to glucose- and lipid-lowering and antihypertensive medication adherence. The interview guide will be structured based on each sampling group's level of medication adherence for all targeted medications as well as levels of C-MCIs.

As part of the interview session, community health workers will ask patients to complete 3 items: demographics, SDOH, and health care use. The patients will be compensated with a gift card of US $100 at the end of the interview. Interviews are expected to last 60 minutes, but owing to the open-ended nature of the probes and to be respectful of different communication styles, such as time to think before answering and telling stories to answer questions, up to an hour and a half may be necessary for adequate discussion. All interviews will be audio-recorded, professionally transcribed verbatim, and validated for accuracy.

Measures

The demographic items include questions on age, gender, household income, number of people living at home, housing type, number of bedrooms, employment status, and education level. The SDOH items include questions on transportation, miles to grocery stores and tribal clinics, involvement with CNO cultural activities, use of CNO food distribution, and trust in providers and pharmacists. The medication and health care use history items include questions on medication regimen, length of time on medication, and frequency of provider appointments. Semistructured and open-ended questions will be structured based on medication adherence levels (at target and below target) and HbA1c control (at target, above target, and uncontrolled). Questions include "What is your understanding about the role of medication in managing your T2D?" and "Tell me what makes taking your medication easy or difficult?" Although our interview questions will focus on medication adherence, we will likely learn from patients' spontaneous comments about their HbA1c, LDL-C, and SBP control through our conversation. This information will be analyzed appropriately.

Data Management

Data will be collected electronically, and interviews will be audio-recorded and transcribed. A CNO community health worker will interview patients and collect questionnaire information electronically using data written on a UF research electronic data capture site specifically created for this study. This information will be stored in locked filing cabinets or on computer servers with secure passwords or encrypted electronic storage devices.

All patients will be assigned a code number, and their data will be identified only with the code number. The link of the code numbers to the subject identifiers will be kept separate from the study data. Only CNO study team members will have access to the code or master key. The data will be stored in a controlled-access computer database on a secure UF server. Any hard copy will be stored in a locked office within CNO, scanned, and uploaded to the research electronic data capture site.

Data Analysis—Aim 3: Identify Facilitators of and Barriers to Medication Adherence Within the Context of SDOH, EHR-derived Medication Adherence (PDC), and C-MCIs (at Target, Above Target, and for Uncontrolled HbA1c)

Results from the demographic, SDOH, and medication and health care use history questionnaires will be analyzed using descriptive statistics. We will use content analysis, a systematic and objective means of describing a phenomenon, to interpret and analyze the 90 interviews. All interviews will be audio-recorded and professionally transcribed verbatim with accuracy verification. In addition, 10% (9/90) of the transcripts will be rechecked for accuracy. The unit of analysis will be at the word or sentence level. A coding manual will be developed to ensure the consistency of coding [43]. Members of the

research team will immerse themselves in the data by reading and rereading interviews. Themes and subthemes of barriers to and facilitators of medication adherence will emerge. Tentative categories will be generated inductively until a final set of categories are developed. Areas of incongruence will be discussed until consensus is reached. We will use a qualitative data management program to analyze and manage the data.

Rigor and Reproducibility

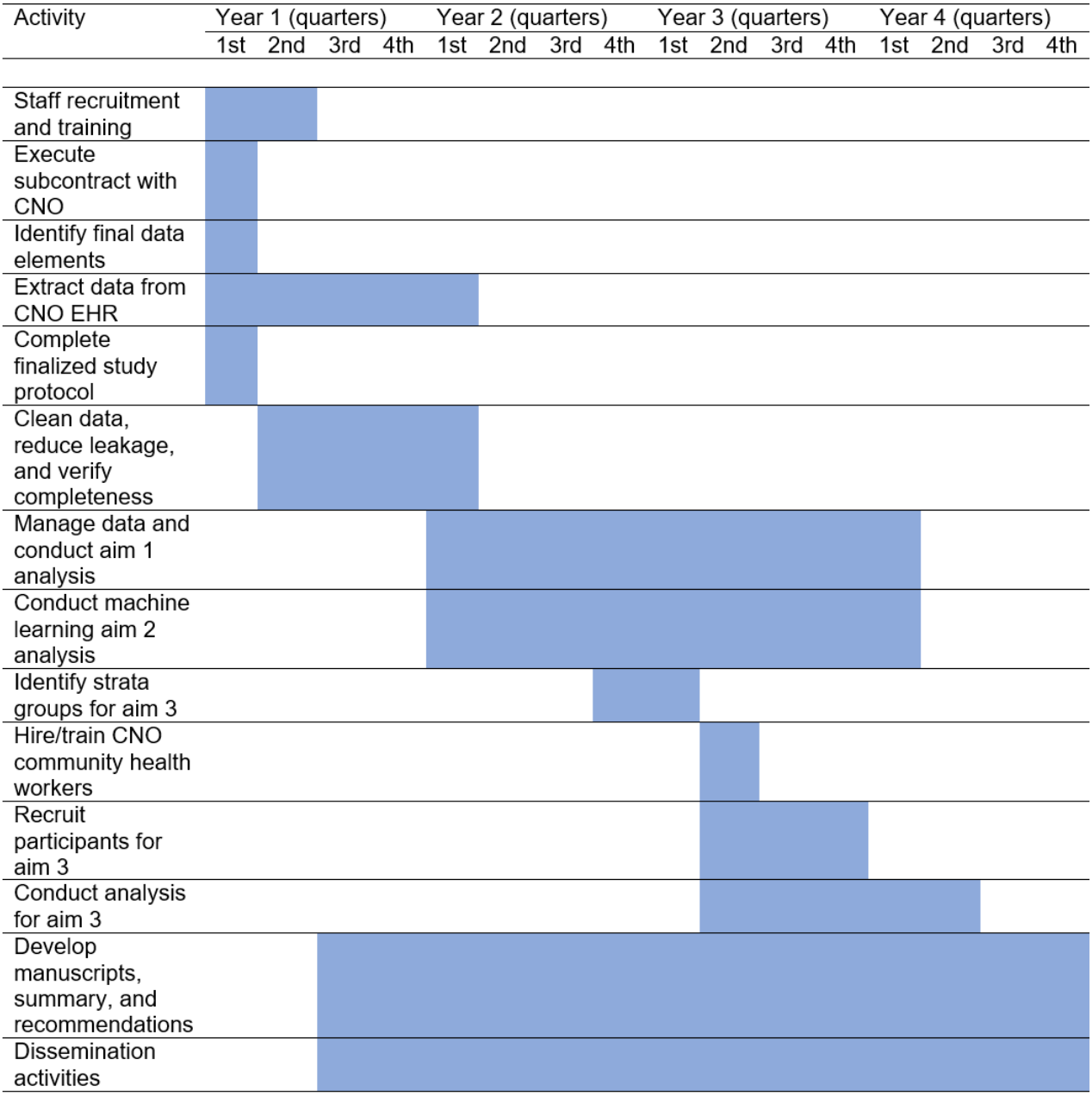
We will use rigorous processes including coding checks and audit trails to support reproducibility. Trustworthiness will be addressed through credibility, dependability, confirmability, and transferability [44]. Credibility will be addressed through investigator and data triangulation [44]. Multiple research team members will code, analyze, and interpret the data. Data triangulation will be attained by using different data sets that emerge such as raw data, codes, concepts, and saturation. Dependability and confirmability will be attained through the use of audit trails, which will describe the detailed steps taken throughout the study and notes from team meetings [44,45]. Finally, transferability will be achieved using a codebook with detailed documentation of the coding scheme definitions, coding rules, and examples [44].

We expect to hear rich stories about facilitators of medication adherence such as family support, free medication fills, and importance of medications as well as discussions around barriers to medication adherence such as negative side effects, not believing the medicine will help, and not trusting their provider.

Timeline

The 4-year timeline for the benchmark for success is presented in Figure 3. We will request and extract CNO data, after the institutional review board (IRB) approval, by month 3. We will complete the study protocol by the end of month 2 and recruitment and training by the end of month 4. We will extract and clean the data, reduce leakage, and verify the data for completeness by the end of the first quarter of year 2. We will complete the analysis of aims 1 and 2 by the end of the first quarter of year 4. On the basis of the data from aim 2, we will identify sampling groups from aim 3 by the first quarter of year 3. We will hire and train CNO community health workers, begin recruitment by the end of the second quarter in year 3, and complete the 90 interviews by the end of year 3 (3-4 per week). We will complete the aim 3 qualitative analysis by the end of the second quarter of year 4. We will finalize manuscripts for all 3 aims and finalize a renewal application by the end of year 4.

Figure 3. Timeline. CNO: Choctaw Nation of Oklahoma; EHR: electronic health record.



Ethics Approval

The CNO IRB (2,022,001) and UF IRB (02200979) approved the study protocol. We also have an executed data use agreement.

Results

Funding was obtained in early 2022. The UF and CNO have approved the IRB protocols and executed the data use agreements. Data extraction is in process. We expect to obtain results from aims 1 and 2 in 2024.

Discussion

Expected Findings

Our study will provide insights into medication adherence and its potential to predict C-MCIs, which will allow CNO to provide precision behavioral health care to patients by identifying those who may benefit from targeted interventions to prevent future T2D-related complications. High-quality metrics will be available for future CNO program planning and will shape the specific design and sample size of adequately powered future T2D-related studies. Furthermore, understanding the facilitators of and barriers to medication adherence within the context of SDOH will help move us toward eliminating health disparities and reaching health equity for American Indian adults.

Potential Problems and Alternate Plans

We may experience 2 important issues during the implementation of our study. First, there may be patients diagnosed with T2D who do not have office visits or laboratory results. However, we do not anticipate this being an issue for many patients because CNO health care providers attempt to see patients with elevated HbA1c levels every 3 months and

those with well-managed HbA1c levels every 6 months. In addition, patients must visit their primary care provider to receive medication refills. The frequency at which patients fill their medication and follow up with their health care provider during the 4-year period will be informative for intervention development. We focused on American Indian adults aged ≥18 years because of the high incidence and prevalence of T2D in this population across the life span. The prevalence of T2D in youth <18 years is increasing; however, owing to the relatively small number of CNO youth with T2D, we excluded them due to concerns of maintaining anonymity in this study of EHR data.

Summary

C-MCIs not at target increase the risk for complications in patients with T2D; however, adherence to glucose- and lipid-lowering and antihypertensive drugs can substantially improve C-MCIs and decrease morbidity and mortality. Currently evidence on medication adherence among reservation-dwelling American Indian adults is lacking. Using EHR data from 5970 CNO patients with T2D, we will examine medication adherence and C-MCIs in American Indian adults aged ≥18 years. In addition, we will use a subsample of patients to identify facilitators of and barriers to medication adherence within the context of SDOH. These findings will help us move toward eliminating health disparities and reaching health equity. Findings from this important study will yield insights to improve medication adherence and C-MCIs among American Indian adults with T2D, which is consistent with CNOs' goal of reducing T2D and its complications (HTN and CVD).

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Data Availability

We are using deidentified data under an executed data use agreement with CNO. Under the data use agreement, we do not have the authority to share these data.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Summary statement.
[PDF File (Adobe PDF File), 151 KB - resprot_v11i10e39193_app1.pdf]

References

1. National Diabetes Statistics Report 2020. Centers for Disease Control and Prevention. 2020. URL: https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf [accessed 2021-03-23]
2. Kim Y, Lee J, Kang H, Park SM. Effect of medication adherence on long-term all-cause-mortality and hospitalization for cardiovascular disease in 65,067 newly diagnosed type 2 diabetes patients. Sci Rep 2018 Aug 15;8(1):12190 [FREE Full text] [doi: 10.1038/s41598-018-30740-y] [Medline: 30111867]
3. Mazzaglia G, Ambrosioni E, Alacqua M, Filippi A, Sessa E, Immordino V, et al. Adherence to antihypertensive medications and cardiovascular morbidity among newly diagnosed hypertensive patients. Circulation 2009 Oct 20;120(16):1598-1605. [doi: 10.1161/CIRCULATIONAHA.108.830299] [Medline: 19805653]
4. Schmittdiel JA, Steiner JF, Adams AS, Dyer W, Beals J, Henderson WG, et al. Diabetes care and outcomes for American Indians and Alaska natives in commercial integrated delivery systems: a SUrveillance, PREvention, and ManagEment of Diabetes Mellitus (SUPREME-DM) Study. BMJ Open Diabetes Res Care 2014 Nov 17;2(1):e000043 [FREE Full text] [doi: 10.1136/bmjdrc-2014-000043] [Medline: 25452877]
5. Jacobs A, Kemppainen JK, Taylor JS, Hadsell C. Beliefs about diabetes and medication adherence among Lumbee Indians living in rural southeastern North Carolina. J Transcult Nurs 2014 Apr 19;25(2):167-175. [doi: 10.1177/1043659613515718] [Medline: 24648433]
6. Shiyanbola O, Nelson J. Illness perceptions, beliefs in medicine and medication non-adherence among South Dakota minority women with diabetes: a pilot study. S D Med 2011 Oct;64(10):365-368. [Medline: 22016925]
7. Aronson BD, Sittner KJ, Walls ML. The mediating role of diabetes distress and depressive symptoms in type 2 diabetes medication adherence gender differences. Health Educ Behav 2020 Jun 30;47(3):474-482 [FREE Full text] [doi: 10.1177/1090198119885416] [Medline: 31665927]

8. Chernew ME, Shah MR, Wegh A, Rosenberg SN, Juster IA, Rosen AB, et al. Impact of decreasing copayments on medication adherence within a disease management environment. Health Aff (Millwood) 2008 Jan;27(1):103-112. [doi: 10.1377/hlthaff.27.1.103] [Medline: 18180484]
9. Pawaskar MD, Xu L, Tang Y, Puckrein GA, Rajpathak SN, Stuart B. Effect of medication copayment on adherence and discontinuation in medicare beneficiaries with type 2 diabetes: a retrospective administrative claims database analysis. Diabetes Ther 2018 Oct 24;9(5):1979-1993 [FREE Full text] [doi: 10.1007/s13300-018-0489-y] [Medline: 30143964]
10. Welty TK, Rhoades DA, Yeh F, Lee ET, Cowan LD, Fabsitz RR, et al. Changes in cardiovascular disease risk factors among American Indians. Ann Epidemiol 2002 Feb;12(2):97-106. [doi: 10.1016/s1047-2797(01)00270-8]
11. Lee E, Welty T, Fabsitz R, Cowan LD, Le NA, Oopik AJ, et al. The strong heart study. A study of cardiovascular disease in American Indians: design and methods. Am J Epidemiol 1990 Dec;132(6):1141-1155. [doi: 10.1093/oxfordjournals.aje.a115757] [Medline: 2260546]
12. Howard BV. Risk factors for cardiovascular disease in individuals with diabetes. Acta Diabetol 1996 Sep;33(3):180-184. [doi: 10.1007/bf02048540]
13. Resnick HS, Strong Heart Study Investigators. Metabolic syndrome in American Indians. Diabetes Care 2002 Jul;25(7):1246-1247. [doi: 10.2337/diacare.25.7.1246] [Medline: 12087031]
14. The relationship between rural setting and health: factors that influence individuals with or at risk of CVD. American Heart Association. URL: https://www.heart.org/-/media/files/about-us/policy-research/policy-positions/social-determinants-of-health/rural-health-policy-guidance.pdf?la=en&hash=246F1C4D6C876A1317A43876FBCE8B2FD32B1144 [accessed 2022-01-28]
15. LTSS research: diabetes in Indian country annotated literature review. Department of Health & Human Services, Centers for Medicare & Medicaid Services. 2018 May 18. URL: https://www.cms.gov/Outreach-and-Education/American-Indian-Alaska-Native/AIAN/LTSS-TA-Center/pdf/Emerging-LTSS-Issues-in-Indian-Country-Diabetes-in-Indian-Country-Annotated-Literature-Review.pdf [accessed 2022-01-28]
16. Batsis JA, Pletcher SN, Stahl JE. Telemedicine and primary care obesity management in rural areas - innovative approach for older adults? BMC Geriatr 2017 Jan 05;17(1):6 [FREE Full text] [doi: 10.1186/s12877-016-0396-x] [Medline: 28056832]
17. Ratner N, Davis E, Lhotka L, Wille S, Walls M. Patient-centered care, diabetes empowerment, and type 2 diabetes medication adherence among American Indian patients. Clin Diabetes 2017 Dec;35(5):281-285 [FREE Full text] [doi: 10.2337/cd17-0008] [Medline: 29263570]
18. Wheat L, Roane TE, Connelly A, Zeigler M, Wallace J, Kim J, et al. Using a pharmacist-community health worker collaboration to address medication adherence barriers. J Am Pharm Assoc (2003) 2020 Nov;60(6):1009-1014. [doi: 10.1016/j.japh.2020.08.021] [Medline: 32943338]
19. Borne RT, O'Donnell C, Turakhia MP, Varosy PD, Jackevicius CA, Marzec LN, et al. Adherence and outcomes to direct oral anticoagulants among patients with atrial fibrillation: findings from the veterans health administration. BMC Cardiovasc Disord 2017 Sep 02;17(1):236 [FREE Full text] [doi: 10.1186/s12872-017-0671-6] [Medline: 28865440]
20. Kagiyama N, Shrestha S, Farjo PD, Sengupta PP. Artificial intelligence: practical primer for clinical research in cardiovascular disease. J Am Heart Assoc 2019 Sep 03;8(17):e012788. [doi: 10.1161/jaha.119.012788]
21. Sevakula RK, Au - Yeung WM, Singh JP, Heist EK, Isselbacher EM, Armoundas AA. State - of - the - art machine learning techniques aiming to improve patient outcomes pertaining to the cardiovascular system. J Am Heart Assoc 2020 Feb 18;9(4):e013924. [doi: 10.1161/jaha.119.013924]
22. Shameer K, Johnson KW, Glicksberg BS, Dudley JT, Sengupta PP. Machine learning in cardiovascular medicine: are we there yet? Heart 2018 Jul 19;104(14):1156-1164. [doi: 10.1136/heartjnl-2017-311198] [Medline: 29352006]
23. National Diabetes Statistics Report. Centers for Disease Control and Prevention. 2022. URL: https://www.cdc.gov/diabetes/data/statistics-report/index.html [accessed 2022-01-28]
24. State of the Nation Health Report. Durant, OK: Choctaw Nation of Oklahoma; 2017.
25. Quandt SA, Bell RA, Snively BM, Smith SL, Stafford JM, Wetmore LK, et al. Ethnic disparities in glycemic control among rural older adults with type 2 diabetes. Ethn Dis 2005;15(4):656-663 [FREE Full text] [Medline: 16259490]
26. Hill-Briggs F, Adler NE, Berkowitz SA, Chin MH, Gary-Webb TL, Navas-Acien A, et al. Social determinants of health and diabetes: a scientific review. Diabetes Care 2020 Nov 02;44(1):258-279 [FREE Full text] [doi: 10.2337/dci20-0053] [Medline: 33139407]
27. Wilder ME, Kulie P, Jensen C, Levett P, Blanchard J, Dominguez LW, et al. The impact of social determinants of health on medication adherence: a systematic review and meta-analysis. J Gen Intern Med 2021 May 29;36(5):1359-1370 [FREE Full text] [doi: 10.1007/s11606-020-06447-0] [Medline: 33515188]
28. Choctaw Nation Reservation. Choctaw Nation of Oklahoma. URL: https://www.choctawnation.com/about/reservation/ [accessed 2022-01-28]
29. Palacio AM. Capsule commentary on Lafata et al., medication adherence does not explain black-white differences in cardiometabolic risk factor control among insured patients with diabetes. J Gen Intern Med 2016 Feb 29;31(2):223 [FREE Full text] [doi: 10.1007/s11606-015-3510-4] [Medline: 26791537]

30. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2021. Diabetes Care 2021 Jan;44(Suppl 1):S15-S33. [doi: 10.2337/dc21-S002] [Medline: 33298413]
31. American Diabetes Association. 6. Glycemic targets: standards of medical care in diabetes-2021. Diabetes Care 2021 Jan;44(Suppl 1):S73-S84. [doi: 10.2337/dc21-S006] [Medline: 33298417]
32. Grundy SM, Stone NJ, Bailey AL. Correction to: 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. Circulation 2019 Jun 18;139(25):e1182-e1186. [doi: 10.1161/cir.0000000000000698]
33. Whelton PK, Carey RM, Aronow WS. Correction to: 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. Hypertension 2018 May 9;71(6):e136-e139. [doi: 10.1161/hyp.0000000000000075]
34. Optimizing health by advancing the quality of medication use. Pharmacy Quality Alliance. URL: https://www.pqaalliance.org/assets/Measures/PQA_Measures_in_CMS_Programs.pdf [accessed 2021-05-29]
35. Roebuck M, Kaestner R, Dougherty J. Impact of medication adherence on health services utilization in medicaid. Med Care 2018 Mar;56(3):266-273. [doi: 10.1097/MLR.0000000000000870] [Medline: 29309392]
36. Lo-Ciganic W, Donohue JM, Thorpe JM, Perera S, Thorpe CT, Marcum ZA, et al. Using machine learning to examine medication adherence thresholds and risk of hospitalization. Med Care 2015 Aug;53(8):720-728 [FREE Full text] [doi: 10.1097/MLR.0000000000000394] [Medline: 26147866]
37. Tueller SJ, Deboeck PR, Van Dorn RA. Getting less of what you want: reductions in statistical power and increased bias when categorizing medication adherence data. J Behav Med 2016 Dec 27;39(6):969-980 [FREE Full text] [doi: 10.1007/s10865-016-9727-9] [Medline: 26921166]
38. Proportion of Days Covered: Diabetes All Class (PDC-DR). Pharmacy Quality Alliance. 2019 Oct 4. URL: https://www.pqaalliance.org/measures-overview#pdc-dr [accessed 2021-05-24]
39. Adams AJ, Stolpe SF. Defining and measuring primary medication nonadherence: development of a quality measure. J Manag Care Spec Pharm 2016 May;22(5):516-523. [doi: 10.18553/jmcp.2016.22.5.516] [Medline: 27123913]
40. DM-2 (NQF 0059): Diabetes: Hemoglobin A1c (HbA1c) Poor Control (>9%). CMS Web Interface V4.0. 2019 Nov. URL: https://qpp.cms.gov/docs/QPP_quality_measure_specifications/Web-Interface-Measures/2020_Measure_DM-2_CMSWebInterface.pdf [accessed 2021-05-27]
41. Morse J. Designing funded qualitative research. In: Handbook of Qualitative Research. Thousand Oaks, California: SAGE Publications; 1994.
42. Scarton L, Velazquez I, O'Neal LJ, Iyerm S, Cannady T, Choate A, et al. Developing a culturally tailored multigenerational intervention to prevent and manage type 2 diabetes in American Indian families living in rural settings: findings from a focus group study. Res Nurs Health 2019 Jun 10;42(3):226-233 [FREE Full text] [doi: 10.1002/nur.21941] [Medline: 30854672]
43. Weber R. Basic content analysis. In: Quantitative Applications in the Social Sciences. Thousand Oaks, California: SAGE Publications; 1990.
44. Lincoln YS, Guba EG. Naturalistic Inquiry. Thousand Oaks: SAGE Publishing; 1985.
45. Sandelowski M. The problem of rigor in qualitative research. ANS Adv Nurs Sci 1986 Apr;8(3):27-37. [doi: 10.1097/00012272-198604000-00005] [Medline: 3083765]

Abbreviations

CKD: chronic kidney disease
C-MCI: cardiometabolic control indicator
CNO: Choctaw Nation of Oklahoma
CVD: cardiovascular disease
EHR: electronic health record
ESRD: end-stage renal disease
HbA1c: hemoglobin A1c
HTN: hypertension
ICD-10: International Classification of Diseases, Tenth Revision
IHS: Indian Health Service
IRB: institutional review board
LDL-C : low-density lipoprotein cholesterol
PDC: proportion of days covered
PMN: primary medication nonadherence
PQA: Pharmacy Quality Alliance
SBP: systolic blood pressure

SDOH: social determinants of health
SHS: Strong Heart Study
T2D: type 2 diabetes
UF: University of Florida

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Protocol

Upper Extremity Examination for Neuromuscular Diseases (U-EXTEND): Protocol for a Multimodal Feasibility Study

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Abstract

Background: Neuromuscular diseases, such as spinal muscular atrophy (SMA) and Duchenne muscular dystrophy (DMD), may result in the loss of motor movements, respiratory failure, and early mortality in young children and in adulthood. With novel treatments now available, new evaluation methods are needed to assess progress that is not currently captured in existing motor scale tests.

Objective: With our feasibility study, our interdisciplinary team of investigators aims to develop a novel, multimodal paradigm of measuring motor function in children with neuromuscular diseases that will revolutionize the way that clinical trial end points are measured, thereby accelerating the pipeline of new treatments for childhood neuromuscular diseases. Through the Upper Extremity Examination for Neuromuscular Diseases (U-EXTEND) study, we hypothesize that the novel objective measures of upper extremity muscle structure and function proposed herein will be able to capture small changes and differences in function that cannot be measured with current clinical metrics.

Methods: U-EXTEND introduces a novel paradigm in which concrete, quantitative measures are used to assess motor function in patients with SMA and DMD. Aim 1 will focus on the use of ultrasound techniques to study muscle size, quality, and function, specifically isolating the biceps and pronator muscles of the upper extremities for follow-ups over time. To achieve this, clinical investigators will extract a set of measurements related to muscle structure, quality, and function by using ultrasound imaging and handheld dynamometry. Aim 2 will focus on leveraging wearable wireless sensor technology to capture motion data as participants perform activities of daily living. Measurement data will be examined and compared to those from a healthy cohort, and a motor function score will be calculated.

Results: Data collection for both aims began in January 2021. As of July 2022, we have enrolled 44 participants (9 with SMA, 20 with DMD, and 15 healthy participants). We expect the initial results to be published in summer 2022.

Conclusions: We hypothesize that by applying the described tools and techniques for measuring muscle structure and upper extremity function, we will have created a system for the precise quantification of changes in motor function among patients with neuromuscular diseases. Our study will allow us to track the minimal clinically important difference over time to assess progress in novel treatments. By comparing the muscle scores and functional scores over multiple visits, we will be able to detect small changes in both the ability of the participants to perform the functional tasks and their intrinsic muscle properties.

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KEYWORDS

mHealth; ubiquitous computing; neuromuscular disorders; inertial measurement unit; motor function; specific torque; cross-sectional area; echogenicity

Introduction

Spinal muscular atrophy (SMA) is a neuromuscular disease that occurs in approximately 1 in 11,000 live births [1,2]. SMA is characterized by severe muscle atrophy and weakness that are attributed to motor neuron degeneration. The cause of SMA is a variation of the survival motor neuron 1 gene that results in the death of the motor nerves, leading to reduced muscle size and function and increased muscle fibrosis [3]. Together, these changes cause severe muscle weakness and the atrophy of muscle, as observed in patients. The recent development of novel therapies, such as nusinersen [4], risdiplam, and onasemnogene abeparvovec (Zolgensma), which target motor neuron survival, has allowed for extended life expectancy and improved motor function. However, the previous lack of treatments for SMA and the coinciding lack of progress for children with SMA have resulted in a dearth of meaningful evaluation methods for precisely and quantitatively measuring muscle and motor function in these children to capture what is the most meaningful to them and their families.

Duchenne muscular dystrophy (DMD) is another progressive neuromuscular disease of childhood that occurs in 1 in 6000 boys [5]. DMD is caused by a lack of the dystrophin protein at the subcellular level in skeletal muscle. This missing linkage to the extracellular matrix results in a chronic state of inflammation and dysregulated muscle repair, leading to muscles being replaced with muscles with fibrosis and fat infiltration. This decrease of contractile muscle material results in the loss of motor movements, respiratory failure, and early mortality in young adulthood. New treatments are also being developed for DMD, and evaluation methods are direly needed.

The explosion of new potential treatments for these diseases presents the urgent need for more specific, more quantitative metrics that can be used to quickly and effectively evaluate motor function and, potentially, the efficacy of a treatment or the progression of these diseases. This is especially important for pediatrics because the standard metrics that are used for adults do not always apply to children and vice versa. Additionally, clinical trials are not inclusive of patients with cognitive challenges due to current analyses of clinical outcomes requiring patient participation. We recognized a critical absence of tools and systems for quantifiably and objectively capturing meaningful motor function in an inclusive way for this population.

By following these patients, we have identified multiple ways in which motor function evaluations could be dramatically improved. The Upper Limb Module (ULM) was developed as an international effort among clinicians, physical therapists, and researchers to address the shortcomings of previous SMA motor function assessments [6]. The ULM was targeted toward younger children and overcame the flooring effects found in the Hammersmith Functional Motor Scale-Expanded (HFMSE). However, the ULM had issues with the ceiling effect, which led to the creation of the Revised ULM (RULM) [6]. A few of the tasks that were added in the RULM included picking up coins, pushing a button light with 1 hand, and raising a 200-g cup to the mouth. Although the tasks were related to activities of daily living and allowed for a complete range of motion in different joints, the RULM does not explicitly measure each task. The HFMSE and Children's Hospital of Philadelphia: Infant Test of Neuromuscular Disorders [7] are neurological assessments for infants; however, patients in our clinic currently range in age from 0 (birth) to 35 years. Therefore, the metrics of these assessments are less relevant to many of our patients. Further, these assessments are performed in clinics and therefore may have less relevance to a patient's functions in their normal daily environments. This has been frequently observed by parents and caregivers, who have reported progress that is not captured by standard clinical assessments. Finally, the current assessments are qualitative and may not be able to capture specific changes in muscle strength and function.

Ultrasound imaging may be used to measure architectural characteristics of skeletal muscle. These architecture measurements can be used to estimate the force-generating capacity of a muscle based on the established relationships between muscle size and function [8]. Recently, ultrasound imaging has been used to measure disease progress directly in vivo for various neuromuscular disorders, including SMA and DMD, by measuring tissue echogenicity (brightness) or increased fibrosis [9-14]. Fibrosis leads to a loss of contractile muscle tissue, thereby reducing the effective force-generating capacity of the muscle. It has been observed that patients with SMA exhibit severe muscle atrophy and increased fibrosis in their muscles [13]. However, there is no standard quantification method for either of these characteristics. Increasing the understanding of the structural changes in SMA and DMD will help us to better understand how the force-generating capacity decreases throughout these diseases' progression.

As wearable technology becomes more ubiquitous, mobile health apps have grown immensely. Wearable sensors are often embedded in smartphones, smartwatches, and many app-specific devices. Previous efforts have attempted to score motion assessments via various modalities of motion tracking technology, from cameras to inertial measurement units [15,16]. Many of these works used cameras and multiple wireless sensors to track upper limb movement to report angles of motion [17,18]. However, these studies focused on classifying movements according to the assessment scale rather than quantifying movements directly, which can introduce experimenters' biases into the algorithm.

To more precisely track the changes in muscles and functions among patients with SMA, DMD, or other neuromotor disorders, we must first understand what we can easily measure in a clinic setting. By improving function tracking in clinics via methods that are more objective and sensitive, we will be able to better recognize functional changes that are indicative of treatment

efficacy. We will combine measurements of tissue quality and muscle size to estimate muscle function based on image-based methods. We will use wireless sensors to quantify the quality of motions and make more nuanced comparisons than those that can be performed with nominal clinical assessment ratings. By combining imaging methods that provide theoretical estimates of function and wireless sensor measurements of actual function, we can better understand the changes that occur in muscle structure and how they result in functional changes that are reflected by sensor measurements. These proposed novel methods for assessing muscle and motor function will be easily implemented into the standard of care and normal clinical visits. In summary, our proposed research is novel, and it will advance the treatment of patients with neuromuscular disease.

We propose a research program to develop sensitive and novel measures for muscle function in patients with SMA and DMD. We have found these measures to be greatly needed in our clinical care, as well as in the research that is so vital to promoting treatments for these patients. Our pilot study introduces a novel paradigm in which concrete, quantitative measures are used to assess motor function in patients with SMA and DMD. The major developments include leveraging (1) ultrasound imaging and handheld dynamometry to measure and comparatively track upper extremity muscle structure and function over time and (2) motion mechanics measurements by using accelerometers and gyroscopes with wireless sensing technology.

Methods

Study Design

In collaboration with the University of Virginia Children's Hospital Pediatric Neuromuscular Disease Clinic, which is run by RS, we will recruit a cohort of patients with SMA (n=9) and patients with DMD (n=20) and a cohort of age- and sex-matched healthy controls (n=15). For the age matching process, control participants will be accepted if they are aged within 1 year above or 1 year below the patient participants, allowing 1 control participant to serve as the control for multiple patient participants in the study. These participants will be recruited and consented according to the institutional review board–approved procedures. Participants will range in age from 0 (birth) to 35 (adulthood) years. At routine checkups (generally conducted every 4-6 months), we will measure upper extremity muscle size, quality, function, and contraction strength. We will examine the data for distributions and look at trends in muscle measurements across the study cohorts and over time. We will generate scores for theoretical muscle function and the quality of motor movements. This information will be used to compare a patient's muscle structure and improvements over time.

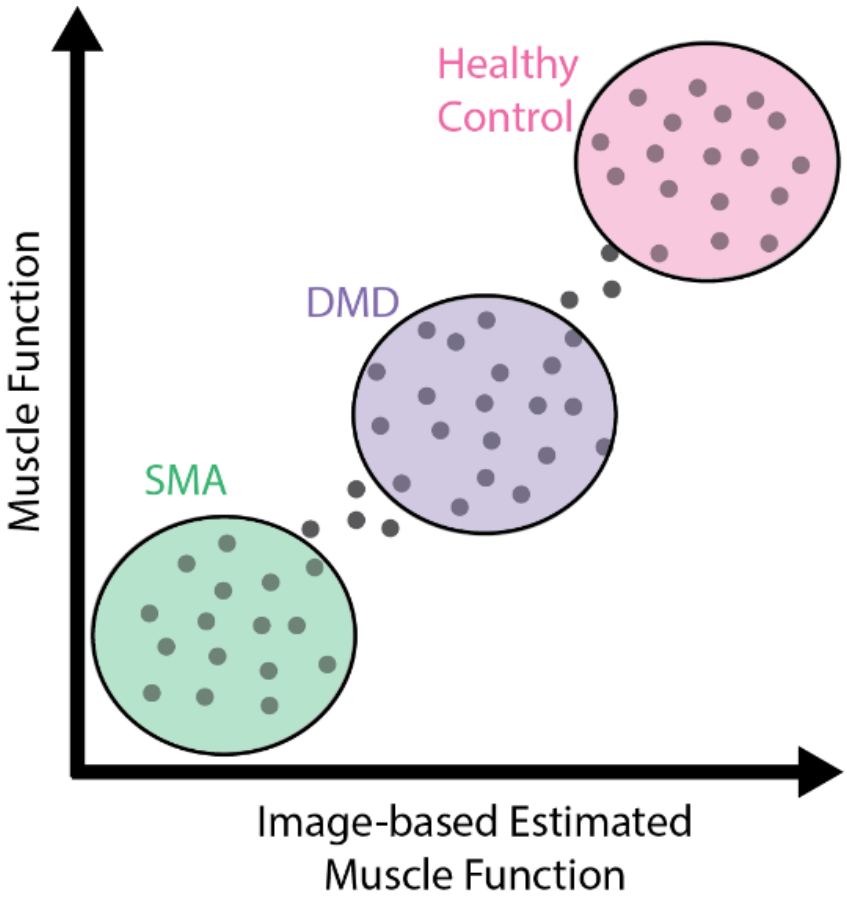
We performed initial pilot studies to determine the feasibility of ultrasound imaging and the relationship between the ultrasound imaging data and the wearable sensor data. Our exploratory study was designed to recruit as many patients from the clinic as possible to determine the characteristics of muscle structure and motor function in each neuromuscular disease. We plan to develop an image-based theoretical measure of muscle function and a movement function score; correlate the muscle function measures to the movement function scores; and then aggregate them into a functional score, which we will correlate to the clinical function assessment scores.

Aim 1: Ultrasound Measurements of Muscle Architecture

Ultrasound images will be collected to measure biceps brachii and brachioradialis muscle structures in participants with SMA and DMD and age- and sex-matched healthy controls. A linear array transducer (H9.0/40, LS 128 CEXT; Telemed Medical Systems) will be used, with settings kept constant across participants to allow for consistent measurements. The depth will be kept at 50 mm, the frequency will be kept at 8 Hz, and the gain will be set to 88%. The dominant arm's biceps brachii and brachioradialis muscles will be imaged at the approximate midsection in the longitudinal and transverse planes. The maximum voluntary elbow flexor torque will be measured by using a handheld dynamometer (Chatillon DFS II; John Chatillon & Sons Company), which will be placed on the forearm at a measured distance from the elbow joint center, with the elbow positioned at approximately 90° (flexed). The measured distance will then be multiplied by the force measurement from the dynamometer to calculate elbow torque. We will collect 5 measurements and average them to calculate the maximum voluntary elbow flexion torque.

A custom image processing algorithm that was developed in MATLAB (The MathWorks Inc) [19] will be used to measure the cross-sectional areas (CSAs) and average echogenicities of the muscles. In total, 5 images of the same region will be measured and averaged to generate 1 average measurement for a participant. The CSAs will be manually traced for each transverse image frame, and the areas will be computed by calculating the number of pixels in the region of interest and converting this measurement to squared centimeters. To compare CSAs across cohorts, CSAs will be normalized by forearm length to mitigate the effects of participants' size. The average echogenicity of the transverse plane will be calculated from the manually traced areas by averaging the pixel grayscale intensity values, which range from 0 (black) to 256 (white). The average echogenicity of the longitudinal plane will be calculated by manually drawing a rectangle across the region of interest in the muscle and averaging the pixel grayscale intensity values. The two planar echogenicities will then be averaged to create 1 measurement of echogenicity for each muscle and to minimize transducer orientation effects. A measure of muscle function or the amount of torque per unit area (specific torque) will be estimated by dividing the elbow flexor torque (N·m) by the CSA (cm^2). We will then generate an image-based estimate of muscle function by using the abovementioned calculated parameters. We will validate this metric by comparing it to the elbow flexor torque, which will be a uniform measure of muscle function across all participants (Figure 1). All statistics will be calculated in R (R Foundation for Statistical Computing; α=.05) [20].

Figure 1. A theoretical comparison between image-based estimates of muscle function and measurements of muscle function. DMD: Duchenne muscular dystrophy; SMA: spinal muscular atrophy.



Aim 2: Inertial Measurement Unit Measurements of Arm Function

We will use multimodal wireless inertial sensors (MetaMotionR+; Mbient Lab) and the Microsoft Kinect V2 camera for motion tracking to measure movements in space (Figure 2). Attaching sensor nodes to a participant's hand (Figure 3) will allow us to measure progress with medication or during physical therapy in small gradations to detect micromovements. We will gather measurements from dominant and nondominant arms by having the child participants press against the manometer and pinch the grip strength gauge with each hand or arm. Through a series of prescribed motions (similar to those in the RULM for SMA; eg, picking up tokens and raising a cup), participants will perform tasks that are related to everyday activities, with the help of the activity board (Figure 3).

The list of tasks includes turning a door knob; performing a closed-fist knock; performing paddle pronation and supination; performing the finger-thumb test; opening and closing the fist; pressing a piano key; raising a cup to the mouth; performing a bicep curl; performing a hand clap; and rotating the shoulder sideways, forward, and backward. For each task, 3 measurements will be collected, and the strongest measurement for each task will be used. The wireless sensing technology will be first piloted with participants from the healthy control group to adjust and calibrate our protocol. The technology will then be used with the full cohort of 20 patients. These controlled data collection processes will be done in the clinic to drive the development and validation of the sensing requirements (ie, for both the sensors and the sampling rates) and data analytics methods for conducting the motion assessments with our patient population, thereby allowing for subsequent out-of-clinic deployments for continuous monitoring.

Figure 2. Upper Extremity Examination for Neuromuscular Diseases methodology overview. Participants will perform a set of motions that will be measured via ultrasound imaging and wearable sensors. The data will then be analyzed to infer the quality of motion metrics.

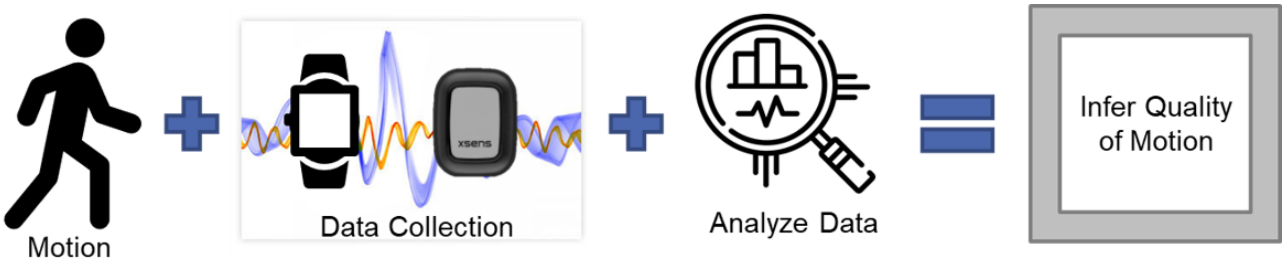
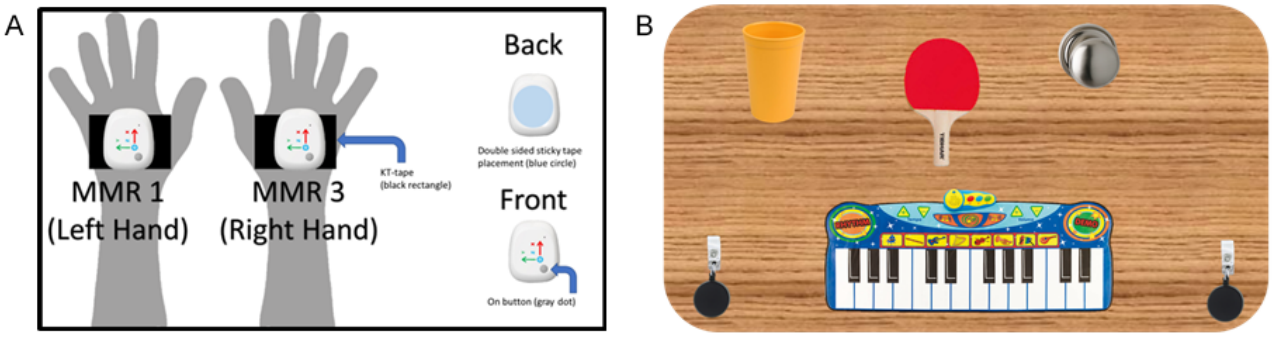


Figure 3. Wearable sensor diagram (A) and activity board prototype (B). KT Tape: Kinesiology Therapeutic Tape; MMR: MetaMotionR+.



Ethics Approval

The study was approved by the University of Virginia's Institutional Review Board for Health Sciences Research (protocol number: 200178) on September 25, 2020. The participants or the parents of the minor participants provided written informed consent for participating in the study.

Results

Data collection for both aims began in January 2021. As of July 2022, we have enrolled 44 participants (9 with SMA, 20 with DMD, and 15 healthy participants). We expect the initial results to be published in summer 2022.

Discussion

Study Overview

We hypothesize that by applying the described tools and techniques for measuring muscle structure and upper extremity function, we will have created a system for the precise quantification of changes in motor function among patients with neuromuscular diseases. Since traditional motor function assessments provide scores on a scale, patient assessment scores remain relatively the same, despite patient-reported improvements. Our study will allow us to track the minimal clinically important difference over time to assess progress in novel treatments. From a clinical standpoint, a physician could track a patient's movements in reference to the control population, as well as in reference to a patient's initial baseline. Therefore, regardless of the amount of movement, every patient will receive a quantitative score for the movements that they can do, which can be tracked for future comparisons. Similarly, the scores and the overall motion shapes can be used to understand range of motion limitations, fatigue, and the impact of novel therapies.

The ability to use ultrasound imaging to assess muscle architecture will not only lower the financial burdens of patients, insurance companies, and hospitals but also reduce the stress of patients. We expect that our measures will allow us to identify early changes in muscle architecture and may ultimately be able to predict long-term improvements or deteriorations in function. By comparing the muscle scores and functional scores over multiple visits, we will be able to detect small changes in both the ability of the participants to perform the functional tasks and their intrinsic muscle properties.

The potential impacts of our pilot study are revolutionizing the way that clinical trials are performed and accelerating the pipeline of new treatments for childhood neuromuscular diseases. This protocol is especially important for pediatrics because the standard metrics that are used for adults do not always apply to children. By tracking incremental changes, our study will also aid in the development of a methodology for identifying which treatments support the progression or sustainment of muscle structure and function. The proposed assessment could drive the development of software and applications that aid occupational and physical therapy, and it could provide a more objective, quantitative way of evaluating functional upper extremity motions and the quality of such movements. Our study will also help pave the way for home-based activity tracking, which can ease the burdens of patients and their families. Our results will have the potential to inform treatment efficacy and help provide evidence for making decisions regarding the effectiveness of SMA and DMD therapies.

Dissemination Plan

The results from our research will be presented at relevant technical and clinical academic conferences and published in scholarly peer-reviewed publications. As we are a highly interdisciplinary team, per our dissemination plan, we will aim to reach diverse audiences within the systems engineering, biomedical engineering, and medicine fields. We also anticipate sharing our findings with care teams for patients with neuromuscular diseases.

Limitations

The primary limitation of our study is the large variations in motor function between the healthy controls and the patients. Comparing control functionality to patient functionality has proven to be difficult, since patient functionality can be vastly different; however, we are focused on capturing more precise measures at the lower end of the functional scale and are not very concerned about any potential ceiling effects at the higher end of the functional scale. Patient participation can be affected by neurodevelopmental challenges, such as autism and intellectual disabilities, resulting in partial or inadequate data collection. This limitation could be mitigated through the inclusion of additional supports to allow for improved participation. External factors, such as medical illnesses or additional medical appointments, may also limit attendance for data collection.

Conclusion

Our study is poised to make a valuable contribution to the understanding of functional changes and advance the care of the patients. We see particularly exciting opportunities for translating this work into the clinic to support current clinical assessments by providing additional information on detailed changes in muscle function. Our next steps include (1) expanding the number of participants that are longitudinally tracked to further validate our novel functional metrics, (2) including additional raters (clinicians, radiographers, physical therapists, and occupational therapists), (3) expanding to other sites to explore our metrics' wider applicability to other clinic settings; and (4) applying our framework to other neuromuscular diseases to provide detailed assessments of motor function to other patient groups.

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We would like to acknowledge the patients and families of the patients who are participating in our study.

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Data Availability

The data sets that will be generated and/or analyzed during the study will not be publicly available due to patient confidentiality and data sharing agreements. Data may be available from the corresponding author on a case-by-case basis.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the University of Virginia - Center for Engineering in Medicine - Engineering-in-Medicine Seed Grant Program (Virginia, USA).
[PDF File (Adobe PDF File), 25 KB - resprot_v11i10e40856_app1.pdf]

References

1. Bowerman M, Becker CG, Yáñez-Muñoz RJ, Ning K, Wood MJA, Gillingwater TH, UK SMA Research Consortium. Therapeutic strategies for spinal muscular atrophy: SMN and beyond. Dis Model Mech 2017 Aug 01;10(8):943-954 [FREE Full text] [doi: 10.1242/dmm.030148] [Medline: 28768735]
2. Farrar MA, Park SB, Vucic S, Carey KA, Turner BJ, Gillingwater TH, et al. Emerging therapies and challenges in spinal muscular atrophy. Ann Neurol 2017 Mar;81(3):355-368 [FREE Full text] [doi: 10.1002/ana.24864] [Medline: 28026041]
3. Lefebvre S, Bürglen L, Reboullet S, Clermont O, Burlet P, Viollet L, et al. Identification and characterization of a spinal muscular atrophy-determining gene. Cell 1995 Jan 13;80(1):155-165 [FREE Full text] [doi: 10.1016/0092-8674(95)90460-3] [Medline: 7813012]
4. Finkel RS, Chiriboga CA, Vajsar J, Day JW, Montes J, De Vivo DC, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. Lancet 2016 Dec 17;388(10063):3017-3026. [doi: 10.1016/S0140-6736(16)31408-8] [Medline: 27939059]
5. Emery AE. Population frequencies of inherited neuromuscular diseases--a world survey. Neuromuscul Disord 1991;1(1):19-29. [doi: 10.1016/0960-8966(91)90039-u] [Medline: 1822774]
6. Mazzone ES, Mayhew A, Montes J, Ramsey D, Fanelli L, Young SD, et al. Revised Upper Limb Module for spinal muscular atrophy: Development of a new module. Muscle Nerve 2017 Jun;55(6):869-874. [doi: 10.1002/mus.25430] [Medline: 27701745]
7. Glanzman AM, Mazzone E, Main M, Pelliccioni M, Wood J, Swoboda KJ, et al. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): test development and reliability. Neuromuscul Disord 2010 Mar;20(3):155-161 [FREE Full text] [doi: 10.1016/j.nmd.2009.11.014] [Medline: 20074952]
8. Lieber RL, Fridén J. Functional and clinical significance of skeletal muscle architecture. Muscle Nerve 2000 Nov;23(11):1647-1666. [doi: 10.1002/1097-4598(200011)23:11<1647::aid-mus1>3.0.co;2-m] [Medline: 11054744]
9. Scholten RR, Pillen S, Verrips A, Zwarts MJ. Quantitative ultrasonography of skeletal muscles in children: normal values. Muscle Nerve 2003 Jun;27(6):693-698. [doi: 10.1002/mus.10384] [Medline: 12766980]
10. Pillen S, Verrips A, van Alfen N, Arts IMP, Sie LTL, Zwarts MJ. Quantitative skeletal muscle ultrasound: diagnostic value in childhood neuromuscular disease. Neuromuscul Disord 2007 Jul;17(7):509-516. [doi: 10.1016/j.nmd.2007.03.008] [Medline: 17537635]

11. Shklyar I, Geisbush TR, Mijialovic AS, Pasternak A, Darras BT, Wu JS, et al. Quantitative muscle ultrasound in Duchenne muscular dystrophy: a comparison of techniques. Muscle Nerve 2015 Feb;51(2):207-213 [FREE Full text] [doi: 10.1002/mus.24296] [Medline: 24862337]
12. Zaidman CM, Wu JS, Kapur K, Pasternak A, Madabusi L, Yim S, et al. Quantitative muscle ultrasound detects disease progression in Duchenne muscular dystrophy. Ann Neurol 2017 May;81(5):633-640 [FREE Full text] [doi: 10.1002/ana.24904] [Medline: 28241384]
13. Wu JS, Darras BT, Rutkove SB. Assessing spinal muscular atrophy with quantitative ultrasound. Neurology 2010 Aug 10;75(6):526-531 [FREE Full text] [doi: 10.1212/WNL.0b013e3181eccf8f] [Medline: 20697104]
14. Janssen MMHP, Harlaar J, Koopman B, de Groot IJM. Dynamic arm study: quantitative description of upper extremity function and activity of boys and men with duchenne muscular dystrophy. J Neuroeng Rehabil 2017 May 26;14(1):45 [FREE Full text] [doi: 10.1186/s12984-017-0259-5] [Medline: 28549441]
15. Del Din S, Patel S, Cobelli C, Bonato P. Estimating Fugl-Meyer clinical scores in stroke survivors using wearable sensors. Annu Int Conf IEEE Eng Med Biol Soc 2011;2011:5839-5842. [doi: 10.1109/IEMBS.2011.6091444] [Medline: 22255667]
16. Lee S, Lee YS, Kim J. Automated evaluation of upper-limb motor function impairment using Fugl-Meyer assessment. IEEE Trans Neural Syst Rehabil Eng 2018 Jan;26(1):125-134. [doi: 10.1109/TNSRE.2017.2755667] [Medline: 28952944]
17. Wang J, Chen Y, Hao S, Peng X, Hu L. Deep learning for sensor-based activity recognition: A survey. Pattern Recognit Lett 2019 Mar;119:3-11. [doi: 10.1016/j.patrec.2018.02.010]
18. Oubre B, Daneault JF, Jung HT, Whritenour K, Miranda JGV, Park J, et al. Estimating upper-limb impairment level in stroke survivors using wearable inertial sensors and a minimally-burdensome motor task. IEEE Trans Neural Syst Rehabil Eng 2020 Mar;28(3):601-611. [doi: 10.1109/TNSRE.2020.2966950] [Medline: 31944983]
19. R2021a - MATLAB and Simulink. MathWorks. URL: https://www.mathworks.com/help/matlab/release-notes-R2021a.html [accessed 2022-08-30]
20. R: A language and environment for statistical computing. R Foundation for Statistical Computing. URL: https://cran.r-project.org/doc/manuals/r-release/fullrefman.pdf [accessed 2022-08-30]

Abbreviations

CSA: cross-sectional area
DMD: Duchenne muscular dystrophy
HFMSE: Hammersmith Functional Motor Scale-Expanded
RULM: Revised Upper Limb Module
SMA: spinal muscular atrophy
U-EXTEND: Upper Extremity Examination for Neuromuscular Diseases
ULM: Upper Limb Module

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Protocol

Group Telegaming Through Immersive Virtual Reality to Improve Mental Health Among Adolescents With Physical Disabilities: Pre- and Posttrial Protocol

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Abstract

Background: Adolescents with physical disabilities have higher rates of mental health conditions and issues than adolescents without disabilities, and this disparity was exacerbated by the onset of the COVID-19 pandemic. They also have limited access to on-site programs and nearby peers.

Objective: This pilot aims to investigate the potential effects of a low-dose multiplayer virtual reality telegaming program on depression, socialization, and loneliness among a cohort of children with physical disabilities. A secondary aim is to describe feasibility metrics, namely, recruitment and adherence rates and perceived program enjoyment and satisfaction. The tertiary aim is to describe behavioral mechanisms that affect participant adherence and social participation in the classes.

Methods: This study is a single-group pre- and posttest–designed trial. A single cohort of 12 children with physical disabilities will pilot a 1-month program that includes 2 supervised 1-hour sessions per week of group-based exergaming. Participants will complete questionnaires before and after the program. The primary aim measures will include the Children's Depression Inventory 2 Short Form, a measure of feelings of depression, and the UCLA Loneliness Scale, a measure of both loneliness and social isolation. Secondary aim measures will include three posttest Likert scale questionnaires: perceived program enjoyment, program satisfaction, and satisfaction with multiplayer experiences. At postintervention or dropout, participants will undergo semistructured interviews to identify behavioral mechanisms that underlie participation. Data will be reported descriptively and be supported by *t* tests as appropriate.

Results: Recruitment procedures started in July 2022. All data are expected to be collected by January 2023. Full trial results are expected to be published by March 2023. Secondary analyses of data will be subsequently published.

Conclusions: This trial tests a peer-to-peer virtual reality telegaming program that includes a completely remote enrollment, assessment, and intervention protocol. This program is accessible and short in duration and frequency, allowing it to be integrated into other interventions. Knowledge obtained from this study will inform the development of a larger trial for improving the mental health and well-being of adolescents with physical disabilities.

Trial Registration: ClinicalTrials.gov NCT05259462; https://clinicaltrials.gov/ct2/show/NCT05259462

International Registered Report Identifier (IRRID): PRR1-10.2196/42651

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KEYWORDS

disability; physical activity; active video gaming; mindfulness

Introduction

For people with physical disabilities, adolescence is a critical period for school educators and health professionals to provide quality education and health services. In adolescence, people with disabilities build their self-identity and adopt vocational skills and health behaviors that increase the likelihood of living healthy independent lifestyles as they transition into early adulthood [1-3]. Prior to COVID-19, adolescents with disabilities lagged behind in the development of adult life skills [4] and experienced alarmingly higher rates of mental health disorders such as depression and isolation than peers without disabilities [5]. They were also far less likely to engage in social- and health-enhancing physical activities [1,6-8]. Physical activity is a critical behavior for improving gross motor function [9] and health conditions (eg, cardiovascular disease, pain, and fatigue) [10-12], and developing meaningful social relationships with peers in this population.

Disappointingly, reports from the COVID-19 era have found that stress, depression, isolation, and physical activity participation have substantially worsened since the outbreak of COVID-19 among adolescents with disabilities [13-17]. A local report in the southeast United States found that basic needs were met for most of the families [13]. However, 32.7% of adolescents felt down or depressed, 47.5% felt little pleasure in doing things, and 64.4% felt isolated after COVID-19. Moreover, 74.3% reported decreased socialization, and 51.5% reported reduced exercise participation.

In April 2020, one author (BL) and an adapted fitness instructor conducted a home-based community virtual reality program for adolescent members of a fitness facility for people with disabilities. The program included low-cost virtual reality equipment, and people could participate from home during the height of the COVID-19 pandemic amid social distancing mandates, occupancy limits, and facility closures. The program was 1 month in duration and included two 30-minute sessions per week of synchronous group exercise. The program included a total of 10 participants, completed in two intervention waves (n=5 per wave). Since this project was not a research study, the anecdotal resultant themes were *COVID-19–created barriers to physical activity opportunities*; *virtual reality group exercise-filled voids in exercise participation and human connectedness that were created by the COVID-19 pandemic*; and *the virtual reality headset fostered immersion, which increased their motivation to game*. In summary, group virtual reality gaming provided an accessible opportunity for adolescents with disabilities to build new friendships with peers, which enhanced their mental health. There is a need to start confirming these benefits through quantitative investigation, particularly among adolescents living in the Southeast, a geographic region with some of the lowest rates of health care access across the United States (as reported by the United Health Foundation) [18].

This study has 3 purposes. The first purpose is to examine the effects of a home-based virtual reality multiplayer gaming program on depression, socialization, and loneliness among 12 adolescents with physical disabilities (ages 13-19 years). The second purpose is to describe the acceptability of the program as measured by participant adherence, total play time, exercise time, and perceived program satisfaction and enjoyment. The third purpose is to describe behavioral mechanisms that affect participant engagement. We will qualitatively explore participants' perceptions of barriers and facilitators that affected their adherence and social participation in the classes.

Methods

Study Design

This study is a single group pre-to-post design trial that will last 1 year and include 2 waves (n=6 per wave). Participants will be recruited from the medical and billing record databases at the Children's Hospital, as well as through the collaborative network of the university and an adapted fitness facility for people with disabilities (Lakeshore Foundation, Homewood, Alabama). We plan to recruit a convenience sample of 12 people to satisfy minimum recommendations for a feasibility study that aims to inform sample size considerations for a larger trial [19].

Ethics Approval

The protocol and informed consent and assent forms were approved by the Institutional Review Board for Human Use of the University (IRB-300008913) on May 23, 2022. Prospective participants and their caregivers will be mailed a consent and assent form, along with the study questionnaires. Participants will be instructed to review the consent and assent forms carefully, sign them, and then complete the study questionnaires. Once completed, they will be instructed to mail the documents back in a return envelope to research staff. Should the participants not want to participate, no action will be needed. Consent and assent documents will be written in English.

Eligibility Criteria

Eligibility criteria will include self-reported mobility disability (eg, use of a mobility device or presence of a mobility impairment), between the ages of 13-19 years (World Health Organization definition of adolescence and the minimum age of 13 years as recommended by the manufacturer of the virtual reality headset), access to a Wi-Fi internet connection in the home, and a caregiver to support the child if <18 years of age. The exclusion criteria will be as follows: physically active (defined as >150 minutes/week of moderate-to-vigorous intensity exercise), cannot use their arms for exercise or operate the controller buttons using their fingers, and complete blindness or deafness.

Procedures

Before starting the intervention, participants will be mailed consent/assent forms and baseline surveys. Once the forms are

received by research staff, participants will be mailed the intervention equipment. Post intervention (week 5), participants will be mailed another packet of surveys to complete and return to research staff. Participants will then be asked to participate in a one-on-one semistructured interview via phone call or Zoom (Zoom Video Communications, Inc) with the principal investigator, which will be audio recorded and transcribed for qualitative analysis. Participants will receive an electronic US $40 gift card for each packet of surveys returned (total of US $80 for completing the study).

Home-Based Intervention

The program will last 4 weeks and include two 1-hour sessions per week of supervised peer-to-peer gaming. Further details of the program prescription are shown in Multimedia Appendix 1. Participants will use an Oculus Quest 2 headset to meet peers and 2 coaches (a gaming coach and a mindfulness coach) in an online virtual private party. Each session will include participation in one of several games, including RecRoom (a massive online multiplayer game with countless social and active gaming experiences), VRChat (a game focused on building social relationships), Beat Saber (a rhythmic music-to-movement game), and After the Fall (a cooperative first-person shooter). Each session will include a 5-minute introduction that will include behavior change and mindfulness coaching to promote autonomy, competence, and relatedness through a respectful, cohesive, and positive atmosphere (strategies framed by the self-determination theory [20-22], learned from the mindfulness coaching workshops hosted by the National Center on Health, Physical Activity and Disability). Some of the mindfulness-based strategies will include guided breathing focused exercises, body scanning, meditation, and acceptance of social anxiety and shyness. Game order prescriptions (ie, duration, intensity, time, and type) will be conducted on a *learn-as-you-go* approach based on participants' preferences.

Outcomes

Baseline participant characteristics will include age, sex, and ethnicity. Aim 1 measures will include the Children's Depression Inventory 2 Short Form, a measure of feelings of depression with strong psychometric properties among adolescents with and without disabilities [23,24], and version 3 of the UCLA Loneliness Scale 20 items (UCLA-20) [25-27]. The UCLA-20, version 3, is a measure of both loneliness and social isolation with strong psychometric properties among a variety of age groups and disability groups [27,28]. These measures will be completed at baseline and post intervention (week 5).

Aim 2 will be evaluated through feasibility metrics: recruitment rates, implementation and resource management issues, participant attendance in class (percent of classes attended divided by the total) and outside of class (play time not within the scheduled class sessions), and program satisfaction and enjoyment. Two components of satisfaction will be measured, namely, satisfaction with program delivery and satisfaction with playing with others. Both components will be measured by Likert scale surveys (Multimedia Appendix 2). Survey questions for program delivery will ask participants how satisfied they were with social interactions, online gameplay, and how classes were conducted by the instructors. Survey questions for "playing with others" will ask participants if and how often they played with both peers and people outside of class, and the strength of the friendships or relationships that were created. Overall enjoyment of the program will be measured in a similar manner with a single Likert scale question (Multimedia Appendix 2).

Aim 3 will be measured through one-on-one semistructured interviews of participants' perceptions of the program. Interviews will be conducted via phone call with the participant and principal investigator (BL). Interviews will last up to 30 minutes and contain 10 general questions, examining barriers and facilitators to adherence, likes and dislikes with the program and equipment, and recommendations to improve the program (Multimedia Appendix 3). General questions will include follow-up questions that probe underlying behavioral mechanisms to participation and perceived benefits to participation. The interviewer (BL) has completed over 400 interviews related to disability and exercise. Interviews will be audio recorded and then transcribed for analysis. The qualitative component will be published in a secondary analysis publication.

Analyses

The research team's philosophical assumptions will align with dialectical pluralism [29]. This paradigm posits that the research team should hold separate theoretical perspectives for the quantitative and qualitative methods. The research team will conduct the quantitative component of the study under the conventional positivism perspective, while the qualitative component will be conducted under an interpretivist perspective.

As a preliminary study, the study is not powered for efficacy. Instead, the findings will provide outcome estimates that will inform sample size and design considerations for a larger trial. Descriptive statistics for all quantitative outcomes will include means, SDs, effect sizes, box and whisker plots, and 95% CIs as appropriate. Aim 1 will include *t* tests to compare pre-to-post changes in survey scores. Aim 2 feasibility metrics will be reported in a descriptive manner with no a priori criteria for acceptability.

Aim 3 will be analyzed using a qualitative 6-step process of thematic analysis [30] by two members of the research team. In summary, two analysts will generate codes from segments of the transcribed interviews. The codes will be organized into representative subthemes. The analysts will repeat this process for each transcription. The subthemes will then be merged into higher order themes, which will be reported. The analysts will use a relativist approach of enhancing the quality of the qualitative research findings [31]. First, the research findings will aim to provide a *substantive contribution* [32], that is, the findings will aim to understand how participants interact with the program to inform other investigators who develop similar interventions. Second, *coherence* will be sought by ensuring that qualitative study procedures throughout the project align with the goals of the study [33]. Third, *transparency* will be maintained throughout the study by receiving in-depth feedback from a *critical friend* [34]. The qualitative researchers of the study will scrutinize matters including the theoretical preferences, qualitative procedures, and resultant findings to

encourage reflexivity and alternative explanations and interpretations of the data.

Results

This study was approved by the university institutional review board on May 23, 2022. The study was initiated in February 2022, and the first participant was enrolled in July 2022. Recruitment of the last participant is anticipated in October 2022.

Discussion

Anticipated Findings

This study will investigate the preliminary benefits of a home-based mindfulness program that is combined with peer-to-peer virtual reality gaming on mental health among adolescents with disabilities. A program that is beneficial toward depression, anxiety, and isolation, and connects peers remotely at the home using low-cost equipment could greatly benefit this population, which has experienced poorer mental health since the outbreak of the COVID-19 pandemic [5]. The quantitative study component will provide outcomes estimates of the effects of the program on depression, social isolation, and loneliness, and the results will be used to inform sample size considerations for a large clinical trial. The qualitative results will aid in understanding behavioral mechanisms that underlie successful participation, which will help us operationalize implementation procedures in a future trial and explain changes in quantitative outcomes.

In addition to concerns of poor mental health among adolescents with disabilities, health professionals are often concerned with maintaining or improving physical function [35,36] or alleviating and preventing a variety of other health conditions that arise from sedentary behavior (eg, pain, obesity, pressure ulcers, and low bone mineral density) [37]. There is evidence to suggest that physical health concerns can be addressed by combining health-enhancing interventions with the latest immersive virtual reality technology [38,39], but to the best of our knowledge, there is no peer-to-peer group-based intervention for improving mental health. Given the multifaceted nature of health promotion among this population, this study will test a brief low-dose program so that it can be easily integrated within clinical practice and disseminated with other health-enhancing interventions.

Strengths and Limitations

An innovative component of the study is that it incorporates remote study procedures. Due to difficulties with allocating transportation, a remote study procedure increases accessibility by eliminating the need for on-site visitation. This study has limitations. The sample size is small, and the results will need to be confirmed with larger clinical trials. Additionally, this study requires participants to be able to use the handheld controllers and view the screen of the virtual reality headsets, which may not be appropriate for some people who have functional or visual impairments.

Conclusions

Should the findings of this study suggest a potential benefit toward some aspects of mental health, the study may discover an innovative and, most importantly, scalable method for addressing mental health among children with physical disabilities.

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Data Availability

The data sets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

BL, JHR, and DD contributed to the design of the study. All authors contributed to the second draft of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Intervention plan.
[DOCX File , 13 KB - resprot_v11i10e42651_app1.docx]

Multimedia Appendix 2
Study survey questions for program satisfaction and enjoyment.
[PDF File (Adobe PDF File), 84 KB - resprot_v11i10e42651_app2.pdf]

Multimedia Appendix 3
Interview questions.
[PDF File (Adobe PDF File), 98 KB - resprot_v11i10e42651_app3.pdf]

Multimedia Appendix 4
Peer review report from the Center for Engagement in Disability Health and Rehabilitation Sciences (CEDHARS) Pilot Grant Funding Program: Addressing Health Disparities in Adults or Children with Disabilities - University of Alabama at Birmingham (USA).
[PDF File (Adobe PDF File), 295 KB - resprot_v11i10e42651_app4.pdf]

References

1. Waltersson L, Rodby-Bousquet E. Physical activity in adolescents and young adults with cerebral palsy. Biomed Res Int 2017;2017:8080473. [doi: 10.1155/2017/8080473] [Medline: 29423412]
2. Chamberlain MA, Kent RM. The needs of young people with disabilities in transition from paediatric to adult services. Eura Medicophys 2005 Jun;41(2):111-123 [FREE Full text] [Medline: 16200026]
3. Hallum A. Disability and the transition to adulthood: issues for the disabled child, the family, and the pediatrician. Curr Probl Pediatr 1995 Jan;25(1):12-50. [doi: 10.1016/s0045-9380(06)80013-7] [Medline: 7720408]
4. Donkervoort M, Wiegerink DJHG, van Meeteren J, Stam HJ, Roebroeck ME, Transition Research Group South West Netherlands. Transition to adulthood: validation of the Rotterdam Transition Profile for young adults with cerebral palsy and normal intelligence. Dev Med Child Neurol 2009 Jan;51(1):53-62. [doi: 10.1111/j.1469-8749.2008.03115.x] [Medline: 19021680]
5. Downs J, Blackmore AM, Epstein A, Skoss R, Langdon K, Jacoby P, Cerebral Palsy Mental Health Group. The prevalence of mental health disorders and symptoms in children and adolescents with cerebral palsy: a systematic review and meta-analysis. Dev Med Child Neurol 2018 Jan;60(1):30-38. [doi: 10.1111/dmcn.13555] [Medline: 28914445]
6. Shkedy Rabani A, Harries N, Namoora I, Al-Jarrah MD, Karniel A, Bar-Haim S. Duration and patterns of habitual physical activity in adolescents and young adults with cerebral palsy. Dev Med Child Neurol 2014 Jul;56(7):673-680. [doi: 10.1111/dmcn.12394] [Medline: 24506509]
7. Carlon SL, Taylor NF, Dodd KJ, Shields N. Differences in habitual physical activity levels of young people with cerebral palsy and their typically developing peers: a systematic review. Disabil Rehabil 2013 Apr;35(8):647-655. [doi: 10.3109/09638288.2012.715721] [Medline: 23072296]
8. Blackman JA, Conaway MR. Adolescents with cerebral palsy: transitioning to adult health care services. Clin Pediatr (Phila) 2014 Apr;53(4):356-363. [doi: 10.1177/0009922813510203] [Medline: 24275216]
9. Ryan JM, Cassidy EE, Noorduyn SG, O'Connell NE. Exercise interventions for cerebral palsy. Cochrane Database Syst Rev 2017 Jun 11;6:CD011660 [FREE Full text] [doi: 10.1002/14651858.CD011660.pub2] [Medline: 28602046]
10. Hallal PC, Victora CG, Azevedo MR, Wells JCK. Adolescent physical activity and health: a systematic review. Sports Med 2006;36(12):1019-1030. [doi: 10.2165/00007256-200636120-00003] [Medline: 17123326]
11. Slaman J, Roebroeck M, van der Slot W, Twisk J, Wensink A, Stam H, LEARN 2 MOVE Research Group. Can a lifestyle intervention improve physical fitness in adolescents and young adults with spastic cerebral palsy? A randomized controlled trial. Arch Phys Med Rehabil 2014 Sep;95(9):1646-1655. [doi: 10.1016/j.apmr.2014.05.011] [Medline: 25067790]
12. Vogtle LK, Malone LA, Azuero A. Outcomes of an exercise program for pain and fatigue management in adults with cerebral palsy. Disabil Rehabil 2014;36(10):818-825. [doi: 10.3109/09638288.2013.821181] [Medline: 23924251]
13. Lai B, Wen H, Sinha T, Davis D, Swanson-Kimani E, Wozow C, et al. The impact of COVID-19 on the lifestyles of adolescents with cerebral palsy in the Southeast United States. Disabil Health J 2022 Apr;15(2):101263 [FREE Full text] [doi: 10.1016/j.dhjo.2021.101263] [Medline: 35000878]
14. Cacioppo M, Bouvier S, Bailly R, Houx L, Lempereur M, Mensah-Gourmel J, ECHO Group. Emerging health challenges for children with physical disabilities and their parents during the COVID-19 pandemic: the ECHO French survey. Ann Phys Rehabil Med 2021 May;64(3):101429 [FREE Full text] [doi: 10.1016/j.rehab.2020.08.001] [Medline: 32818674]
15. Lebrasseur A, Fortin-Bédard N, Lettre J, Bussières EL, Best K, Boucher N, et al. Impact of COVID-19 on people with physical disabilities: a rapid review. Disabil Health J 2021 Jan;14(1):101014 [FREE Full text] [doi: 10.1016/j.dhjo.2020.101014] [Medline: 33158795]
16. Theis N, Campbell N, De Leeuw J, Owen M, Schenke KC. The effects of COVID-19 restrictions on physical activity and mental health of children and young adults with physical and/or intellectual disabilities. Disabil Health J 2021 Jul;14(3):101064 [FREE Full text] [doi: 10.1016/j.dhjo.2021.101064] [Medline: 33549499]
17. Varengue R, Brochard S, Bouvier S, Bailly R, Houx L, Lempereur M, et al. Perceived impact of lockdown on daily life in children with physical disabilities and their families during the COVID-19 pandemic. Child Care Health Dev 2021 Dec 28:10.1111/cch.12952. [doi: 10.1111/cch.12952] [Medline: 34964148]
18. 2017 Annual Report. America's Health Rankings. 2017. URL: https://www.americashealthrankings.org/learn/reports/2017-annual-report [accessed 2022-09-29]

19. Julious SA. Sample size of 12 per group rule of thumb for a pilot study. Pharm Stat 2005 Oct;4(4):287-291. [doi: 10.1002/pst.185]
20. Saebu M, Sørensen M, Halvari H. Motivation for physical activity in young adults with physical disabilities during a rehabilitation stay: a longitudinal test of self-determination theory. J Appl Soc Psychol 2013 Feb 21;43(3):612-625. [doi: 10.1111/j.1559-1816.2013.01042.x]
21. Bentzen M, Malmquist LK. Differences in participation across physical activity contexts between adolescents with and without disability over three years: a self-determination theory perspective. Disabil Rehabil 2022 May;44(9):1660-1668. [doi: 10.1080/09638288.2021.1894489] [Medline: 33721549]
22. Walsh R. Lifestyle and mental health. Am Psychol 2011 Oct;66(7):579-592. [doi: 10.1037/a0021769] [Medline: 21244124]
23. Kovacs M. Children's Depression Inventory (CDI and CDI 2). In: The Encyclopedia of Clinical Psychology. Hoboken, NJ: John Wiley & Sons; 2014:1-5.
24. de la Vega R, Racine M, Sánchez-Rodríguez E, Solé E, Castarlenas E, Jensen MP, et al. Psychometric properties of the short form of the Children's Depression Inventory (CDI-S) in young people with physical disabilities. J Psychosom Res 2016 Nov;90:57-61 [FREE Full text] [doi: 10.1016/j.jpsychores.2016.09.007] [Medline: 27772560]
25. Russell D, Peplau LA, Ferguson ML. Developing a measure of loneliness. J Pers Assess 1978 Jun;42(3):290-294. [doi: 10.1207/s15327752jpa4203_11] [Medline: 660402]
26. Weeks DG, Michela JL, Peplau LA, Bragg ME. Relation between loneliness and depression: a structural equation analysis. J Pers Soc Psychol 1980 Dec;39(6):1238-1244. [doi: 10.1037/h0077709] [Medline: 7205551]
27. Alsubheen SA, Oliveira A, Habash R, Goldstein R, Brooks D. Systematic review of psychometric properties and cross-cultural adaptation of the University of California and Los Angeles loneliness scale in adults. Curr Psychol 2021 Nov 12:1-15 [FREE Full text] [doi: 10.1007/s12144-021-02494-w] [Medline: 34785877]
28. Balandin S, Berg N, Waller A. Assessing the loneliness of older people with cerebral palsy. Disabil Rehabil 2006 Apr 30;28(8):469-479. [doi: 10.1080/09638280500211759] [Medline: 16513580]
29. Johnson RB. Dialectical pluralism: a metaparadigm whose time has come. J Mixed Methods Res 2016 Jul 08;11(2):156-173. [doi: 10.1177/1558689815607692]
30. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Res Psychol 2006 Jan;3(2):77-101. [doi: 10.1191/1478088706qp063oa]
31. Smith B, Sparkes AC, editors. Routledge Handbook of Qualitative Research in Sport and Exercise. London, UK: Routledge; 2016.
32. Denzin NK, Lincoln YS, editors. The Sage Handbook of Qualitative Research, 3rd ed. Thousand Oaks, CA: Sage; 2005:959-978.
33. Lieblich A, Tuval-Mashiach R, Zilber T. Narrative Research: Reading, Analysis, and Interpretation. Thousand Oaks, CA: Sage; 1998.
34. Tracy SJ. Qualitative quality: eight “Big-Tent” criteria for excellent qualitative research. Qualitative Inquiry 2010 Oct 01;16(10):837-851. [doi: 10.1177/1077800410383121]
35. Shortland A. Muscle deficits in cerebral palsy and early loss of mobility: can we learn something from our elders? Dev Med Child Neurol 2009 Oct;51 Suppl 4:59-63. [doi: 10.1111/j.1469-8749.2009.03434.x] [Medline: 19740211]
36. Hanna SE, Rosenbaum PL, Bartlett DJ, Palisano RJ, Walter SD, Avery L, et al. Stability and decline in gross motor function among children and youth with cerebral palsy aged 2 to 21 years. Dev Med Child Neurol 2009 Apr;51(4):295-302. [doi: 10.1111/j.1469-8749.2008.03196.x] [Medline: 19391185]
37. Rimmer JH, Schiller W, Chen M. Effects of disability-associated low energy expenditure deconditioning syndrome. Exerc Sport Sci Rev 2012 Jan;40(1):22-29. [doi: 10.1097/JES.0b013e31823b8b82] [Medline: 22016146]
38. Ravi DK, Kumar N, Singhi P. Effectiveness of virtual reality rehabilitation for children and adolescents with cerebral palsy: an updated evidence-based systematic review. Physiotherapy 2017 Sep;103(3):245-258. [doi: 10.1016/j.physio.2016.08.004] [Medline: 28109566]
39. Lai B, Davis D, Narasaki-Jara M, Hopson B, Powell D, Gowey M, et al. Feasibility of a commercially available virtual reality system to achieve exercise guidelines in youth with spina bifida: mixed methods case study. JMIR Serious Games 2020 Sep 03;8(3):e20667 [FREE Full text] [doi: 10.2196/20667] [Medline: 32880577]

Abbreviations

UCLA-20: UCLA Loneliness Scale 20 items

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Protocol

Developing an Immersive Virtual Reality Training System for Novel Pediatric Power Wheelchair Users: Protocol for a Feasibility Study

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Abstract

Background: Power wheelchairs can empower children with physical limitations to gain independence in their everyday lives; however, traditional methods of power wheelchair training are often limited by poor accessibility and safety concerns. Immersive virtual reality technology (IVRT) uses advanced display technology to place users in a fully immersive web-based environment that can support real-time skills training, often requiring less resources and fewer safety concerns than real-world methods. IVRT interventions have shown to be a feasible training option among adult power wheelchair users; however, there is still a need to understand the technical and clinical feasibility of developing an IVRT power wheelchair training tool for the pediatric population.

Objective: This proposed study aims to use expert feedback and an iterative design process to develop an IVRT training intervention for pediatric power wheelchair skill development.

Methods: This 3-phase feasibility study will be conducted within the assistive technology unit of a public pediatric hospital. Separate participant groups will be recruited for each phase, consisting of approximately 10 to 15 clinicians (phase 1), 10 pediatric power wheelchair users (phase 2), and 15 to 20 additional pediatric power wheelchair users (phase 3). Phase 1 will be conducted to gather feedback on the baseline IVRT training intervention. Clinicians will test the intervention and assess its usability and acceptability using qualitative and quantitative methods. Phase 1 participants will also be invited back for a subsequent session to reassess a revised version of the training intervention that has been updated based on their previous feedback. Phase 2 and phase 3 will also use mixed methods to gather feedback on the usability, acceptability, and user experience of the IVRT training intervention from current pediatric power wheelchair users. In addition, phase 3 participants will perform a skills transfer assessment to compare power mobility skill performance between the virtual reality and real-life environments. Data gathered in phase 2 will be used to further refine the IVRT intervention, whereas phase 3 data will be used to statistically evaluate the final version.

Results: This study was approved by the Izaak Walton Killam Health Centre research ethics board in August 2021. Phase 1 testing began in February 2022. The entire study is expected to be completed by 2023.

Conclusions: The results of this study will be used to create an IVRT training intervention for pediatric power wheelchair skill development through an iterative and collaborative design process. Results may also assist in directing future studies in this area.

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KEYWORDS

immersive virtual reality; power wheelchair; training; pediatric rehabilitation; feasibility

Introduction

Background

The inability to mobilize independently can have significant deleterious effects on the psychosocial development of children, often affecting their ability to participate in age-relevant activities [1,2]. For children with physical disabilities that limit their ability to ambulate, assistive devices such as power wheelchairs empower them to mobilize with independence and create great opportunities for play, leading to enhanced intrapersonal and interpersonal relationships [2-7]. Children who use power wheelchairs describe feeling liberated and gaining autonomy with powered mobility use, with some even reporting the device as an integral part of their identity and an extension of the self [6]. Despite the benefits of power wheelchair use, methods of its training can be highly variable and difficult to access [8]. Many children are unable to participate in training opportunities owing to common barriers such as limited access, safety concerns, and inadequate availability of resources [5,6]. Furthermore, the rate of skill acquisition is often not a linear process, and it can be difficult for training interventions to account for individual differences among clients, including skill level and age range [5-8]. Access to power wheelchair training opportunities is essential to develop the skills required for independent participation and overall development [1,2]. As such, there exists a need for an approach that offers effective training for novel power wheelchair users within a safe and accessible environment.

Virtual Reality for Rehabilitation

Virtual reality (VR) is emerging as a promising modality for therapeutic and rehabilitative interventions in health care [9,10]. VR interventions have been shown to help support the rehabilitative process, by improving functional and cognitive performance in diverse populations such as patients with Parkinson disease [11], patients with chronic stroke [12], older adults with cognitive impairment [13], and power wheelchair users [14]. The growing interest in VR may be owing to the unique opportunity that allows individuals to engage in task-specific interventions by interacting in a real-time simulation of a computer-controlled activity or environment [9,10,15]. The use of a computer interface can also allow clinicians to quickly adjust the intervention to suit the user's current ability (eg, modification of the difficulty level), thus promoting user awareness and confidence [16,17].

Children who use a VR application to practice their power wheelchair skills have shown increased overall improvement when transferring their skills into real-world navigation compared with their pretraining scores or a control group with no training [16,18-20]. A study examining the efficacy of a desktop VR system in teaching novel power wheelchair skills found that the VR intervention improved children's skills to a greater extent than the control group who had no VR training; however, statistical significance was not reached [20]. In this case, individual performance scores varied greatly owing to potential confounders (eg, sex differences and potential motivation discrepancies), and it was suggested that future VR interventions should consider individualizing their training methods to meet the varying needs and interests of participants [20].

Immersive VR Technology

Recent VR modalities such as immersive VR technology (IVRT) may elicit increased performance improvements over time compared with nonimmersive VR systems owing to an increase in user engagement [21-24]. IVRT is a specific subset of VR that uses display technology such as head-mounted display (HMD) goggles or multiple screen projections to make the user feel physically present in a 3D setting [25]. The use of screen projections to create a fully immersive environment can be resource-intensive, often requiring a large space and multiple pieces of technological equipment to achieve a realistic setting. In contrast, HMD technology requires less costly resources and small physical space and can be easily transported to allow for clinical or at-home use [26,27]. Therefore, IVRT interventions using HMD tend to be the primary choice for recent skills-based training applications [28].

One of the greatest benefits of IVRT is the sense of presence that can be experienced by users during gameplay. The feeling of truly *being there* in the VR environment is heightened within an immersive VR system compared with a nonimmersive system and has been linked to better performance [21-24]. In a 2017 study comparing wheelchair performance and visual technology devices, the sense of presence and driving performance were both increased among users who trained with the IVRT modality compared with those who trained with a computer monitor [21]. Studies have also shown that users participating in an IVRT simulator are able to naturally mimic the same wheelchair-specific movement patterns (eg, trunk posture and chair propulsion) as executed in the real world, thus demonstrating the feeling of realism that can be experienced in the immersive environment [29].

IVRT has shown promise as a feasible rehabilitation tool for power wheelchair users; however, most studies have been conducted only among the adult population [14]. A 2019 scoping review found that most published studies using HMD-based IVRT for power wheelchair simulation included only adult participants, whereas a limited number of studies have extended into the pediatric population [14,16,30]. Morère et al [30] used a 3D wheelchair simulator to conduct a chronic training intervention and identified a positive change in pediatric participants' outdoor driving abilities after completion of the training period; however, this study included only 12 participants in total. Another pediatric study revealed improvements in real-world power wheelchair skills following training with HMD compared with pretraining levels, but this study was also limited in sample size [16].

IVRT has the potential to become a valuable training tool for pediatric power wheelchair users, but there is a paucity of literature on this topic, with weak descriptions of methodology and limited sample populations [8,31]. Introducing IVRT training for pediatric power wheelchair users may help to enhance opportunities for safe and accessible skill development, leading to increased independence and improved early-life psychosocial development [2-7]. To develop an effective method of power wheelchair training, there exists a need for

collaborative studies in which expert-driven feedback can be used to design a training intervention that meets the needs of pediatric power wheelchair users.

Objectives and Research Questions

Overview

This proposed 3-phase feasibility study will collect feedback from experienced clinicians and pediatric power wheelchair users to collaboratively develop an HMD-based IVRT training platform designed for pediatric power wheelchair skill development. Participants will engage in the training intervention and provide feedback on the usability and acceptability of the intervention for novel skill development. In this study, usability refers to the ease with which participants can successfully engage in the IVRT training intervention [32]. Feedback related to usability will assist in identifying features of the intervention that may help to achieve specific goals easily and effectively with limited confusion during gameplay. Acceptability is the perceived appropriateness of the intervention to meet the needs of the target population (novel pediatric power wheelchair users) [33]. Acceptability feedback will describe features of the IVRT training intervention that may help to enhance clinical uptake and accurately capture the training requirements of the pediatric population. Clinicians will also assist in developing a list of potential power wheelchair skills to be targeted in the training intervention.

Feedback gathered during each of the 3 phases will be carefully implemented in the technical design to continuously refine the training platform and produce a final version that can be used as a practical training tool for effective skill development in the future [34]. The efficacy of the final IVRT training intervention for power wheelchair skills training will be measured in future studies. To the best of our knowledge, this is the first study as of April 2022 that will gather iterative feedback from clinicians and experienced power wheelchair users to develop an IVRT training intervention intended for pediatric power wheelchair skill development.

Objective

Overview

To determine the feasibility of using an IVRT training intervention for pediatric power wheelchair skill development, as determined by the following:

1. Expert opinion from clinicians experienced in working with pediatric power wheelchair users
2. User feedback and skill performance metrics gathered from current pediatric power wheelchair users

Research Question 1

What is the usability of the IVRT training intervention for novel skill development, from the clinician's and current power wheelchair user's perspectives?

Research Question 2

What is the acceptability of the IVRT training intervention for pediatric power wheelchair users, from the clinician's and current power wheelchair user's perspectives?

Research Question 3

What set of skills should be included in the IVRT training intervention for appropriate power wheelchair skill development, from the clinician's perspective?

We hypothesized that iterative feedback gathered from clinicians and current power wheelchair users will create an IVRT training intervention that is appropriate for our target population and can be successfully used for future power wheelchair skill development.

Methods

Study Design

This is a 3-phase feasibility study that will assess the usability and acceptability of an IVRT training intervention that has been collaboratively designed to support power wheelchair skill development. Mixed methods will be applied to provide qualitative and quantitative data on the outcome measures.

Study Setting

This study will be conducted within the assistive technology unit of a public pediatric hospital, the Izaak Walton Killam Health Centre in Halifax, Nova Scotia, Canada. An experienced researcher will facilitate all in-laboratory IVRT sessions and collect training intervention data. All power wheelchair skills performed in the IVRT training system and in the real world during phase 3 will be independently assessed by a clinician trained in power wheelchair skills assessment.

Participants and Recruitment

Eligible participants for this feasibility study will belong to one of 2 population groups. The first population group will consist of clinicians with at least three months of experience in working with individuals who use power wheelchairs (by means of training or offering care services) and who practice in a health care profession such as physiotherapists, occupational therapists, or child life specialists. The second population group will consist of children (aged 4-18 years) who currently use power wheelchairs. The lower age limit is selected to ensure that the VR headset will properly fit all participants, whereas the upper limit is representative of the pediatric population. A complete list of inclusion and exclusion criteria is provided in Textbox 1.

For phase 1, our target sample size is approximately 10 to 15 participants, consistent with common sample sizes used in technology feasibility studies with an iterative design process [35-37]. The target sample size for phase 2 will be 10 participants, to gather user experience data and facilitate 1 round of iterative development based on user feedback. For phase 3, we aim to recruit 15 to 20 participants for the purpose of statistically assessing the final version of the IVRT training intervention through user feedback and skill transferability. The target sample size for phase 3 is consistent with large studies piloting non-VR power wheelchair training methodologies [38,39] and is also greater than that used in previous pediatric IVRT feasibility studies [16,30].

Clinicians will be recruited for phase 1 via web-based advertisements (email lists and web-based newsletters) and word of mouth. Pediatric participants will be recruited for phase 2 and phase 3 via web-based newsletters, poster advertisements displayed within the host hospital, and discussion with their care provider. Researchers will distribute study information forms to care providers, which will outline the study design, purpose, and contact information. Care providers will be encouraged to offer these forms to their patients if it is believed that they may be interested in participating. Then, the individuals will indicate their interest to a research team member via email or verbally, and eligible individuals will be invited to participate in the study.

Textbox 1. Inclusion and exclusion criteria for each participant group.

Inclusion criteria for clinicians (phase 1)

- Overall, ≥3 months of experience in working with power wheelchair users
- Practices in a health care setting
- Able to communicate fluently in English (verbal and writing)
- Able to operate a standard power wheelchair joystick

Exclusion criteria for clinicians (phase 1)

- History or suspicion of a photosensitive seizure disorder
- Unable to tolerate wearing head-mounted display goggles for prolonged periods of time
- Impairment in visual functioning that cannot be corrected with lenses or contacts (eg, 3D depth perception, cataracts, and oculomotor dysfunction)

Inclusion criteria for current power wheelchair users (phases 2 and 3)

- Aged 4-18 years
- Current power wheelchair user, with ≥1 year of experience in using power wheelchair as primary means of mobility
- Able to communicate verbally in English
- Able to operate a standard power wheelchair joystick

Exclusion criteria for current power wheelchair users (phases 2 and 3)

- History or suspicion of a photosensitive seizure disorder
- Unable to tolerate wearing head-mounted display goggles for prolonged periods of time
- Impairment in visual functioning that cannot be corrected with lenses or contacts (eg, 3D depth perception, cataracts, and oculomotor dysfunction)
- Participated in phase 2 of this study (phase 3 participants only)

Ethics Approval

This study has been approved by the Izaak Walton Killam Health Centre research ethics board (Office of Research Ethics 1026934) in Halifax, Nova Scotia, Canada. Informed consent will be obtained from all study participants before their participation; participants aged <18 years will complete the assent form, and participants aged ≥18 years will complete the consent form.

Procedure

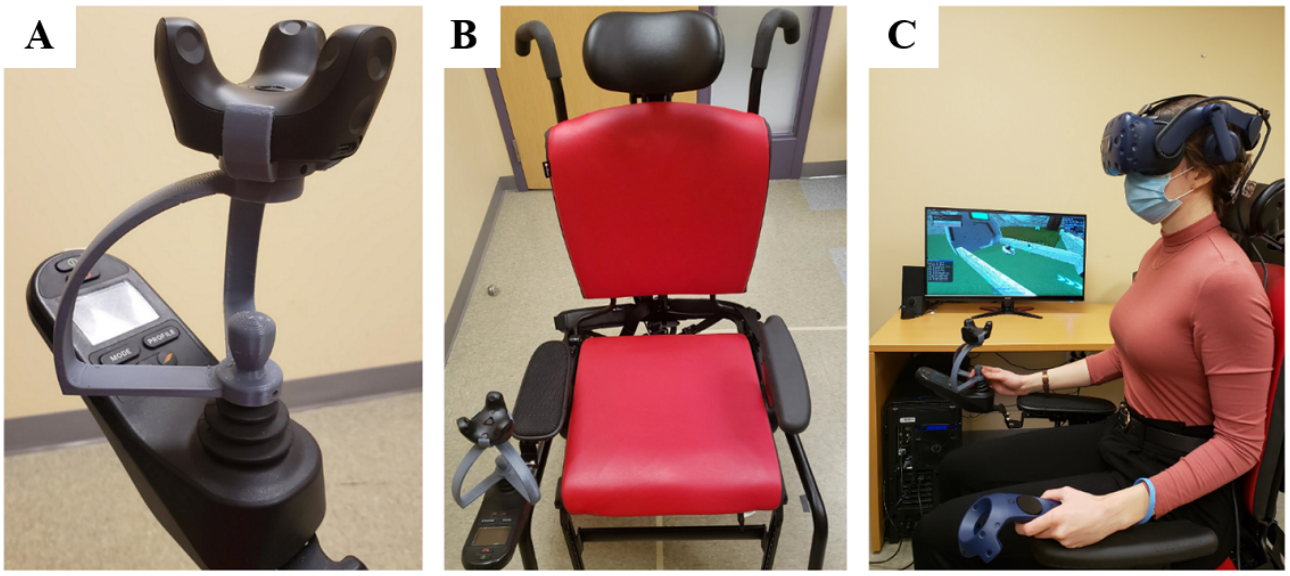
IVRT Equipment

The IVRT training application has been built using Unity3D, a Unity Technologies game engine that allows developers to create and manage web-based gaming environments. Participants will engage in the IVRT training intervention using the HTC Vive Pro, a commercially available VR technology from HTC Corporation that places users in a fully immersive VR environment using the HMD headset, tracking devices, and controllers (Figure 1) [40]. The wheelchair joystick used for this study has been built by an engineering team using a 3D printer and specifications that closely match a real-world power wheelchair joystick. An HTC Vive Pro tracking device is attached to the top of the joystick to allow for accurate control of the power wheelchair within the IVRT environment (Figure 1). Henceforth, this joystick will be referred to as the "tracker joystick." The user can also engage in hand-based activities (eg, turning on the power wheelchair) in the IVRT environment by moving a controller held in their nondominant hand.

In phase 1, participants will sit in a Rifton Equipment Activity Chair [41] that replicates the seating and joystick setup of a power wheelchair. The Activity Chair is a positioning chair that provides adaptable seating for a range of patient populations and has been slightly modified to accommodate an arm attachment for easy operation of the tracker joystick (Figure 1). In phase 2 and phase 3, participants will sit in their own power wheelchair, and the tracker joystick will be attached to their personal joystick controller stem. The tracker joystick is fitted to easily screw onto any standard-size joystick controller stem, allowing for users to participate in the IVRT intervention without the need to transfer to a new chair. During the IVRT simulation, users will progress through the intervention in a

power wheelchair that replicates the natural movement of a real power wheelchair. The in-game power wheelchair movement patterns (eg, acceleration and deceleration speeds and turning trajectories) have been designed in collaboration with an occupational therapist to ensure that all movements are simulated with accuracy.

Figure 1. An HTC Corporation tracker and IVRT joystick (A) attached to the Rifton Activity Chair (B) and in-use during gameplay of the training intervention (C). IVRT: immersive virtual reality technology.



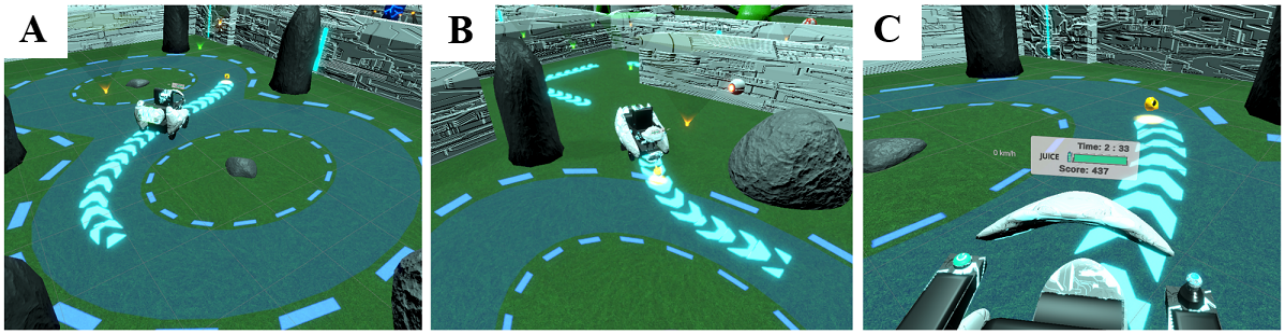
IVRT Intervention

The IVRT training intervention has been designed to help users develop core power wheelchair skills in a motivating and engaging manner. The baseline version of the training intervention was created in collaboration with the research committee (consisting of power wheelchair rehabilitation experts, including a pediatric physiatrist and a pediatric occupational therapist) and software development team. The research committee identified power wheelchair tasks that were commonly taught to novel power wheelchair users as beginner to moderate–level skills (eg, moving forward, moving backward, and turning 90°) [42]. Then, the software development team integrated the skills into the IVRT system within an environment that was approved by the research team to be acceptable for the pediatric population (ie, containing age-appropriate graphics and characters). The baseline training intervention is intended to introduce participants to the potential of an IVRT system for pediatric power wheelchair training and gather expert feedback on how to improve the skills, environment, and overall user experience.

The intervention places participants in a colorful cartoon environment with robotic characters. Users begin the intervention in the main lobby, where the instructor of the game explains the instructions and wheelchair controls using audio and visual cues. Then, the participants are brought to the outside world to begin level 1, where they must use the tracker joystick to control their power wheelchair and move through specific areas in the game to complete each level. Users will be challenged to participate in tasks that integrate various power wheelchair skills, such as backing up in a narrow hallway, driving over a ramp, and following a figure-eight path (Figure 2). In addition, players are also provided with various opportunities to increase their scores during gameplay, including driving on the correct path and collecting fruits to power up their wheelchair. The inclusion of a reward system that allows for positive reinforcement has been shown to enhance a child's attention and motivation when training within a VR environment [43-45]. Therefore, it is anticipated that these additional components will help to increase user engagement and improve performance outcomes.

The IVRT system offers a range of options to measure client performance, which will otherwise be difficult to capture in real-world training. In total, 4 different VR camera angles (overhead, follow camera, first-person view, and free camera) provide the operator with a variety of viewpoints to assess the user's driving skills (Figure 2). Chart selections can also be accessed by the operator to evaluate in-game user behavior, such as *client focus* (measurement of attentional focus) and *pathways* (real-time charting of user's driving patterns). Furthermore, client skills and goals can be easily tracked using the metrics options, which offer real-time speed, collision, and completion time statistics. Taken together, the IVRT system can provide an accurate and comprehensive assessment of driving performance without disrupting the in-game user experience.

Figure 2. Screenshots of the training application showing stages of the figure-eight task from three different camera viewpoints: follow camera (A), free camera (B), and first-person view (C).



Training Intervention—Phase 1

The aim of phase 1 is 2-fold: (1) to use clinician feedback to develop a list of potential power mobility skills to be implemented in future versions of the IVRT training intervention and (2) to assess the usability and acceptability of the intervention from the clinician's perspective. Phase 1 participants, comprising health care clinicians, will be exposed to a baseline version of the IVRT training intervention and participate in a training session during which they will progress through each of the levels, with instructions to carefully evaluate various components of the intervention. Participants will also be given the option to freely explore the game environment following the completion of each level, if they wish to do so.

Participants will be asked to assess the ability of the intervention to teach a range of core power wheelchair skills. Currently, there are no standardized methods that have been established among professionals to assess power mobility skills among children [38]; however, 4 main measures are commonly used: Assessment of Learning Powered Mobility Use [46], Powered Mobility Program [47], Power Mobility Training Tool [48], and Wheelchair Skills Checklist [49]. In the adult population, the Wheelchair Skills Test for Powered Wheelchairs is well validated for the evaluation of power wheelchair capacity [42]. Owing to the lack of an established measurement tool for the pediatric population, the research team identified core skills frequently listed in both the Wheelchair Skills Test for Powered Wheelchairs and common pediatric assessment tools to create a comprehensive skills list for clinician use. This list was developed in consultation with a pediatric rehabilitation specialist to ensure that all skills were appropriate for inclusion.

Immediately following the IVRT training intervention, participants will be provided with a list of 28 individual power mobility skills and asked to indicate their level of agreement with the following statement: "Based on my experience working with power wheelchair users, I believe the immersive virtual reality technology (IVRT) application can be used to teach children and adolescents to (insert skill here)." Consensus on the application's ability to assess each item will be defined as ≥75% of participants indicating that they agree (score=4 out of 5) or strongly agree (score=5 out of 5) for a given item, leading to the inclusion of the skill in subsequent phases. If ≥75% of participants indicate disagreement (score=2 out of 5) or strong disagreement (score=1 out of 5) for a particular item, this will be deemed as consensus that the intervention is not appropriate for the development of that skill, and it will not be included in future phases. If a neutral response (score=3 out of 5) is indicated by ≥75% of participants, the skill will be refined for future versions of the training intervention using participant feedback. If an item is rated <4 out of 5, participants will be asked to provide a specific recommendation for modification of the IVRT intervention pertaining to that skill. If a participant believes that a skill cannot be feasibly modified, they will provide no response in the recommendation section.

Participants will also be provided with 3 separate questionnaires to assess perceived usability, acceptability, and overall user experience. Quantitative data will be collected from (1) the Presence Questionnaire (PQ) [50], (2) an ad hoc usability and acceptability questionnaire, and (3) an ad hoc user experience questionnaire. Qualitative data will be collected from (1) an ad hoc user experience questionnaire; (2) participants' informal in-game comments and reports, as recorded by the researcher; and (3) a semistructured interview (round 2 only). A complete list of the assessment measures included in each phase is provided in Table 1.

The PQ and ad hoc usability and acceptability questionnaire will be provided as paper-based materials. The PQ is a well-validated assessment tool used to measure presence within a VR environment. In this study, the PQ has been adapted to include the 4 subscales most relevant to the IVRT training intervention: realism, possibility to act, quality of interface, and self-evaluation of performance [50]. Participants will be asked to report their experience related to multiple components of each subscale using a 7-point Likert scale rating. The ad hoc usability and acceptability questionnaire has been adapted from the Perceived Usefulness and Perceived Ease of Use scales [51] and System Usability Scale [52]. This questionnaire will be used to explore participants' attitudes toward using the IVRT intervention as a training tool for the pediatric population. Participants will be asked to rank each statement on the questionnaire from 1 to 5, ranging from "strongly agree" to "strongly disagree."

Table 1. Assessments by phase and round.

Assessments	Phase 1 (clinicians)		Phase 2 (power wheelchair users)	Phase 3 (power wheelchair users)
	Round 1	Round 2	Round 1	Round 1
Power wheelchair skills inclusion checklist	✓[a]			
Presence Questionnaire	✓	✓	✓	✓
Usability and acceptability questionnaire	✓	✓	✓	✓
User experience questionnaire	✓	✓	✓	✓
Semistructured user experience interview		✓	✓	✓
Training methods questionnaire and interview (power wheelchair user and caregiver)			✓	✓
Skill transferability assessment				✓

[a]✓: the check mark specifies the assessment measures that will be used in each phase and round of the study.

The ad hoc user experience questionnaire will be hosted on the secure web-based software platform, REDCap (Research Electronic Data Capture; Vanderbilt University) [53]. The web-based questionnaire format was chosen to allow participants to respond to open-ended questions by typing rather than writing; however, they will be provided the option to complete a paper-based questionnaire if it is preferred. This questionnaire will be used to assess participant demographics, user tolerance (a component of usability), and overall user experience. To capture user tolerance to the IVRT intervention, the presence of VR-induced symptoms and effects (VRISE) will be assessed during and after the intervention. VRISE includes symptoms such as nausea, dizziness, disorientation, and fatigue and can occur as a side effect of VR exposure [51]. VR systems using HMD have been found to increase the prevalence of VRISE compared with nonimmersive systems; however, our intervention's length falls below the theoretical limit of exposure to VR for adults (55-70 minutes) [54,55]. Although our intervention session is approximately 20 to 30 minutes in length, it is anticipated that some participants may still experience VRISE symptoms. User experience will be assessed in this questionnaire using open-ended questions that have been developed to better understand participants' experiences within the IVRT application, such as ease of use, appropriateness of tasks and graphics, and suggestions for improvement.

Following the completion of the study session, participant feedback data will be summarized, anonymized, and presented to the research committee. The committee will use these data to produce recommendations for a new iteration of the application, which will be implemented by the software development team.

Participants will be invited back to the laboratory to complete a second session during which they will engage in the IVRT training intervention that has been updated based on feedback from the round-1 sessions. We aim to have at least 60% (ie, >7 out of 12 participants) of phase 1 participants return for second round of testing, based on previous health care studies that have received a similar percentage of participant retention for multiround testing [56,57]. The second round of testing is intended to check for accuracy and ensure that participants are satisfied with the changes implemented based on feedback from the first session. Participants will complete the updated IVRT training intervention, followed by a semistructured interview designed to gather in-depth details of the user experience. The interview questions will be developed based on data from round 1 and will aim to capture feedback regarding the system's new updates (eg, opinions regarding any new skills or levels added and updated graphics or audio) and address any potential areas for further improvement. Finally, participants will also complete the same PQ, ad hoc usability and acceptability questionnaire, and ad hoc user experience questionnaire as in round 1. Participant feedback will be presented to the research committee, and if any items in the IVRT intervention are found to still require significant changes, they will be updated as necessary by the software development team.

Training Intervention—Phase 2

Phase 2 will assess the usability and acceptability of the IVRT system from the pediatric power wheelchair user's perspective. Participants in phase 2 will be comprised of current pediatric power wheelchair users, who will test and evaluate the updated IVRT training system that has been adjusted based on feedback gathered from clinicians in phase 1.

During the IVRT trial, participants will be placed in the IVRT setup and provided with 5 to 10 minutes to freely explore and acclimate to the VR setting. Once the participants indicate that they are ready to begin, they will start the training intervention. The skills selected in phase 1 for inclusion will be integrated into the intervention, and participants will be encouraged to complete each skill as they progress through the levels. Following completion of the intervention, participants will be given the option to exit the system or continue exploring after a mandatory 10-minute break. After the break, participants may freely explore the VR environment for up to an additional 15 minutes at their own discretion. The mandatory 10-minute break has been included in the session to reduce consistent VR exposure and limit the potential of VRISE among children [58].

Immediately following the IVRT intervention, participants will complete the same 3 questionnaires as in phase 1, but with age-appropriate adaptations (eg, changes to wording or question structure). Age-appropriate adaptations will be approved by a child life specialist to ensure suitability for the pediatric

population. All questionnaires will be asked aloud by the researcher, and the pediatric participant's verbal responses will be recorded. As in phase 1, the questionnaires will explore the perceived usability and acceptability of the IVRT system for power wheelchair skill development, IVRT tolerability, and general user experience.

Participants will also engage in a semistructured user experience interview, in which questions will be asked aloud and responses will be audio-recorded for qualitative analysis. The semistructured interview intends to gather in-depth details on the perceived usability, acceptability, and experience in the IVRT environment (eg, most favorite and least favorite parts of the game and why and areas for improvement). The participant's caregiver (parent or proxy) will also be encouraged to provide any additional details that the pediatric participant may not remember (eg, dates and early-life experiences).

Pediatric participants and their caregiver will also participate in a training methods questionnaire and interview during the session. The training methods questionnaire will use Likert scale questions (asked aloud by the researcher) to explore both the child's and caregiver's perceptions of previous power wheelchair training methods. Then, a semistructured interview will be conducted to further explore their experience with power wheelchair training (eg, most exciting or challenging parts of training and confidence in skills after training). This information will provide great understanding of past training techniques and experiences from 2 different perspectives. In all cases where pediatric participants cannot remember specific details, caregiver input will be sought to ensure completeness of the data set.

After all participants have completed their session, data will be collected, summarized, and presented in the same manner as in phase 1. The research committee will use this feedback to identify and implement changes to the application for the final phase.

Training Intervention—Phase 3

Phase 3 of this study will also assess the usability and acceptability of the IVRT system from the perspective of current pediatric power wheelchair users. In addition, participants will complete a real-world trial and an IVRT trial to compare power mobility skill transfer between the VR and real-life environments. Both trials will occur over 1 study session, and the order of trials will be counterbalanced among participants.

All phase 3 participants will test the IVRT training system that has been updated based on phase 1 and phase 2 feedback. To compare and assess participant's skill transferability, an experienced clinician will review in-game and real-world performance. It is anticipated that the IVRT intervention will be designed to closely resemble a real-life setting; therefore, the skills transferability assessment will measure the similarity of participant's skills performance across both the VR and real-life environments.

A computerized recording of the IVRT intervention will be independently assessed by the clinician following the completion of the session to compare in-application versus real-world performance metrics. During the real-world trial, participants will be asked to complete each skill that has been included in the IVRT intervention. Skills will be performed in an environment within the hospital grounds and assessed by an experienced clinician. In-game and real-life performance will be assessed for capacity level (skill performed: "yes" or "no" and skill proficiency rating from 0-3) and time to complete each skill.

Participants will also be asked to complete the same questionnaires and semistructured user experience interview as in phase 2 to explore their experience in the IVRT environment and the perceived usability and acceptability of the intervention. Caregivers will again be encouraged to assist in the user experience interview to provide further details as needed and to complete the same ad hoc training methods questionnaire and interview as in phase 2. Exploratory analyses are planned to be conducted with phase 3 data to further evaluate the final version of the IVRT intervention.

Risk to Participants

Previous studies have shown that IVRT can be administered to children and adults without inducing significant safety risks to participants [54,55,58]. The research team will actively monitor for the presence of VRISE or any signs of discomfort during exposure and provide medical follow-up as necessary. The risk of physical injury to pediatric participants is low and will be mitigated by including only experienced power wheelchair users and conducting the real-world skills assessment in a large open space within hospital grounds.

Primary Outcomes

Acceptability

Acceptability of the skills targeted in the IVRT training intervention will be defined and assessed by clinicians using a core power wheelchair skills list. A structured web-based survey will be presented to clinicians following the completion of the IVRT training intervention, outlining 28 potential skills for inclusion. Participants will be asked to indicate their rating for each of the listed skills using a 5-point Likert scale ranging from "strongly agree" to "strongly disagree" for inclusion. Respondents will also have the option to provide skill modification recommendations in an open text field.

Acceptability of the IVRT training intervention will be assessed in each of the phases using 3 separate questionnaires: the PQ, an ad hoc usability and acceptability questionnaire, and an ad hoc user experience questionnaire. The questionnaires will consist of questions from the same topic for each phase; however, the wording of the questions will be adjusted to suit individual participant groups. Quantitative data will be collected using the questionnaires to investigate the perceived effectiveness of the intervention, suitability for the pediatric population, and sense of presence. Qualitative data will further explore users' attitudes and experiences with IVRT. Open-ended question prompts in the first round of phase 1 (eg, perceived safety, appropriateness of graphics, and areas for improvement) will further evaluate the suitability of the intervention for our target population, whereas semistructured interview responses will capture in-depth qualitative data to check for accuracy and validity related to the updated IVRT intervention.

Usability

Usability of the IVRT training intervention will be determined through the ad hoc usability and acceptability questionnaire, ad hoc user experience questionnaire, and skills transfer assessment (phase 3 only). Phase 3 participants will complete the same skills in their real-world power wheelchair as those in the IVRT intervention and will be assessed by an experienced clinician to compare wheelchair skill performance. In doing so, skill transferability between the VR and real-world environments can be analyzed to identify similarities or discrepancies in user performance across environments. It is anticipated that this study will not be powered to detect any clinically significant discrepancies in skill transferability; however, data will be used to explore IVRT versus real-world skill transfer.

Participants will complete the ad hoc usability and acceptability questionnaire and user experience questionnaire to explore their attitudes toward the system's effectiveness and complexity. Quantitative data will define perceived ease of use, user confidence, and level of satisfaction, whereas qualitative data will help to identify potential barriers or facilitators in using the intervention, such as presence of in-game confusion, uncertainty of tasks, and particular areas of frustration or excitement. Tolerability of the IVRT intervention will be assessed during gameplay and through a VRISE section on the user experience questionnaire to determine any symptoms experienced during or after the intervention. Informal notes taken by the researcher will also record comments or questions asked by the user during the intervention to further measure usability.

Secondary Outcomes

Pediatric participants and their caregivers will be asked to describe their previous experience with power wheelchair training methods and perceived abilities of the power wheelchair user. A semistructured interview and Likert scale questions will inquire about the location, length, and satisfaction of previous wheelchair training methods; confidence in abilities; and support received or challenges faced with training. Responses will be used to further understand the experiences with power wheelchair training from both the pediatric user and caregiver perspectives and integrate this information into future iterations of the IVRT system.

Statistical Analysis Plan

The data analysis plan for phase 1 focuses on descriptive and thematic analyses to compare the usability and acceptability of the IVRT intervention across participants and to create a list of potential power wheelchair skills for inclusion in subsequent phases. Phase 2 analysis will focus on descriptive and thematic analyses to understand user experience via system usability, acceptability, and previous training data. Phase 3 will use a descriptive and thematic analysis approach similar to phase 2 to examine system usability, acceptability, user experience, and descriptive and interferential statistics to assess performance outcomes and compare skill transferability from the real world to the IVRT intervention.

This study will define consensus based on clinical suggestions from Nair et al [59]. Phase 1 consensus for the inclusion of items in the power mobility skills list will be reached if a minimum of 75% (9/12) of participants agree (score=4 out of 5) or strongly agree (score=5 out of 5) on a given skill. Skills that do not achieve consensus will not be included in the IVRT intervention for future phases. The inclusion of skills in the phase 2 version of the IVRT intervention will be based on the perceived usefulness and necessity of the skill (as determined by phase 1 participants) and technical feasibility of integrating the skill into the IVRT environment (as determined by the software developers). Descriptive statistics will also be calculated for each skill item and presented to the panel members as feedback in phase 1.

All questionnaire responses to closed questions and Likert-type rating scales will be analyzed using RStudio. In phase 3, real-world and IVRT skill performance data will use "completed" or "not completed" scores and ratings of capacity from 0 to 3 to assess participants' performance outcomes for each specific skill. Then, a composite score will be created and included in the descriptive analysis to compare the performance metrics across participants and environments. In phase 3, inferential statistical testing will also be conducted to evaluate skill transferability; it is anticipated that Wilcoxon signed-rank test will be used to compare real-world and in-application performance data among participants.

Open-ended questionnaire and semistructured interview responses will be thematically analyzed using NVivo (version 12; QSR International) [60]. Questions have been developed in consultation with a pediatric rehabilitation specialist to ensure clarity and appropriateness for each population group. The semistructured interview questions in each phase will be developed to reflect topics of interest (eg, highly variable responses or recurring topics) that arise from the initial feedback round and subsequent rounds. Results will be formatted in a document file and presented to the research panel after the completion of each round.

Results

Institutional review board approval was received in August 2021, and recruitment for phase 1 of this study began in February 2022. As of September 2022, a total of 12 participants enrolled in round 1 and 5 (42%) participants returned for round 2. Phase 1 is expected to be completed in October 2022.

Preliminary data analysis was conducted on phase 1–round 1 data in June 2022. Qualitative data explored the clinician's user experience and revealed a positive perception of the IVRT system as a feasible tool for the pediatric population; however, adjustments in the system's graphics and audio were suggested to reduce overstimulation, complex language, and nausea. Quantitative data further supported the clinical usability of the system and determined potential skills for inclusion into future versions. It is expected that full analysis for phase 1 data will begin in October 2022.

Phase 2 and phase 3 are anticipated to begin in fall of 2022 and winter of 2023, respectively, and it is expected that the entire study will be completed by summer 2023. Results are planned to be published in a peer-reviewed journal in early 2024 and

used to develop a future research trial that will test the efficacy of the IVRT training intervention.

Discussion

Overview

Providing pediatric power wheelchair users with adequate skills training is fundamental when looking to improve their independence and well-being [1,2]. Unfortunately, many children are often restricted from accessing traditional training opportunities owing to physical and environmental barriers [5,6]. Without the knowledge of basic power mobility skills, children with physical disabilities are often unable to participate in activities that help to foster long-term social and cognitive development [1,2]. Therefore, it is essential to create an avenue through which children can develop power mobility skills in a manner that is accessible, easy to use, and safe.

VR is an innovative technique that can create expansive power wheelchair training opportunities within a setting that is often safer and less resource-intensive than a traditional training environment. HMD-based IVRT offers significant training benefits owing to the system's fully immersive components and low resource requirements [26-28]. Although IVRT is beginning to emerge as a potential approach to power mobility training for children, current studies are still in their infancy [8,31]. This study will use the knowledge of multiple expert groups to collaboratively assess and design an IVRT training system that can be used for power wheelchair skill development in the future.

The IVRT application developed through this project will be deliberately designed for engaging pediatric populations; however, by assessing core power wheelchair skills relevant to novel users of all ages, future versions of the IVRT training system may be tailored for a variety of populations. In the future, we also hope to integrate machine learning engines into IVRT technology. These engines will apply real-time data output to generate specific tasks and graphics that can be tailored to match the individual needs of each user.

The short-term goal of this study is to develop an IVRT training intervention that has high usability and acceptability ratings among clinicians and pediatric power wheelchair users. The long-term goal is to provide novel power wheelchair users with a high-quality clinical training intervention that can be easily accessed to safely develop their power wheelchair skills. We also anticipate that the findings from this study will contribute to enhancing the current knowledge on IVRT for clinical practices, as IVRT is currently an underused technology that has the potential to improve patient outcomes by increasing user motivation [15,16], reducing resource requirements [26,27], and enhancing opportunities for task individualization [42-44].

Strengths and Limitations

A main strength of this study lies within the involvement of multiple participant groups to collectively critique and develop the IVRT training intervention. Although it is more time intensive to include both pediatric power wheelchair users and clinician participant groups, collecting data from people across various professions, ages, and life experiences will ensure that diverse opinions can be integrated into the development process. In addition, the use of consensus testing in this study will ensure that the final skills chosen for inclusion in the training intervention are relevant to our pediatric population and approved by experienced clinicians. The use of a mixed methods technique also strengthens our study by providing a detailed understanding of the perspectives, barriers to, and facilitators of IVRT skills training, as recognized by each participant group. Mixed methods can be a particularly useful tool when working in disability and rehabilitation research, as it uses multiple techniques to capture information for both population-based and individual analysis that may be otherwise missed when using only one structured method [61,62]. Given the novelty of our IVRT training intervention, it is particularly important to understand user experience from various angles to develop a final product that has been assessed by multiple expert groups.

A primary weakness of this study is the potential homogeneity of participants' attitudes toward the use of technology for rehabilitative purposes. It is possible that individuals who decline to participate in the study may have differing opinions on the usefulness or acceptability of IVRT compared with participants who agree to participate. We aim to mitigate this potential bias by intentionally recruiting participants with a range of demographics (eg, age and profession) to gather diverse perspectives. The limited sample size in this study will also affect the generalizability of the findings and underpower any inferential statistical analysis performed. Therefore, statistical analyses will be interpreted with caution and used to inform future development of the IVRT intervention rather than to define any conclusive results. Similarly, our pediatric sample is limited by the exclusion of participants who are nonverbal. To obtain comprehensive user feedback in this study, all participants must be able to communicate verbally; however, we hope to include both participants who are verbal and those who are nonverbal in future IVRT studies to gather training data that can be generalized to both population groups. Finally, the visually immersive quality of the IVRT intervention may create feelings of fatigue or motion sickness among users, possibly affecting in-game user performance or postgame assessment measures. The IVRT application is equipped with antinausea settings that can be added to the user's visual field to help reduce VRISE. Aspects of VRISE will also be measured after exposure to identify any distress that may be further alleviated and minimized in future versions.

Conclusions

This proposed feasibility study aims to develop and assess an HMD-based IVRT training intervention intended to benefit children with mobility limitations by creating a safe and accessible means of power wheelchair skill development. Exploring the acceptability and usability of the intervention is the first step in creating a final version that may be further tested in future studies and eventually implemented as part of clinical practices in rehabilitation health care. Given the limited number of pediatric studies using HMD-based IVRT for power wheelchair training currently published [16,30], findings from this study may also be used to inform the methodology, study procedures, and assessment protocol of future large-scale IVRT trials.

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Data Availability

Data sharing is not applicable to this paper, as no complete data sets were generated at this stage of the study. However, upon completion of this study, the data generated and analyzed will be available from the corresponding author (SD) upon reasonable request. Results are also expected to be published in a peer-reviewed journal.

Authors' Contributions

All authors contributed to the study design and refinement of the study protocol and procedures. LP and SD prepared and submitted relevant materials for ethics approval. SD is implementing the protocol with input from JS and ST. SD wrote the manuscript with support from LP. All authors read and approved the final manuscript.

Conflicts of Interest

The Izaak Walton Killam (IWK) Health Centre has a collaboration agreement with MARS VR Lab Inc [63], which includes provisions for the potential payment of royalties in the event of successful commercialization of virtual reality products tested as a part of the study. These royalties are payable to the IWK Health Centre. There are no plans to share profits directly with the study participants. Any royalties will be received by the IWK Health Centre, not by individual researchers, and will be directed back to the hospital's research and operations consistent with its mission and mandate, including innovation, research, and education within the pediatric rehabilitation program. None of the researchers have previous or current direct relationships with MARS VR Lab Inc beyond that outlined in the collaboration agreement. The study design was developed without input from MARS VR Lab Inc. The conduct, analysis of results, and reporting will be performed independently by the research team, without input from MARS VR Lab Inc.

References

1. Early Childhood Development and Disability: A Discussion Paper. Geneva: World Health Organization; 2012.
2. Hardy P. Powered wheelchair mobility: an occupational performance evaluation perspective. Aust Occ Ther J 2004 Mar;51(1):34-42. [doi: 10.1111/j.1440-1630.2004.00413.x]
3. Livingstone R, Field D. Systematic review of power mobility outcomes for infants, children and adolescents with mobility limitations. Clin Rehabil 2014 Oct 24;28(10):954-964. [doi: 10.1177/0269215514531262] [Medline: 24764156]
4. Feldner HA, Logan SW, Galloway JC. Why the time is right for a radical paradigm shift in early powered mobility: the role of powered mobility technology devices, policy and stakeholders. Disabil Rehabil Assist Technol 2016 Feb;11(2):89-102. [doi: 10.3109/17483107.2015.1079651] [Medline: 26340446]
5. Kenyon LK, Mortenson WB, Miller WC. 'Power in Mobility': parent and therapist perspectives of the experiences of children learning to use powered mobility. Dev Med Child Neurol 2018 Oct;60(10):1012-1017 [FREE Full text] [doi: 10.1111/dmcn.13906] [Medline: 29777530]
6. Pituch E, Rushton PW, Ngo M, Heales J, Poulin Arguin A. Powerful or powerless? Children's, parents', and occupational therapists' perceptions of powered mobility. Phys Occup Ther Pediatr 2019;39(3):276-291. [doi: 10.1080/01942638.2018.1496964] [Medline: 30204532]
7. Rousseau-Harrison K, Rochette A. Impacts of wheelchair acquisition on children from a person-occupation-environment interactional perspective. Disabil Rehabil Assist Technol 2013 Jan;8(1):1-10. [doi: 10.3109/17483107.2012.670867] [Medline: 22455384]
8. Kenyon LK, Hostnik L, McElroy R, Peterson C, Farris JP. Power mobility training methods for children: a systematic review. Pediatr Phys Ther 2018 Jan;30(1):2-8. [doi: 10.1097/PEP.0000000000000458] [Medline: 29252826]
9. Klinger E, Weiss PL, Joseph PA. Virtual reality for learning and rehabilitation. In: Rethinking Physical and Rehabilitation Medicine. Paris: Springer; 2010:203-221.
10. Ravi DK, Kumar N, Singhi P. Effectiveness of virtual reality rehabilitation for children and adolescents with cerebral palsy: an updated evidence-based systematic review. Physiotherapy 2017 Sep;103(3):245-258. [doi: 10.1016/j.physio.2016.08.004] [Medline: 28109566]

11. Lei C, Sunzi K, Dai F, Liu X, Wang Y, Zhang B, et al. Effects of virtual reality rehabilitation training on gait and balance in patients with Parkinson's disease: a systematic review. PLoS One 2019;14(11):e0224819 [FREE Full text] [doi: 10.1371/journal.pone.0224819] [Medline: 31697777]
12. Lee HS, Park YJ, Park SW. The effects of virtual reality training on function in chronic stroke patients: a systematic review and meta-analysis. Biomed Res Int 2019;2019:7595639 [FREE Full text] [doi: 10.1155/2019/7595639] [Medline: 31317037]
13. Zhu S, Sui Y, Shen Y, Zhu Y, Ali N, Guo C, et al. Effects of virtual reality intervention on cognition and motor function in older adults with mild cognitive impairment or dementia: a systematic review and meta-analysis. Front Aging Neurosci 2021;13:586999 [FREE Full text] [doi: 10.3389/fnagi.2021.586999] [Medline: 34025384]
14. Arlati S, Colombo V, Ferrigno G, Sacchetti R, Sacco M. Virtual reality-based wheelchair simulators: a scoping review. Assist Technol 2020 Nov 01;32(6):294-305. [doi: 10.1080/10400435.2018.1553079] [Medline: 30615571]
15. Lohse KR, Hilderman CG, Cheung KL, Tatla S, Van der Loos HF. Virtual reality therapy for adults post-stroke: a systematic review and meta-analysis exploring virtual environments and commercial games in therapy. PLoS One 2014;9(3):e93318 [FREE Full text] [doi: 10.1371/journal.pone.0093318] [Medline: 24681826]
16. Inman DP, Loge K, Cram A, Peterson M. Learning to drive a wheelchair in virtual reality. J Spec Educ Technol 2011 Sep 01;26(3):21-34. [doi: 10.1177/016264341102600303]
17. Vailland G, Devigne L, Pasteau F, Nouviale F, Fraudet B, Leblong E, et al. VR based power wheelchair simulator: usability evaluation through a clinically validated task with regular users. In: Proceedings of the IEEE Virtual Reality and 3D User Interfaces (VR). 2021 Presented at: IEEE Virtual Reality and 3D User Interfaces (VR); Mar 27 -Apr 01, 2021; Lisboa, Portugal. [doi: 10.1109/vr50410.2021.00065]
18. Adelola IA, Cox SL, Rahman A. Virtual environments for powered wheelchair learner drivers: case studies. Technol Disabil 2009 Nov 13;21(3):97-106. [doi: 10.3233/tad-2009-0276]
19. Hasdai A, Jessel AS, Weiss PL. Use of a computer simulator for training children with disabilities in the operation of a powered wheelchair. Am J Occup Ther 1998 Mar;52(3):215-220. [doi: 10.5014/ajot.52.3.215] [Medline: 9521997]
20. Linden MA, Whyatt C, Craig C, Kerr C. Efficacy of a powered wheelchair simulator for school aged children: a randomized controlled trial. Rehabil Psychol 2013 Nov;58(4):405-411. [doi: 10.1037/a0034088] [Medline: 24295530]
21. Alshaer A, Regenbrecht H, O'Hare D. Immersion factors affecting perception and behaviour in a virtual reality power wheelchair simulator. Appl Ergon 2017 Jan;58:1-12. [doi: 10.1016/j.apergo.2016.05.003] [Medline: 27633192]
22. Borrego A, Latorre J, Alcañiz M, Llorens R. Embodiment and presence in virtual reality after stroke. A comparative study with healthy subjects. Front Neurol 2019;10:1061 [FREE Full text] [doi: 10.3389/fneur.2019.01061] [Medline: 31649608]
23. Grassini S, Laumann K, Rasmussen Skogstad M. The use of virtual reality alone does not promote training performance (but sense of presence does). Front Psychol 2020;11:1743 [FREE Full text] [doi: 10.3389/fpsyg.2020.01743] [Medline: 32765384]
24. Nash EB, Edwards GW, Thompson JA, Barfield W. A review of presence and performance in virtual environments. Int J Human Comput Interact 2000 May;12(1):1-41. [doi: 10.1207/S15327590IJHC1201_1]
25. Tieri G, Morone G, Paolucci S, Iosa M. Virtual reality in cognitive and motor rehabilitation: facts, fiction and fallacies. Expert Rev Med Devices 2018 Feb;15(2):107-117. [doi: 10.1080/17434440.2018.1425613] [Medline: 29313388]
26. John NW, Pop SR, Day TW, Ritsos PD, Headleand CJ. The implementation and validation of a virtual environment for training powered wheelchair manoeuvres. IEEE Trans Vis Comput Graph 2018 May;24(5):1867-1878. [doi: 10.1109/TVCG.2017.2700273] [Medline: 28475060]
27. Cruz-Neira C, Sandin D, DeFanti T. Surround-screen projection-based virtual reality: the design and implementation of the CAVE. In: Proceedings of the 20th annual conference on Computer graphics and interactive techniques. 1993 Presented at: SIGGRAPH93: 20th Annual Conference and Exhibition on Computer Graphics and Interactive Techniques; Aug 2 - 6, 1993; Anaheim CA. [doi: 10.1145/166117.166134]
28. Xie B, Liu H, Alghofaili R, Zhang Y, Jiang Y, Lobo FD, et al. A review on virtual reality skill training applications. Front Virtual Real 2021 Apr 30;2. [doi: 10.3389/frvir.2021.645153]
29. Yang Y, Koontz AM, Hsiao Y, Pan C, Chang J. Assessment of wheelchair propulsion performance in an immersive virtual reality simulator. Int J Environ Res Public Health 2021 Jul 29;18(15):8016 [FREE Full text] [doi: 10.3390/ijerph18158016] [Medline: 34360309]
30. Morère Y, Bourhis G, Cosnuau K, Guilmois G, Rumilly E, Blangy E. ViEW: a wheelchair simulator for driving analysis. Assist Technol 2020 May 03;32(3):125-135. [doi: 10.1080/10400435.2018.1503204] [Medline: 30085901]
31. Bray N, Kolehmainen N, McAnuff J, Tanner L, Tuersley L, Beyer F, et al. Powered mobility interventions for very young children with mobility limitations to aid participation and positive development: the EMPoWER evidence synthesis. Health Technol Assess 2020 Oct;24(50):1-194 [FREE Full text] [doi: 10.3310/hta24500] [Medline: 33078704]
32. Heynsbergh N, Heckel L, Botti M, Livingston PM. Feasibility, useability and acceptability of technology-based interventions for informal cancer carers: a systematic review. BMC Cancer 2018 Mar 02;18(1):244 [FREE Full text] [doi: 10.1186/s12885-018-4160-9] [Medline: 29499663]
33. Ayala GX, Elder JP. Qualitative methods to ensure acceptability of behavioral and social interventions to the target population. J Public Health Dent 2011;71 Suppl 1:S69-S79 [FREE Full text] [doi: 10.1111/j.1752-7325.2011.00241.x] [Medline: 21656958]

34. Niederberger M, Spranger J. Delphi technique in health sciences: a map. Front Public Health 2020;8:457 [FREE Full text] [doi: 10.3389/fpubh.2020.00457] [Medline: 33072683]
35. Richardson J, Letts L, Sinclair S, Chan D, Miller J, Donnelly C, et al. Using a web-based app to deliver rehabilitation strategies to persons with chronic conditions: development and usability study. JMIR Rehabil Assist Technol 2021 Mar 18;8(1):e19519 [FREE Full text] [doi: 10.2196/19519] [Medline: 33734090]
36. Olney CM, Vos-Draper T, Egginton J, Ferguson J, Goldish G, Eddy B, et al. Development of a comprehensive mobile assessment of pressure (CMAP) system for pressure injury prevention for veterans with spinal cord injury. J Spinal Cord Med 2019 Nov;42(6):685-694 [FREE Full text] [doi: 10.1080/10790268.2019.1570437] [Medline: 30702395]
37. Nazneen N, Rozga A, Smith CJ, Oberleitner R, Abowd GD, Arriaga RI. A novel system for supporting autism diagnosis using home videos: iterative development and evaluation of system design. JMIR Mhealth Uhealth 2015 Jun 17;3(2):e68 [FREE Full text] [doi: 10.2196/mhealth.4393] [Medline: 26085230]
38. Field DA, Livingstone RW. Power mobility skill progression for children and adolescents: a systematic review of measures and their clinical application. Dev Med Child Neurol 2018 Oct;60(10):997-1011 [FREE Full text] [doi: 10.1111/dmcn.13709] [Medline: 29542110]
39. Kirby RL, Swuste J, Dupuis DJ, MacLeod DA, Monroe R. The wheelchair skills test: a pilot study of a new outcome measure. Arch Phys Med Rehabil 2002 Jan;83(1):10-18. [doi: 10.1053/apmr.2002.26823] [Medline: 11782826]
40. VIVE Pro Full Kit | The professional-grade VR headset. Vive. URL: https://www.vive.com/ca/product/vive-pro-full-kit/ [accessed 2021-12-08]
41. Activity Chair. Rifton Equipment. URL: https://www.rifton.com/products/special-needs-chairs/rifton-activity-chairs [accessed 2021-12-09]
42. Smith EM, Low K, Miller WC. Interrater and intrarater reliability of the wheelchair skills test version 4.2 for power wheelchair users. Disabil Rehabil 2018 Mar;40(6):678-683. [doi: 10.1080/09638288.2016.1271464] [Medline: 28110553]
43. Levac D, Rivard L, Missiuna C. Defining the active ingredients of interactive computer play interventions for children with neuromotor impairments: a scoping review. Res Dev Disabil 2012;33(1):214-223. [doi: 10.1016/j.ridd.2011.09.007] [Medline: 22093667]
44. Levac D, Sveistrup H. Motor learning and virtual reality. In: Virtual Reality for Physical and Motor Rehabilitation. New York: Springer; 2014.
45. Chen Y, Fanchiang HD, Howard A. Effectiveness of virtual reality in children with cerebral palsy: a systematic review and meta-analysis of randomized controlled trials. Phys Ther 2018 Jan 01;98(1):63-77 [FREE Full text] [doi: 10.1093/ptj/pzx107] [Medline: 29088476]
46. Nilsson L, Durkin J. Assessment of learning powered mobility use--applying grounded theory to occupational performance. J Rehabil Res Dev 2014;51(6):963-974 [FREE Full text] [doi: 10.1682/JRRD.2013.11.0237] [Medline: 25357100]
47. Furumasu J, Guerette P, Tefft D. The development of a powered wheelchair mobility program for young children. Technol Disabil 1996 Jul 01;5(1):41-48. [doi: 10.3233/tad-1996-5106]
48. Kenyon LK, Farris JP, Cain B, King E, VandenBerg A. Development and content validation of the power mobility training tool. Disabil Rehabil Assist Technol 2018 Jan;13(1):10-24. [doi: 10.1080/17483107.2016.1278468] [Medline: 28125299]
49. Butler C, Okamoto GA, McKay TM. Motorized wheelchair driving by disabled children. Arch Phys Med Rehabil 1984 Feb;65(2):95-97. [Medline: 6230066]
50. Witmer BG, Jerome CJ, Singer MJ. The factor structure of the presence questionnaire. Presence Teleoperators Virtual Environ 2005 Jun;14(3):298-312. [doi: 10.1162/105474605323384654]
51. Davis FD. Perceived usefulness, perceived ease of use, and user acceptance of information technology. MIS Q 1989 Sep;13(3):319-340. [doi: 10.2307/249008]
52. Brooke J. SUS - A quick and dirty usability scale. In: Usability Evaluation In Industry. Boca Raton, Florida, United States: CRC Press; 1996.
53. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009 Apr;42(2):377-381 [FREE Full text] [doi: 10.1016/j.jbi.2008.08.010] [Medline: 18929686]
54. Sharples S, Cobb S, Moody A, Wilson JR. Virtual reality induced symptoms and effects (VRISE): comparison of head mounted display (HMD), desktop and projection display systems. Displays 2008 Mar;29(2):58-69. [doi: 10.1016/j.displa.2007.09.005]
55. Kourtesis P, Collina S, Doumas LA, MacPherson SE. Validation of the virtual reality neuroscience questionnaire: maximum duration of immersive virtual reality sessions without the presence of pertinent adverse symptomatology. Front Hum Neurosci 2019;13:417 [FREE Full text] [doi: 10.3389/fnhum.2019.00417] [Medline: 31849627]
56. van Houwelingen CT, Moerman AH, Ettema RG, Kort HS, Ten Cate O. Competencies required for nursing telehealth activities: a Delphi-study. Nurse Educ Today 2016 Apr;39:50-62 [FREE Full text] [doi: 10.1016/j.nedt.2015.12.025] [Medline: 27006033]
57. Bovopoulos N, Jorm AF, Bond KS, LaMontagne AD, Reavley NJ, Kelly CM, et al. Providing mental health first aid in the workplace: a Delphi consensus study. BMC Psychol 2016 Aug 02;4(1):41 [FREE Full text] [doi: 10.1186/s40359-016-0148-x] [Medline: 27485609]

58. Tychsen L, Foeller P. Effects of immersive virtual reality headset viewing on young children: visuomotor function, postural stability, and motion sickness. Am J Ophthalmol 2020 Jan;209:151-159. [doi: 10.1016/j.ajo.2019.07.020] [Medline: 31377280]
59. Nair R, Aggarwal R, Khanna D. Methods of formal consensus in classification/diagnostic criteria and guideline development. Semin Arthritis Rheum 2011 Oct;41(2):95-105 [FREE Full text] [doi: 10.1016/j.semarthrit.2010.12.001] [Medline: 21420149]
60. NVivo qualitative data analysis software. QSR International. URL: https://www.qsrinternational.com/ [accessed 2021-12-10]
61. Kroll T, Neri MT, Miller K. Using mixed methods in disability and rehabilitation research. Rehabil Nurs 2005;30(3):106-13; discussion 113. [doi: 10.1002/j.2048-7940.2005.tb00372.x] [Medline: 15912675]
62. Tariq S, Woodman J. Using mixed methods in health research. JRSM Short Rep 2013 Jun;4(6):2042533313479197 [FREE Full text] [doi: 10.1177/2042533313479197] [Medline: 23885291]
63. Medical and Rehabilitation Systems. MARS VR Lab Inc. URL: https://www.marsvrlab.com/ [accessed 2021-12-17]

Abbreviations

HMD: head-mounted display
IVRT: immersive virtual reality technology
IWK: Izaak Walton Killam
PQ: Presence Questionnaire
REDCap: Research Electronic Data Capture
VR: virtual reality
VRISE: virtual reality–induced symptoms and effects

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Protocol

A Tailored SMS Text Message–Based Intervention to Facilitate Patient Access to Referred Community-Based Social Needs Resources: Protocol for a Pilot Feasibility and Acceptability Study

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Abstract

Background: Health care providers are increasingly screening patients for unmet social needs (eg, food, housing, transportation, and social isolation) and referring patients to relevant community-based resources and social services. Patients' connection to referred services is often low, however, suggesting the need for additional support to facilitate engagement with resources. SMS text messaging presents an opportunity to address barriers related to contacting resources in an accessible, scalable, and low-cost manner.

Objective: In this multi-methods pilot study, we aim to develop an automated SMS text message–based intervention to promote patient connection to referred social needs resources within 2 weeks of the initial referral and to evaluate its feasibility and patient acceptability. This protocol describes the intervention, conceptual underpinnings, study design, and evaluation plan to provide a detailed illustration of how SMS technology can complement current social needs screening and referral practice patterns without disrupting care.

Methods: For this pilot prospective cohort study, this SMS text message–based intervention augments an existing social needs screening, referral, and navigation program at a federally qualified health center. Patients who received at least one referral for any identified unmet social need are sent 2 rounds of SMS messages over 2 weeks. The first round consists of 5-10 messages that deliver descriptions of and contact information for the referred resources. The second round consists of 2 messages that offer a brief reminder to contact the resources. Participants will evaluate the intervention via a survey and a semistructured interview,

informed by an adapted technology acceptance model. Rapid qualitative and thematic analysis will be used to extract themes from the responses. Primary outcomes are implementation feasibility and patient acceptability. Secondary outcomes relate to intervention effectiveness: self-reported attempt to connect and successful connection to referred resources 2 weeks after the initial referral encounter.

Results: The study received regulatory approval in May 2021, and we anticipate enrolling 15-20 participants for this initial pilot.

Conclusions: This protocol presents detailed implementation methods about a novel automated SMS intervention for social care integration within primary care. By sharing the study protocol early, we intend to facilitate the development and adoption of similar tools across different clinical settings, as more health care providers seek to address the unmet social needs of patients. Study findings will provide practical insights into the design and implementation of SMS text message–based interventions to improve social and medical care coordination.

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KEYWORDS

text messaging; primary health care; social determinants of health; needs assessment; community health centers; vulnerable populations

Introduction

Background

Social determinants of health lead to profound inequities within a wide range of health outcomes [1]. Accumulated research on social determinants of health has resulted in many health care systems implementing interventions in the clinical setting, which screen patients for unmet social needs (eg, food and housing) [2]. Patients with identified needs can then be referred to relevant community resources and services (eg, food pantries and public housing programs). Previous studies demonstrate the potential benefits of social needs screening and referral, including the resolution of identified social needs, improvements in health, and decreases in avoidable health care utilization [3-6].

Patients, however, often face structural and personal barriers in the process of contacting and initiating services [7,8], which threaten the realization of these longer-term benefits. Despite success in the implementation of screening and referral, patients' actual use of referred services is mixed: the reported proportion of successful connection (ie, initiation of referred services) ranges from 32% to 64% for interventions that screen and refer individuals for multiple social needs in primary care settings [9,10]. Further, clinics often have cost constraints that limit the ability to provide labor-intensive case management services to ensure referral success and service initiation [11]. Therefore, it is critical to design scalable interventions that address barriers and facilitate service access. In particular, patient-reported barriers related to engaging with referred resources suggest that different modes of information delivery may be important to explore [12].

Leveraging SMS text messaging within social needs screening and response interventions could offer an accessible, affordable, and scalable alternative to in-person or telephonic case management and service navigation [13]. According to the Pew Research Center, more than 97% of Americans own a cell phone among different income, education, age, and race and ethnicity groups [14]. The ubiquity of cell phones has been accompanied by a large number of studies that have used SMS text messaging as an intervention medium to promote health self-management and behavior change [15], including weight loss [16,17], chronic care management [18-22], medication adherence [23-25], smoking cessation [26], mental health [27,28], and clinic attendance [29,30]. There is evidence that people living in underresourced communities also benefit from SMS for various health-related applications [31-36]. Thus, SMS may be an effective technology to reach patients who are disproportionately affected by systemic social inequity and, as a result, present with high levels of unmet social need.

Given the broad evidence base for SMS text message–based interventions, integrating automated SMS text messages within social needs screening and response may be an optimal application of SMS text messaging. Previous studies have identified increased intervention dosage (ie, the number of contacts between a patient and the care team) as a significant factor associated with successful social needs resource connection [37], especially within the first 30 days of referral [38]. Increasing in-person or telephone follow-up, however, may be challenging given that screening and referral for social needs is often already a resource-intensive and time-consuming process for providers [39,40]. Further, frequent telephone calls may be costly for low-income patients with limited calling plans [41] and difficult to schedule given patients' work, caregiving, and other responsibilities.

These considerations motivate the development of an automated and scalable intervention that uses SMS text messages to deliver tailored information and reminders about referred resources. SMS text messaging may be a potential modality to increase patient contact without increasing the workload of busy providers and staff. As an asynchronous mode of communication, SMS text message delivery also allows patients to access messages at their convenience and stores them for easy reference. Although SMS text messages alone cannot address complex, system-level barriers to connection, they may be able to address more proximate barriers such as gaps in the

presentation and distribution of referral information, which extend the capacity of the care team to navigate other challenges.

Study and Protocol Aims

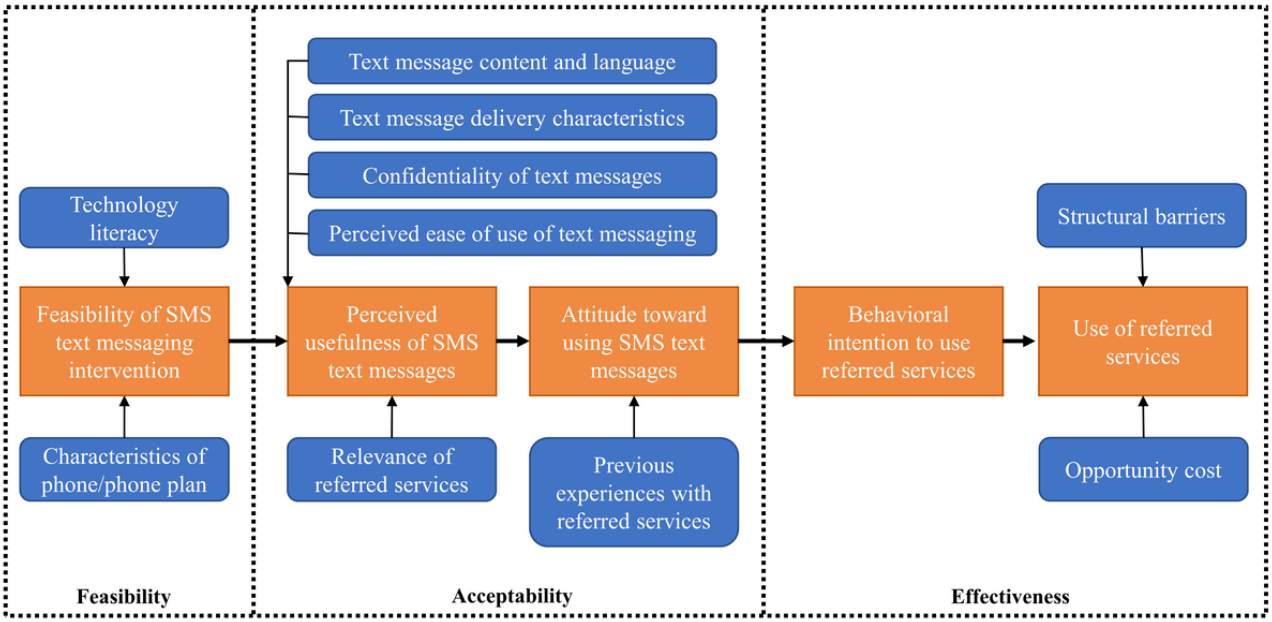
Our multi-methods pilot study aims to assess the feasibility and acceptability of a novel SMS text message–based intervention to promote patients' connection to referred resources for unmet social needs within 3 weeks of the initial referral. This protocol describes the intervention, development, study design, and evaluation plan for the pilot. Our objective is to provide a detailed illustration of how SMS technology can complement an existing social needs screening, referral, and navigation program at a federally qualified health center (FQHC) without disrupting usual clinical care. This protocol makes a novel contribution by presenting one approach to using automated messages that can readily scale to other clinical settings. Results from the pilot can inform the adaptation of SMS text message technologies for social needs screening and response to increase the uptake of community-based resources and health-related services.

Conceptual Model and Outcomes

This pilot study is guided by the technology acceptance model (TAM), a widely used conceptual framework for modeling user acceptance of technology or technology-based interventions (Figure 1) [42,43]. Owing to unique factors that influence the uptake of technology in underresourced settings, this study further adapted the TAM for resource-limited settings (TAM-RLS) [44]. TAM-RLS posits that perceived usefulness and attitudes toward the use of the SMS text message–based intervention influence the intention to use and actual use of the referred services. The model provides a theoretical scaffolding for the primary outcomes of interest (acceptability and feasibility) and secondary outcome of interest (effectiveness).

Feasibility represents the technical and implementation considerations in executing the intervention [45]. Acceptability consists of patient perspectives on the content, characteristics, and delivery of the SMS text messages [45]. Effectiveness corresponds to the latter 2 outcomes (ie, intention to use and actual use). A patient's attempt to connect with a referred service represents an intention to use and successful connection represents actual use of that referred service. This study operationalizes the components of feasibility, acceptability, and effectiveness in this model through survey questions, qualitative interview data, and quantitative measures of patient enrollment and referral service use, which together assess all model constructs (Multimedia Appendix 1).

Figure 1. Conceptual model for the SMS text message–based intervention to facilitate patients' connection to referred services, adapted from the technology acceptance model for resource-limited settings (TAM-RLS). The model connects several patient and intervention inputs (blue boxes) to outcomes (orange boxes) of perceived usefulness of and attitude toward the intervention, as well as intention to use and use of referred services.



Methods

Setting and Community Needs Assessment

This pilot prospective cohort study will be conducted at a FQHC—a publicly funded, community-based health care center for underserved areas—in the southeastern United States, which services a mostly metropolitan, low-income patient population. In 2020, the partnering FQHC saw about 35,000 unique patients, of whom 51% were uninsured and 92% self-identified in electronic health records as racial or ethnic minorities, most of whom identified as Black or Hispanic/Latino. Of the approximately 25,000 patients with known income status, 97% earned incomes at or below 200% of the federal poverty level [46].

Since 2017, case managers with social work licensure have screened and referred patients for unmet social needs using the Protocol of Responding to and Assessing Patients' Assets, Risks, and Experiences (PRAPARE) within pediatric, adult medicine, and family medicine clinics [47]. One of the most prevalent assessment tools in the United States [48], PRAPARE consists of a validated set of national core measures integrated into the electronic health record, which include patient demographics

(eg, race and education) and social needs (eg, housing stability and material security) [49]. Based on identified needs, case managers can refer patients to one or more community-based organizations, government agencies, or services internal to the health center. Since 2019, trained student volunteers have served as community resource navigators to follow up and provide further assistance to patients who received referrals [50]. These volunteers call patients 2 and 4 weeks after the initial referral is made to offer navigation support, as well as record patient's ability to connect with referred resources.

These efforts to advance screening, referral, and navigation for social needs at the FQHC are the product of a community-academic partnership between the FQHC and a nearby university. At least once a month, providers, navigators, and administrative leadership of the FQHC meet with university researchers to advance initiatives that identify and address needs in the local community.

During these meetings, frontline clinical stakeholders relayed patient requests for the incorporation of SMS into the existing social needs program. The potential benefits of an SMS text message–based intervention were further bolstered by studies of patient-reported barriers [12] and low proportions of resource connection (33%) [10] at the FQHC. With stakeholder support, a convenience sample of 16 patients was surveyed about SMS text messaging during navigator follow-up calls: 87.5% of patients stated that they were comfortable with receiving SMS text messages about referred social needs resources, and 56.3% of them even preferred to receive this information via SMS text message rather than by telephone or in person. Researchers also conducted semistructured interviews with a separate purposive sample of 10 patients, most of whom were amenable to receiving SMS text messages as part of their social care but emphasized that messages should not displace person-to-person relationships with social workers and community resource navigators [51]. This preliminary needs assessment motivated the development of the present SMS text message–based intervention and pilot protocol, which are shaped by regular and ongoing stakeholder engagement.

Eligibility and Recruitment

Prospective participants will be identified by a case manager during primary care or behavioral health visits at the partnering FQHC. To be eligible, participants must be at least 18 years of age, have at least one referral from a community resource navigator, understand English, have access to a device with an active service plan to send and receive SMS text messages, and be able to provide informed consent. In addition, patients who have already connected with a referred resource prior to enrolling will not be eligible for the study. We will recruit 15-20 patients using a purposive sampling strategy to ensure diversity with regard to age, race, ethnicity, and education, as well as social need characteristics (eg, food and medication assistance). After recruiting 10 patients, the demographic diversity of the sample will be assessed relative to the FQHC's general primary care population (eg, a majority of Black or Hispanic individuals and food and health care access as leading social needs referrals) [10,46].

Recruitment progress is reported to an advisory committee comprising FQHC clinical leadership, who will determine adjustments to the recruitment protocol to ensure representative participant selection. As participants complete the study, the study team will also engage key clinical stakeholders and FQHC leadership during monthly meetings for interim assessment of the intervention and overall study, discussing participant feedback and further adaptations if necessary. Participants will receive a one-time US $25 gift card after completing the survey and interview for the study.

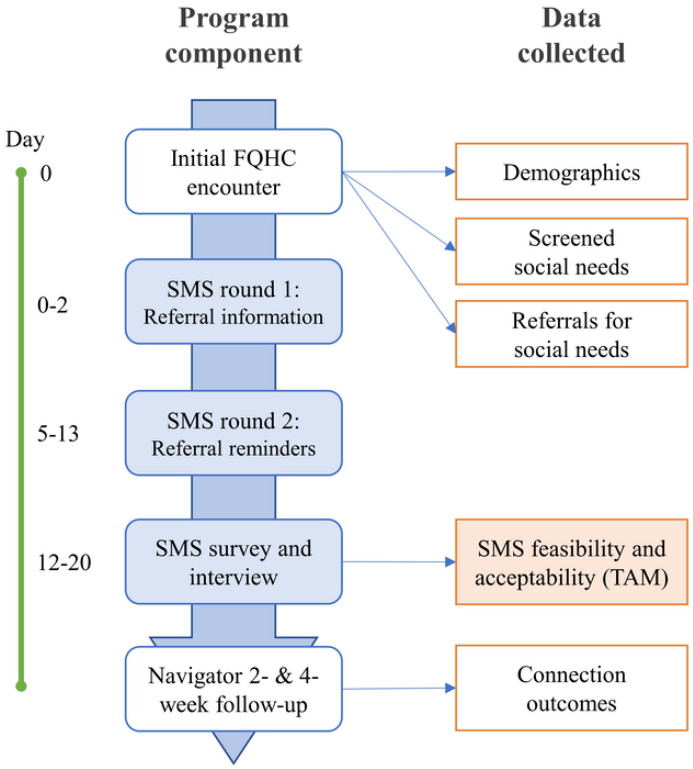
The primary purpose of this pilot is to determine feasibility and acceptability to refine the use of SMS text message–based outreach in clinical practice and to develop a larger trial, and not to detect significant effects of the intervention on outcomes. A sample size of 15-20 patients was determined to be appropriate for this pilot to allow for recruitment of a sample representative of the broader patient population within a reasonable time frame, given staffing and resource capacity.

Intervention Overview

The goal of the SMS text message–based intervention is to increase the number of patients who attempt to connect with a referred resource in the 2 weeks after referral and, ultimately, increase the number of patients who successfully connect (Figure 2). An intervention mapping approach informed intervention development, incorporating the following: needs assessment, objective and theory selection, message and program design, and pretesting with plans for evaluation and revision [15,52]. In response to preliminary patient input, a key priority in intervention design was ensuring that SMS messages would integrate within existing screening, referral, and navigation activities without the disruption of critical person-to-person interactions and care. Two rounds of SMS text messages will be sent to the enrolled participants. The first round consists of 5-10 messages (depending on the number of referrals) with information about the participant's referred services for identified unmet social needs, sent upon participant consent within 2 days of screening. The second round of SMS text messages, sent approximately 1 week later to all participants, consists of 2 messages that offer a brief reminder to connect with these services if they have not already. Following the second round of messages, participants will be contacted by a community resource navigator by telephone for follow-up, resuming standard navigation protocol.

SMS text messages will be delivered through Twilio Inc, a third-party web service, integrated into a Research Electronic Data Capture (REDCap) tool database [53,54]. REDCap is a secure, web-based software platform designed to support data capture for research studies. This delivery method was chosen for its relative simplicity, ease of use, and cost-effectiveness at US $0.0075 per message. Many community resource navigation programs already use REDCap to coordinate patient follow-up, including the program at the partnering FQHC [50]. Researchers and clinical staff can schedule automated message triggers (using "Alerts & Notifications") directly from the database platform without significant technical knowledge or training, making this a suitable and practical approach for future scale-up.

Figure 2. Outline of the SMS text message–based intervention and data collection. Shaded boxes correspond to SMS text message–based intervention components, and unshaded boxes correspond to usual care. FQHC: federally qualified health center; TAM: technology acceptance model.



Message Development and Delivery

Existing community resource navigator scripts informed the design of the message content for both rounds of messages (Table 1). The first round of messages, which will be sent on the day of participant consent, delivers information tailored to their referred resources, including the name, a brief description of the organization or program, and the contact information (eg, telephone numbers, addresses, and URLs) necessary to connect. The second round of messages, which will be sent on Monday morning (5-11 days later or 2-6 business days), offers a brief reminder to attempt to connect with referred resources. This timing is based on clinician and stakeholder input from the FQHC and provides the participant an opportunity to attempt to contact a resource during regular business hours. Message content and referred resource descriptions are automatically populated on the basis of patient data, and messages are automatically sent on the basis of prescheduled triggers (which can be cancelled at any time if the participant chooses to leave the study).

Table 1. SMS text message content and timing.

Message category	Message
Round 1: Information (timing: day of consent, within 2 days of screening)	
Message 1: Introduction	Hi [name]! Thank you for signing up. Our team at [FQHC] hopes that these texts can help remind you to reach out to resources that you've been referred to.
Message 2: Disclaimer and Support	These texts are automated. If you ever want to speak to a person who can help you, please leave a message with [FQHC] Behavioral Health at (000-000-0000).
Message 3: Call-back to Conversation	You and [responsible_case_manager] discussed these resource(s) that may be useful for you:
Message(s) 4A-4D: Service Descriptions	*Descriptions for 1-4 services that the patient was referred to.* *Example:* SNAP: Federal food program. Apply online at [URL] or by calling [organization] at (000-000-000).
Message 5: Conclusion	We hope that you'll reach out to the resources that you two discussed, if you haven't already! We'll send a reminder next week in case it slips your mind.
Round 2: Reminders (timing: 5-11 days after consent, Monday at 9 AM)	
Message 1: Connection Reminder	Good morning! This is a reminder from your care team at [FQHC]. Try to follow up on [provider]'s resources if you haven't already been in touch!
Message 2: Data Collection Reminder	You will receive a call soon to learn about your experience with these messages. Thank you for your help and participation!

Measures

This study adapts the acceptability of intervention measures to assess attitudes toward SMS text messages [55]. Otherwise, in the absence of validated tools to assess many constructs of technology acceptance for mobile health applications, this study leverages the TAM-RLS to guide the development of measures and facilitate an exploration of feasibility and acceptability tailored to our study and intervention context, the predominant approach in the literature [56].

All data for a given participant will be collected and stored within a secure REDCap database. The participants' demographic information will be obtained retrospectively from case managers, which includes sex, race, ethnicity, and education. Screening and referral information will also be collected by the case manager, using the PRAPARE screening assessment. Screened social needs include the following domains: food, clothing, phone access, childcare, utilities, medicine or health care access, housing, transportation, employment, stress, and social isolation. Referred services were organized into groups corresponding to the social need domains: food, transportation, housing, financial assistance, utilities, health care access, social or emotional health, childcare, clothing, or phone or technology assistance. For this pilot, referrals to domestic or interpersonal violence organizations are omitted from SMS text messages to protect participant safety.

Three days to a week after the second round of messages, a trained study team member will call the participant to conduct a quantitative survey about their experience with the SMS text messages, including Likert scale measures of attitudes toward message frequency, content, and usefulness (Multimedia Appendix 2). During the call, the team member will also conduct a semistructured qualitative interview to supplement and add depth to the quantitative survey measures (Multimedia Appendix 3). Questions for both the survey and interview are designed to map onto all of the constructs of this study's conceptual model (Multimedia Appendix 1). The total survey and interview are expected to last 30-45 minutes, and deidentified, encrypted recordings of the qualitative interview and interview notes will be stored securely.

One week after the second round of SMS text messages, the participant will also resume standard of care: a 2- and 4-week follow-up telephonic encounter with a community resource navigator. During these follow-up calls, data about resource connection will be collected as preliminary evidence of effectiveness—this pilot's secondary outcome.

Quantitative Analysis

Quantitative survey data about feasibility and acceptability, as well as patient demographic, social needs, and referral characteristics, will be summarized through univariate, descriptive statistics. To determine preliminary effectiveness, a one-sample binomial test will be used to assess whether the proportion of patients who had attempted to contact a referred resource within 2 weeks of the initial referral is greater than 0.57, the corresponding proportion for the FQHC's screened patients before the pilot.

Qualitative Analysis

In order to rapidly develop rigorous and actionable evidence for this intervention, qualitative interview data will be analyzed using a rapid qualitative approach, which will employ a thematic analysis informed a priori by the constructs of this study's conceptual model [57]. Routine discussions and interview debriefs among both the study team and the advising stakeholders will identify areas where further data should be gathered as well as inform the selection of participants. Recordings and interview notes will be coded by 2 trained researchers and reconciled by a third trained researcher to identify themes. As needed, the larger study team will be queried to reconcile differences in interpretation of themes.

Ethical Considerations

This study received initial approval by the university health system's institutional review board in May 2021 and an amendment approval in November 2021 (Pro00107167).

Results

Recruitment of the pilot study began in January 2022. Data collection and analysis will be carried out through the summer of 2022.

Discussion

Protocol Overview

We describe a protocol to assess the feasibility and acceptability of an SMS text message–based intervention that integrates automated SMS messages into an existing social needs screening and referral program at an FQHC. This study represents a novel application of an evidence-based intervention medium to promote patients' connection to referred services to address their identified unmet social needs. This intervention has the potential to provide a valuable touch point for patients seeking to navigate a complex and often fragmented system of health and social services. For patients, SMS text messaging may be a convenient, affordable, and accessible modality to deliver information and reminders about referred services, improving upon solely verbal dissemination methods that create patient-reported approachability barriers (eg, forgetting about resources and lacking the necessary information to connect) [12]. If feasible and acceptable to patients, SMS text messaging may also offer a scalable means of increasing contact between patients and their care teams without overextending organizational capacity, allowing providers to direct their case management efforts to those cases where more intensive approaches would be most valuable.

This pilot has been designed to anticipate and assess a wide range of possible barriers to the implementation of this SMS intervention, as depicted in this study's TAM-RLS conceptual model. Limited access to or familiarity with SMS within this study's population, whether a result of financial constraints or restricted opportunities to develop digital literacy, may hamper the feasibility of the intervention at the outset. Issues with SMS text message content, timing, confidentiality, or relative advantage or ease of use may affect participant acceptability,

which also depends on the perceived or actual usefulness of the referred services themselves. Larger organizational (eg, staffing, capacity, and practice patterns) and community forces (eg, resource availability, structural barriers, and local policy) also govern whether and how participants are able to connect to referred services, influencing the effectiveness of the intervention. By drawing from the conceptual model, the survey instrument and interview guide will be able to elicit a comprehensive assessment of the factors that interact with this SMS text message–based intervention, which should guide future development and scale. This study's multi-methods approach also enables a nuanced understanding of patient perspectives through quantitative and qualitative methods, providing practical insights into the design, feasibility, and acceptability of SMS text message–based interventions to improve social and medical care coordination.

This study benefits from a long-standing community-academic partnership that has guided the development of this study and intervention from inception to execution, prioritizing the on-the-ground values and context of the study's FQHC. Further, this study can build evidence for larger, more overarching initiatives to consolidate care coordination efforts across the sociomedical care continuum. For example, the state of North Carolina—where this pilot will take place—has launched NCCARE360, a digital platform where health care providers and community-based organizations can manage incoming and outgoing referrals, track outcomes, and communicate with enrollees, with platform support for SMS text messaging [58]. SMS text messaging can complement these digital platforms by providing another contact point between referred services and patients, who may otherwise be left out of provider-to-provider communications that occur on the platforms. Scale-up evidence in subsequent studies about the facilitators, challenges, and best practices of automated SMS text messaging may yield insights to guide implementation of these platforms in specific organizations and health centers and facilitate patients' connection to services organized on the platform.

Limitations

This study has several limitations. First, the sample size and study design limit the ability to draw conclusions on the effectiveness of the SMS text message–based intervention to promote uptake or initiation of services. The aim of this pilot study is to gather evidence about the feasibility and acceptability of the intervention, and the relative effectiveness of the intervention will instead be the focus of a later scale-up trial. Second, the external validity of these findings may be limited by the single-site study design, and the results of the pilot should be expanded by investigation of similar interventions in different settings, program models, and patient populations. In particular, electronic referral platforms—not currently used by this study's partnering FQHC—represent a prominent and advancing innovation where automated messaging and platform-embedded connection outcomes should be studied. Third, more specific measures related to internet accessibility, literacy, privacy, and use—as well as reasons for nonparticipation in general—should be explored to understand broader issues in digital inclusion, especially as smartphones become an increasingly prominent and expected part of everyday life. At the moment, many screening tools including PRAPARE only collect limited information about technological and broadband access. Finally, this intervention uses unidirectional as opposed to bidirectional SMS text messages. Though previous literature has suggested the effectiveness of bidirectional SMS text messages [59], bidirectional messaging posed additional technical and workforce capacity demands.

Conclusions

This intervention aims to explore SMS text messaging as a new potential opportunity for an accessible, affordable, and scalable approach to improving care for patients with unmet social needs, contributing to an expanding evidence base about best practices for incorporating social needs screening and response interventions in clinical settings [60]. The detailed methods described in this protocol may be of interest for researchers and practitioners seeking to incorporate automated SMS text messaging within an existing social needs screening and referral program, with the goal of augmenting rather than disrupting or displacing interpersonal care for an underresourced patient population.

Acknowledgments

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Data Availability

The data set generated during the current study is not publicly available owing to the institutional review board's restrictions for personal health information, but a limited, deidentified data set is available from the corresponding author on reasonable request.

Conflicts of Interest

AAL reports receiving funds from PhRMA Foundation and Otsuka. LLZ has research funded awarded to her institution from PhRMA Foundation and Proteus Digital Health, as well as consulting for Pfizer and Novartis. HBB reports research grants from Otsuka, Novo Nordisk, Sanofi, Improved Patient Outcomes, Boehinger Ingelheim, Walmart, Bebetter, NIH, and VA, as well as consulting from Sanofi, Novartis, Otsuka, Abbott, Xcenda, Preventric Diagnostics, VIDYA, and the Medicines Company. CD reports receiving funds from ZealCare, Inc.

Multimedia Appendix 1
Model Constructs and Associated Measures.
[DOCX File , 18 KB - resprot_v11i10e37316_app1.docx]

Multimedia Appendix 2
Quantitative Exit Survey for SMS Pilot.
[DOCX File , 10 KB - resprot_v11i10e37316_app2.docx]

Multimedia Appendix 3
Qualitative Interview Guide for SMS Pilot.
[DOCX File , 9 KB - resprot_v11i10e37316_app3.docx]

References

1. Braveman P, Gottlieb L. The social determinants of health: it's time to consider the causes of the causes. Public Health Rep 2014;129 Suppl 2:19-31 [FREE Full text] [doi: 10.1177/00333549141291S206] [Medline: 24385661]
2. National Academies of Sciences, Engineering, and Medicine. Integrating social care into the delivery of health care: moving upstream to improve the nation's health. Washington, DC: National Academies Press; 2019.
3. Gottlieb LM, Hessler D, Long D, Laves E, Burns AR, Amaya A, et al. Effects of social needs screening and in-person service navigation on child health: a randomized clinical trial. JAMA Pediatr 2016 Nov 07;170(11):e162521. [doi: 10.1001/jamapediatrics.2016.2521] [Medline: 27599265]
4. Gottlieb LM, Adler NE, Wing H, Velazquez D, Keeton V, Romero A, et al. Effects of in-person assistance vs personalized written resources about social services on household social risks and child and caregiver health: a randomized clinical trial. JAMA Netw Open 2020 Mar 02;3(3):e200701 [FREE Full text] [doi: 10.1001/jamanetworkopen.2020.0701] [Medline: 32154888]
5. Pantell MS, Hessler D, Long D, Alqassari M, Schudel C, Laves E, et al. Effects of in-person navigation to address family social needs on child health care utilization: a randomized clinical trial. JAMA Netw Open 2020 Jun 01;3(6):e206445 [FREE Full text] [doi: 10.1001/jamanetworkopen.2020.6445] [Medline: 32478849]
6. Schickedanz A, Sharp A, Hu YR, Shah NR, Adams JL, Francis D, et al. Impact of social needs navigation on utilization among high utilizers in a large integrated health system: a quasi-experimental study. J Gen Intern Med 2019 Nov;34(11):2382-2389 [FREE Full text] [doi: 10.1007/s11606-019-05123-2] [Medline: 31228054]
7. Hsu C, Cruz S, Placzek H, Chapdelaine M, Levin S, Gutierrez F, et al. Patient perspectives on addressing social needs in primary care using a screening and resource referral intervention. J Gen Intern Med 2020 Feb;35(2):481-489 [FREE Full text] [doi: 10.1007/s11606-019-05397-6] [Medline: 31792864]
8. Accountable health communities (AHC) model evaluation: first evaluation report. RTI International. 2020. URL: https://innovation.cms.gov/data-and-reports/2020/ahc-first-eval-rpt [accessed 2022-09-19]
9. Gottlieb LM, Wing H, Adler NE. A systematic review of interventions on patients' social and economic needs. Am J Prev Med 2017 Nov;53(5):719-729. [doi: 10.1016/j.amepre.2017.05.011] [Medline: 28688725]
10. Lian T, Kutzer K, Gautam D, Eisenson H, Crowder JC, Esmaili E, et al. Factors associated with patients' connection to referred social needs resources at a federally qualified health center. J Prim Care Community Health 2021;12:21501327211024390 [FREE Full text] [doi: 10.1177/21501327211024390] [Medline: 34120507]
11. Drake C, Reiter K, Weinberger M, Eisenson H, Edelman D, Trogdon JG, et al. The direct clinic-level cost of the implementation and use of a protocol to assess and address social needs in diverse community health center primary care clinical settings. J Health Care Poor Underserved 2021;32(4):1872-1888. [doi: 10.1353/hpu.2021.0171] [Medline: 34803048]
12. Sandhu S, Lian T, Smeltz L, Drake C, Eisenson H, Bettger JP. Patient barriers to accessing referred resources for unmet social needs. J Am Board Fam Med 2022;35(4):793-802 [FREE Full text] [doi: 10.3122/jabfm.2022.04.210462] [Medline: 35896446]
13. Hall AK, Cole-Lewis H, Bernhardt JM. Mobile text messaging for health: a systematic review of reviews. Annu Rev Public Health 2015 Mar 18;36:393-415 [FREE Full text] [doi: 10.1146/annurev-publhealth-031914-122855] [Medline: 25785892]
14. Mobile Fact Sheet. Pew Research Center. 2021 Apr 07. URL: https://www.pewresearch.org/internet/fact-sheet/mobile/ [accessed 2022-09-19]

15. Suffoletto B. Text message behavioral interventions: from here to where? Curr Opin Psychol 2016 Feb 01;9:16-21 [FREE Full text] [doi: 10.1016/j.copsyc.2015.09.012] [Medline: 26665157]
16. Shaw R, Bosworth H. Short message service (SMS) text messaging as an intervention medium for weight loss: a literature review. Health Informatics J 2012 Dec;18(4):235-250 [FREE Full text] [doi: 10.1177/1460458212442422] [Medline: 23257055]
17. Shaw RJ, Bosworth HB, Silva SS, Lipkus IM, Davis LL, Sha RS, et al. Mobile health messages help sustain recent weight loss. Am J Med 2013 Nov;126(11):1002-1009 [FREE Full text] [doi: 10.1016/j.amjmed.2013.07.001] [Medline: 24050486]
18. Galdas P, Darwin Z, Kidd L, Blickem C, McPherson K, Hunt K, et al. The accessibility and acceptability of self-management support interventions for men with long term conditions: a systematic review and meta-synthesis of qualitative studies. BMC Public Health 2014 Nov 27;14:1230 [FREE Full text] [doi: 10.1186/1471-2458-14-1230] [Medline: 25428230]
19. Huang L, Yan Z, Huang H. The effect of short message service intervention on glycemic control in diabetes: a systematic review and meta-analysis. Postgrad Med 2019 Nov;131(8):566-571. [doi: 10.1080/00325481.2019.1668723] [Medline: 31524035]
20. Nundy S, Dick JJ, Solomon MC, Peek ME. Developing a behavioral model for mobile phone-based diabetes interventions. Patient Educ Couns 2013 Jan;90(1):125-132 [FREE Full text] [doi: 10.1016/j.pec.2012.09.008] [Medline: 23063349]
21. Yee L, Taylor S, Young M, Williams M, Niznik C, Simon M. Evaluation of a text messaging intervention to support self-management of diabetes during pregnancy among low-income, minority women: qualitative study. JMIR Diabetes 2020 Aug 10;5(3):e17794 [FREE Full text] [doi: 10.2196/17794] [Medline: 32773367]
22. Chen C, Li X, Sun L, Cao S, Kang Y, Hong L, et al. Post-discharge short message service improves short-term clinical outcome and self-care behaviour in chronic heart failure. ESC Heart Fail 2019 Feb;6(1):164-173 [FREE Full text] [doi: 10.1002/ehf2.12380] [Medline: 30478888]
23. Kannisto KA, Koivunen MH, Välimäki MA. Use of mobile phone text message reminders in health care services: a narrative literature review. J Med Internet Res 2014 Oct 17;16(10):e222 [FREE Full text] [doi: 10.2196/jmir.3442] [Medline: 25326646]
24. Shrestha R, Altice FL, DiDomizio E, Sibilio B, Ranjit YS, Copenhaver MM. Feasibility and acceptability of an mHealth-based approach as an HIV prevention strategy among people who use drugs on pre-exposure prophylaxis. Patient Prefer Adherence 2020;14:107-118 [FREE Full text] [doi: 10.2147/PPA.S236794] [Medline: 32021122]
25. Biederman J, Fried R, DiSalvo M, Driscoll H, Green A, Biederman I, et al. A novel digital health intervention to improve patient engagement to stimulants in adult ADHD in the primary care setting: Preliminary findings from an open label study. Psychiatry Res 2020 Sep;291:113158. [doi: 10.1016/j.psychres.2020.113158] [Medline: 32559669]
26. Whittaker R, McRobbie H, Bullen C, Borland R, Rodgers A, Gu Y. Mobile phone-based interventions for smoking cessation. Cochrane Database Syst Rev 2012 Nov 14;11:CD006611. [doi: 10.1002/14651858.CD006611.pub3] [Medline: 23152238]
27. Chandra PS, Sowmya HR, Mehrotra S, Duggal M. 'SMS' for mental health—feasibility and acceptability of using text messages for mental health promotion among young women from urban low income settings in India. Asian J Psychiatr 2014 Oct;11:59-64. [doi: 10.1016/j.ajp.2014.06.008] [Medline: 25453699]
28. Stevens GJ, Hammond TE, Brownhill S, Anand M, de la Riva A, Hawkins J, et al. SMS SOS: a randomized controlled trial to reduce self-harm and suicide attempts using SMS text messaging. BMC Psychiatry 2019 Apr 18;19(1):117 [FREE Full text] [doi: 10.1186/s12888-019-2104-9] [Medline: 30999952]
29. Guy R, Hocking J, Wand H, Stott S, Ali H, Kaldor J. How effective are short message service reminders at increasing clinic attendance? A meta-analysis and systematic review. Health Serv Res 2012 Apr;47(2):614-632 [FREE Full text] [doi: 10.1111/j.1475-6773.2011.01342.x] [Medline: 22091980]
30. Kmiec J, Suffoletto B. Implementations of a text-message intervention to increase linkage from the emergency department to outpatient treatment for substance use disorders. J Subst Abuse Treat 2019 May;100:39-44 [FREE Full text] [doi: 10.1016/j.jsat.2019.02.005] [Medline: 30898326]
31. Moore SL, Fischer HH, Steele AW, Joshua Durfee M, Ginosar D, Rice-Peterson C, et al. A mobile health infrastructure to support underserved patients with chronic disease. Healthc (Amst) 2014 Mar;2(1):63-68. [doi: 10.1016/j.hjdsi.2013.12.016] [Medline: 26250090]
32. Jin H, Wu S. Text messaging as a screening tool for depression and related conditions in underserved, predominantly minority safety net primary care patients: validity study. J Med Internet Res 2020 Mar 26;22(3):e17282 [FREE Full text] [doi: 10.2196/17282] [Medline: 32213473]
33. Albright K, Krantz MJ, Backlund Jarquín P, DeAlleaume L, Coronel-Mockler S, Estacio RO. Health promotion text messaging preferences and acceptability among the medically underserved. Health Promot Pract 2015 Jul;16(4):523-532. [doi: 10.1177/1524839914566850] [Medline: 25586133]
34. Aguilera A, Muñoz RF. Text messaging as an adjunct to CBT in low-income populations: a usability and feasibility pilot study. Prof Psychol Res Pr 2011 Dec 01;42(6):472-478 [FREE Full text] [doi: 10.1037/a0025499] [Medline: 25525292]
35. Gibby CLK, Palacios C, Campos M, Graulau RE, Banna J. Acceptability of a text message-based intervention for obesity prevention in infants from Hawai'i and Puerto Rico WIC. BMC Pregnancy Childbirth 2019 Aug 13;19(1):291 [FREE Full text] [doi: 10.1186/s12884-019-2446-9] [Medline: 31409286]

36. Pop-Eleches C, Thirumurthy H, Habyarimana JP, Zivin JG, Goldstein MP, de Walque D, et al. Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders. AIDS 2011 Mar 27;25(6):825-834 [FREE Full text] [doi: 10.1097/QAD.0b013e32834380c1] [Medline: 21252632]
37. Manian N, Wagner CA, Placzek H, Darby BA, Kaiser TJ, Rog DJ. Relationship between intervention dosage and success of resource connections in a social needs intervention. Public Health 2020 Aug;185:324-331. [doi: 10.1016/j.puhe.2020.05.058] [Medline: 32726729]
38. Fiori KP, Rehm CD, Sanderson D, Braganza S, Parsons A, Chodon T, et al. Integrating social needs screening and community health workers in primary care: the community linkage to care program. Clin Pediatr (Phila) 2020 Jun;59(6):547-556 [FREE Full text] [doi: 10.1177/0009922820908589] [Medline: 32131620]
39. Tong ST, Liaw WR, Kashiri PL, Pecsok J, Rozman J, Bazemore AW, et al. Clinician experiences with screening for social needs in primary care. J Am Board Fam Med 2018;31(3):351-363 [FREE Full text] [doi: 10.3122/jabfm.2018.03.170419] [Medline: 29743219]
40. Byhoff E, De Marchis EH, Hessler D, Fichtenberg C, Adler N, Cohen AJ, et al. Part II: a qualitative study of social risk screening acceptability in patients and caregivers. Am J Prev Med 2019 Dec;57(6 Suppl 1):S38-S46 [FREE Full text] [doi: 10.1016/j.amepre.2019.07.016] [Medline: 31753278]
41. Bernstein SL, Rosner J, Toll B. Cell phone ownership and service plans among low-income smokers: the hidden cost of quitlines. Nicotine Tob Res 2016 Aug;18(8):1791-1793 [FREE Full text] [doi: 10.1093/ntr/ntw042] [Medline: 26920647]
42. Davis FD. Perceived usefulness, perceived ease of use, and user acceptance of information technology. MIS Quarterly 1989 Sep;13(3):319. [doi: 10.2307/249008]
43. Venkatesh V, Davis FD. A model of the antecedents of perceived ease of use: development and test. Decision Sciences 1996 Sep;27(3):451-481. [doi: 10.1111/j.1540-5915.1996.tb01822.x]
44. Campbell JI, Aturinda I, Mwesigwa E, Burns B, Santorino D, Haberer JE, et al. The Technology Acceptance Model for Resource-Limited Settings (TAM-RLS): a novel framework for mobile health interventions targeted to low-literacy end-users in resource-limited settings. AIDS Behav 2017 Nov;21(11):3129-3140 [FREE Full text] [doi: 10.1007/s10461-017-1765-y] [Medline: 28421356]
45. Bowen DJ, Kreuter M, Spring B, Cofta-Woerpel L, Linnan L, Weiner D, et al. How we design feasibility studies. Am J Prev Med 2009 May;36(5):452-457 [FREE Full text] [doi: 10.1016/j.amepre.2009.02.002] [Medline: 19362699]
46. Health Center Program Uniform Data System (UDS) data overview. Health Resources & Services Administration. URL: https://data.hrsa.gov/tools/data-reporting/program-data [accessed 2022-09-19]
47. Drake C, Eisenson H. Assessing and addressing social needs in primary care. New England Journal of Medicine Catalyst 2019;5(6). [doi: 10.1056/CAT.19.0693]
48. Moore J, Adams C, Bakst C, DePriest K, Kloenic GE. Institute for Medicaid Innovation. 2020. URL: https://www.medicaidinnovation.org/_images/content/2020-IMI-Medicaid_MCO_Survey-Report.pdf [accessed 2022-09-19]
49. Weir RC, Proser M, Jester M, Li V, Hood-Ronick CM, Gurewich D. Collecting social determinants of health data in the clinical setting: findings from national PRAPARE implementation. J Health Care Poor Underserved 2020;31(2):1018-1035. [doi: 10.1353/hpu.2020.0075] [Medline: 33410822]
50. Sandhu S, Xu J, Blanchard L, Eisenson H, Crowder C, Munoz VS, et al. A community resource navigator model: utilizing student volunteers to integrate health and social care in a community health center setting. Int J Integr Care 2021 Feb 05;21(1):2 [FREE Full text] [doi: 10.5334/ijic.5501] [Medline: 33597833]
51. Drake C, Batchelder H, Lian T, Cannady M, Weinberger M, Eisenson H, et al. Implementation of social needs screening in primary care: a qualitative study using the health equity implementation framework. BMC Health Serv Res 2021 Sep 17;21(1):975 [FREE Full text] [doi: 10.1186/s12913-021-06991-3] [Medline: 34530826]
52. Abroms LC, Whittaker R, Free C, Mendel Van Alstyne J, Schindler-Ruwisch JM. Developing and pretesting a text messaging program for health behavior change: recommended steps. JMIR Mhealth Uhealth 2015 Dec 21;3(4):e107 [FREE Full text] [doi: 10.2196/mhealth.4917] [Medline: 26690917]
53. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, REDCap Consortium. The REDCap consortium: building an international community of software platform partners. J Biomed Inform 2019 Jul;95:103208 [FREE Full text] [doi: 10.1016/j.jbi.2019.103208] [Medline: 31078660]
54. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009 Apr;42(2):377-381 [FREE Full text] [doi: 10.1016/j.jbi.2008.08.010] [Medline: 18929686]
55. Weiner BJ, Lewis CC, Stanick C, Powell BJ, Dorsey CN, Clary AS, et al. Psychometric assessment of three newly developed implementation outcome measures. Implement Sci 2017 Aug 29;12(1):108 [FREE Full text] [doi: 10.1186/s13012-017-0635-3] [Medline: 28851459]
56. Nadal C, Sas C, Doherty G. Technology acceptance in mobile health: scoping review of definitions, models, and measurement. J Med Internet Res 2020 Jul 06;22(7):e17256 [FREE Full text] [doi: 10.2196/17256] [Medline: 32628122]
57. Lewinski AA, Crowley MJ, Miller C, Bosworth HB, Jackson GL, Steinhauser K, et al. Applied rapid qualitative analysis to develop a contextually appropriate intervention and increase the likelihood of uptake. Med Care 2021 Jun 01;59(Suppl 3):S242-S251 [FREE Full text] [doi: 10.1097/MLR.0000000000001553] [Medline: 33976073]

58. Wortman Z, Tilson EC, Cohen MK. Buying health for North Carolinians: addressing nonmedical drivers of health at scale. Health Aff (Millwood) 2020 Apr;39(4):649-654. [doi: 10.1377/hlthaff.2019.01583] [Medline: 32250668]
59. Anthony CA, Polgreen LA, Chounramany J, Foster ED, Goerdt CJ, Miller ML, et al. Outpatient blood pressure monitoring using bi-directional text messaging. J Am Soc Hypertens 2015 May;9(5):375-381 [FREE Full text] [doi: 10.1016/j.jash.2015.01.008] [Medline: 25771023]
60. Fichtenberg CM, Alley DE, Mistry KB. Improving social needs intervention research: key questions for advancing the field. Am J Prev Med 2019 Dec;57(6 Suppl 1):S47-S54 [FREE Full text] [doi: 10.1016/j.amepre.2019.07.018] [Medline: 31753279]

Abbreviations

FQHC: federally qualified health center
PRAPARE: Protocol of Responding to and Assessing Patients' Assets, Risks, and Experiences
REDCap: Research Electronic Data Capture
TAM: technology acceptance model
TAM-RLS: technology acceptance model for resource-limited settings

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Protocol

Predicting Effective Adaptation to Breast Cancer to Help Women BOUNCE Back: Protocol for a Multicenter Clinical Pilot Study

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Abstract

Background: Despite the continued progress of medicine, dealing with breast cancer is becoming a major socioeconomic challenge, particularly due to its increasing incidence. The ability to better manage and adapt to the entire care process depends not only on the type of cancer but also on the patient's sociodemographic and psychological characteristics as well as on the social environment in which a person lives and interacts. Therefore, it is important to understand which factors may contribute to successful adaptation to breast cancer. To our knowledge, no studies have been performed on the combination effect of multiple psychological, biological, and functional variables in predicting the patient's ability to bounce back from a stressful life event,

such as a breast cancer diagnosis. Here we describe the study protocol of a multicenter clinical study entitled "Predicting Effective Adaptation to Breast Cancer to Help Women to BOUNCE Back" or, in short, BOUNCE.

Objective: The aim of the study is to build a quantitative mathematical model of factors associated with the capacity for optimal adjustment to cancer and to study resilience through the cancer continuum in a population of patients with breast cancer.

Methods: A total of 660 women with breast cancer will be recruited from five European cancer centers in Italy, Finland, Israel, and Portugal. Biomedical and psychosocial variables will be collected using the Noona Healthcare platform. Psychosocial, sociodemographic, lifestyle, and clinical variables will be measured every 3 months, starting from presurgery assessment (ie, baseline) to 18 months after surgery. Temporal data mining, time-series prediction, sequence classification methods, clustering time-series data, and temporal association rules will be used to develop the predictive model.

Results: The recruitment process stared in January 2019 and ended in November 2021. Preliminary results have been published in a scientific journal and are available for consultation on the BOUNCE project website. Data analysis and dissemination of the study results will be performed in 2022.

Conclusions: This study will develop a predictive model that is able to describe individual resilience and identify different resilience trajectories along the care process. The results will allow the implementation of tailored interventions according to patients' needs, supported by eHealth technologies.

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KEYWORDS

resilience; personality; coping; decision-making; cancer; quality of life

Introduction

Overview

Breast cancer is responsible for 28% of all cancer cases in Europe, with more than 2 million new cases in 2018 [1]. Despite continued progress in this area of medicine, dealing with cancers, such as breast cancer, is becoming a major socioeconomic challenge, in part due to increasing incidence. Furthermore, mortality has decreased significantly, with the 5-year survival rate progressing from 75% to 90% for women with breast cancer [2], contributing toward very significant increases in the number of long-term survivors, but with potential long-term losses in quality of life (QOL). Thus, it is of crucial importance to understand which psychological, social, contextual, and physical factors may affect or boost successful adaptation to breast cancer and its treatment. Accruing evidence [3,4] has defined the process of successful adaptation to chronic diseases, such as breast cancer, as "resilience." Resilience is a complex and multidimensional construct that can be defined at different levels: as the individual's potential (ie, the capacity to engage in adaptive coping processes), as a process (ie, the adaptive reaction to adversity), and as an outcome (ie, the final state achieved as the result of coping). A significant effort to reach a consensus definition was made by Southwick and colleagues [4], according to whom resilience includes "healthy, adaptive, or integrated positive functioning over the passage of time in the aftermath of adversity." This definition highlights the two main components of resilience: the presence of adversity and the positive adaptation to it [5]. In fact, when faced with potentially life-threatening events, each person engages in coping strategies that can vary widely in the capacity to provide adaptive solutions and to ensure optimal recovery with respect to the disease itself, as well as to overall QOL.

Important questions remain regarding the determinants of resilience and how it can be measured. Consensus exists that it should be analyzed with a multilevel perspective, including biological, demographic, cultural, economic, psychological, behavioral, and social variables [4]. As such, interest in the impact of biological factors on resilience has increased, with several studies, including research in animal models investigating processes akin to resilience, having shown an association between resilience, inflammation, and immune processes, similar to pathways that have been described in aging [6] and cancer [7-11]. However, there is also evidence that other factors, such as sociodemographic [12-14] and psychological characteristics as well as social environment [15], impact the ability of people with individual differences to manage and adapt to the entire cancer care process. Here we describe the rationale and methods for a study to assess resilience multidimensionally in women with breast cancer.

Sociodemographic and Psychological Characteristics in Cancer Adjustment

Over the last few decades, interest in the contribution of patient characteristics on cancer onset, treatment, and management as well as the ability to cope with cancer have widely increased [16-18]. Higher levels of resilience have been described in patients of younger age, female sex, and higher socioeconomic status as well as those who are married [12-14]. In addition to sociodemographic characteristics, other internal (eg, personality traits, dispositional optimism, and self-efficacy) and external (eg, social support) factors may affect the resilience of patients with cancer [15]. For example, adopting cognitive regulation strategies may help patients cope with strong emotions in order to not get overwhelmed and avoid stressful outcomes [19,20]. In line with these findings, acceptance attitudes and positive thinking also seem to play an important role in patients' psychological well-being, while rumination and catastrophizing

often lead to negative emotions [21-25]. Ultimately, high resilience levels could affect adherence to treatment procedures, thus promoting faster recovery and lower clinical burden [15].

Regarding patients with breast cancer, personality traits may significantly affect psychological status in the process of adaptation to the disease. A recent study showed dispositional optimism as an important short- and long-term predictor of psychological well-being after breast cancer, where patients with more optimistic orientation reported lower distress levels, whereas unpleasant emotions were mainly experienced by people with a pessimistic approach [26]. Furthermore, self-efficacy appears to be associated with higher levels of wellness, better QOL, and decreasing depression and anxiety, even 1 year after diagnosis [27]. In addition, perceived social support acts as a protective factor, allowing better adaptation and promoting positive coping strategies in patients with breast cancer [28]. In line with these findings, it is known that a cancer diagnosis affects not only the patient but also his or her family system, which represents a key source of support for better adaptation to the disease [29]. As an example, in 2018, Faccio and colleagues [30] proposed a model of family resilience that highlighted the key role of family in the patient's decisions and overall well-being. In fact, a cancer diagnosis can be considered as a perturbation of the whole family system, which may result in a smooth adaptation to a new homeostasis or in difficulties that prevent the readjustment process [31]. According to this model, higher cohesion and more clear and consistent communication among the family members, in addition to the possibility of sharing feelings and fears, increase the patient's ability to organize her experience and adapt to the new condition [32].

Novelty and Study Aim

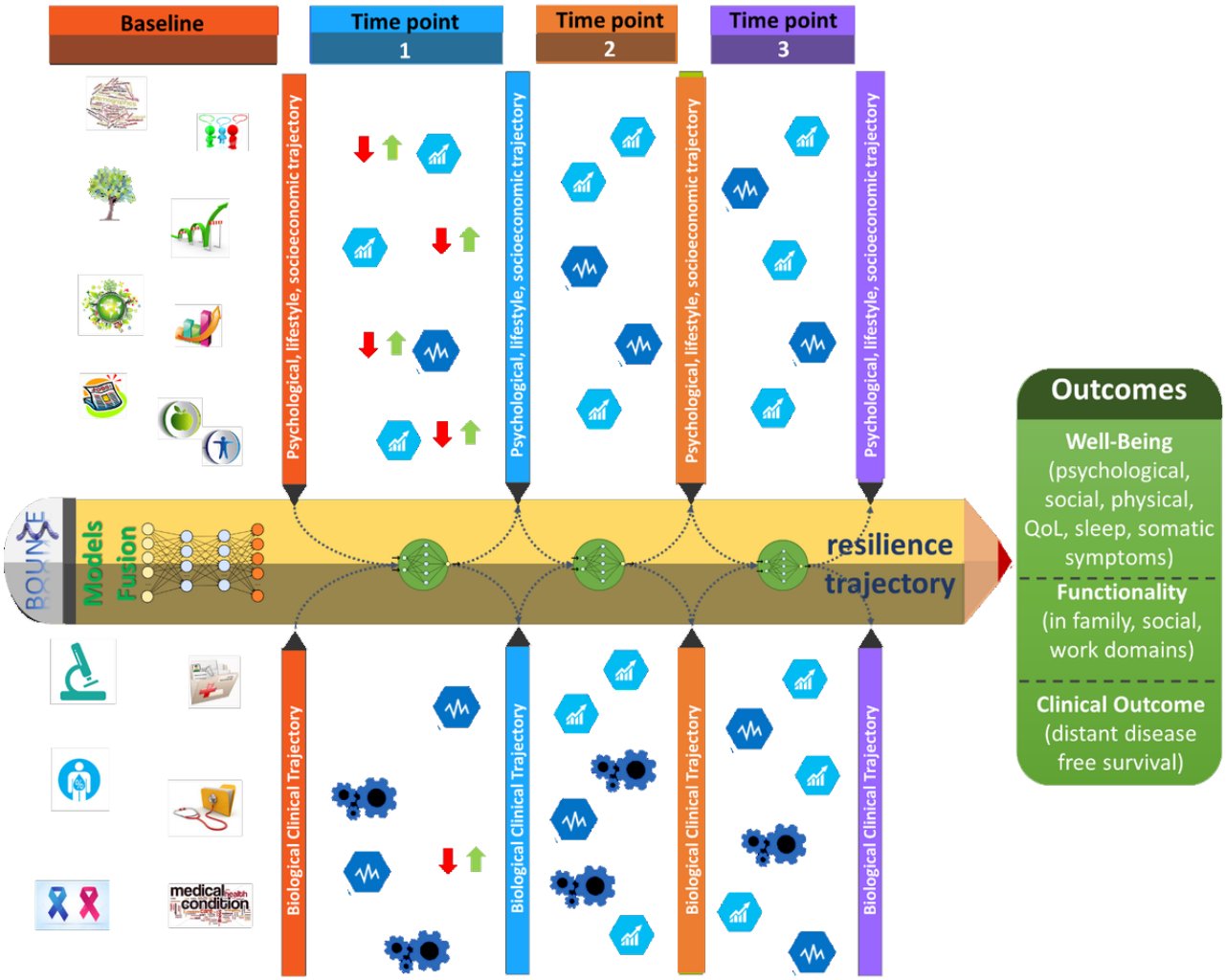
While several theoretical contributions regarding resilience in medical settings have already been published [33], to our best knowledge, no studies have been performed on the combined effect of multiple psychological, biological, and functional variables in predicting the ability of patients to bounce back from a stressful life event, such as a breast cancer diagnosis. There is a growing need for novel strategies to improve the capacity to predict resilience in response to a variety of stressful experiences, including breast cancer. A major objective for the field is to enhance resilience in the face of breast cancer, and its prediction would, thus, be a necessary step toward efficient recovery through personalized interventions.

The bidirectional relationship between medical and psychosocial factors in breast cancer has been well established in previous studies. For example, breast cancer treatments, such as radiation and chemotherapy, have been associated with higher levels of psychological distress, long-term cognitive dysfunction, and lower QOL [34-36]. Consistently, several studies have estimated the prevalence of depression in the early stages of breast cancer to be around 15% to 20% [36,37], whereas Burgess and colleagues [38] found that almost 50% of women with breast cancer report anxiety or depression symptoms in the first year after diagnosis. The prevalence of these symptoms drop to 25% in the second year but remain as high as 15% thereafter [38]. There is evidence that several psychological factors affect the progress of disease. Higher psychological distress, for example, may lead to additional medical examinations, may negatively affect treatment decision-making, and could even disrupt ongoing medical treatments [39,40]. There is also evidence that psychosocial factors, including distress, stressors, low optimism, and poor social support, have an impact on immune responses (eg, lymphocyte proliferation), on physiological activation (eg, along the hypothalamic-pituitary-adrenal axis), and on lifestyle behaviors (eg, smoking and medication adherence), consequently affecting the course of disease [39,41-43].

Drawing from the theoretical and empirical framework described above, here we describe the study protocol of a multicenter clinical study entitled "Predicting Effective Adaptation to Breast Cancer to Help Women to BOUNCE Back" or, in short, BOUNCE. With this study, we intend to identify psychosocial, biomedical, and functional factors that predict the capacity of individual patients to "bounce back" during the highly stressful treatment and recovery period following a diagnosis of breast cancer (Figure 1 [44]). This study has been designed to investigate resilience trajectories starting at diagnosis and for 18 months of follow-up. The underlying hypothesis is that biomedical, psychosocial, and functional factors may predict trajectories of resilience and adjustment to breast cancer.

If confirmed, this would support the general purpose of the study, which is the early identification of women at risk for whom early intervention (eg, through personalized psychological support) would be necessary. This multicenter clinical pilot study is the core of a larger European Union (EU) project named BOUNCE (grant agreement No. 777167), which has been developed to understand and study resilience through the cancer continuum in patients with breast cancer. The main global goal of the BOUNCE project is to build a quantitative mathematical model of factors associated with the capacity for optimal adjustment to cancer; this will initially be done through a data-driven method, including the computation of resilience on the basis of retrospective data, and through a psychometric method, as described here, with prospective assessment of several domains of resilience through questionnaires.

Figure 1. Schematic illustration of the multiple factors affecting the resilience trajectory and outcomes. QoL: quality of life (adapted from Poikonen-Saksela [44], with permission from Paula Poikonen-Saksela).



Objectives

The primary objective of this multicenter clinical pilot study is to identify the interplay of clinical, biomedical, and psychosocial factors in predicting patients' resilience to breast cancer at several time points after diagnosis.

The secondary objectives are as follows:

1. Differentiating between trajectories of psychological adaptation to breast cancer.
2. Developing a multidimensional index of resilience as a function of biomedical status, psychosocial status, and functional status.
3. Examining potential differences in the predictive and outcome variables across the four clinical sites in which the study is conducted.
4. Cross-validating the prediction models in order to assess the accuracy of their performance in practice and to enhance their generalization.

Methods

Study Design and Clinical Partners

The clinical pilot study has been designed as a longitudinal prospective cohort, with assessments at diagnosis of breast cancer and 3, 6, 9, 12, 15, and 18 months later. It involves different clinical centers in several countries, namely the European Institute of Oncology (IEO) in Italy, Helsinki University Hospital (HUS) in Finland, the Champalimaud Clinical Centre (CHAMP) in Portugal, and the Rabin and Shaare Zedek Medical Centers, coordinated by the Hebrew University of Jerusalem (HUJI) in Israel. Data were primarily collected through the Noona Healthcare platform (Noona), a personal health records system designed for patients with cancer. For those patients who do not want or are unable to use Noona, the paper-and-pencil mode are available. Data are then inserted into the Noona platform by a researcher. Noona is a fully responsive web application that is usable with a web browser on any suitable device that is available to the user, including desktop, laptop, tablet, and smartphone devices. Noona is classified as a medical device; more specifically, it is classified as a web platform designed for patients with cancer for remote monitoring and as a support tool for communication between patients with

cancer and health care professionals. However, in the multicenter clinical study, Noona will not be used for communication between the treatment team and patients, but will only be used for the collection of study-relevant information. Thus, the main functionalities, such as reporting symptoms or requesting assistance, will not be taken into consideration. The study was registered at ClinicalTrials.gov (NCT05095675).

Study Participants

Women with histologically confirmed stage I to III breast cancer have been recruited across the several study centers, with 660 patients recruited at baseline. Details on the inclusion and exclusion criteria are provided in the Selection Criteria section below.

Selection Criteria

Inclusion criteria include the following:

- Female patients, 40 to 70 years of age at the time of diagnosis
- Histologically confirmed invasive breast cancer, early or locally advanced but operable
- Tumor stage I, II, and III
- Patients receiving surgery as part of the local treatment
- Patients receiving systemic treatment for breast cancer, regardless of treatment type
- Informed consent form signed.

Exclusion criteria include the following:

- Refusal to provide informed consent
- Presence of distant metastases
- History of another malignancy or contralateral invasive breast cancer within the last 5 years, with the exception of cured basal cell carcinoma of skin or carcinoma in situ of the uterine cervix; the patient's resilience could have been affected by a previous cancer diagnosis
- History of an early-onset (ie, before 40 years of age) mental disorder (eg schizophrenia, psychosis, bipolar disorder, and diagnosis of major depression) or severe neurologic disorder (ie, a neurodegenerative disorder and dementia)
- Other concomitant serious diseases that could affect a patient's resilience and cancer pathway, such as clinically significant (ie, active) cardiac disease (eg, congestive heart failure, symptomatic coronary artery disease, or cardiac arrhythmia not well controlled with medication) or myocardial infarction within the last 12 months
- Major surgery for severe disease or trauma that could affect a patient's psychosocial well-being (eg, major heart or abdominal surgery) within 4 weeks before study entry, or lack of complete recovery from the effects of surgery
- Treatment for other invasive cancer
- Treatment for any major illness in the last 6 months
- Pregnancy or breastfeeding at the time of recruitment.

Instruments and Measures

Psychosocial Instruments

The processes of defining the instruments started with a list of 50 relevant psychological constructs and their measures that were hypothesized to affect resilience. This initial pool was determined in accordance with the results of literature research and the research experience of each of the four clinical teams. The following criteria were used to define instruments for data collection: (1) sound psychometric properties (ie, reliability and construct validity), (2) divergent validity in the context of this research (ie, low overlap with other measures), (3) ability to predict important outcomes in the cancer resilience trajectory or in longitudinal studies (ie, controlling for initial levels of the outcome measures), and (4) reduced number of items. The final questionnaire consists of a set of validated measurement tools related to the following domains: personality, meaning, comprehensibility and manageability of the disease, trauma exposure, coping, social support, resilience, illness perception, QOL, and distress. The scales used to measure such domains are reported in Table 1 [45-63].

The collection of sociodemographic and lifestyle variables includes information about age, level of education, marital status, number of children, employment status and sick days, flexible arrangements at work, return to work, income, faith, smoking and alcohol consumption, drug use, weight and height, diet, exercise, number of professional support sessions, variations in family's work, other leisure activities, and presence of domestic help (Table 2).

Table 1. Psychosocial assessment tools.

Domain and measure names	Month[a]						
	0	3	6	9	12	15	18
Personality							
Ten-Item Personality Inventory [45]	✓						
Life Orientation Test–Revised [46]	✓						
Meaning							
Sense of Coherence scale [47]	✓						
Trauma exposure							
PTSD[b] Checklist [48]			✓		✓		✓
Recent negative life events	✓	✓	✓	✓	✓	✓	✓
Recent illness		✓	✓	✓	✓	✓	✓
Posttraumatic Growth Inventory [58]		✓			✓		✓
Coping							
Perceived Ability to Cope with Trauma scale [49]	✓			✓		✓	
Cognitive Emotion Regulation Questionnaire [50]	✓			✓		✓	
Mindful Attention Awareness Scale [51]	✓				✓		
Mini–Mental Adjustment to Cancer Scale [56]		✓		✓		✓	
Single item: What have you done to cope?		✓	✓	✓	✓	✓	✓
Spirituality coping—a visual analog scale		✓		✓		✓	
Social support							
Modified Medical Outcomes Study Social Support Survey [52]		✓		✓		✓	
Family Resilience Questionnaire [32]		✓		✓		✓	
Instrumental and emotional perceived social support	✓						
Resilience							
Connor-Davidson Resilience Scale [53]	✓			✓		✓	
Single item: How much are you back to yourself?			✓	✓	✓	✓	✓
Illness perception and behaviors							
Illness Perception Questionnaire [54]			✓		✓		✓
Items 3 and 4 from the Brief Illness Perception Questionnaire [55]		✓	✓	✓	✓	✓	✓
Cancer Behavior Inventory [57]	✓		✓		✓		
Modified Medical Outcomes Study Social Support Survey [52]		✓	✓	✓	✓	✓	✓
Quality of life							
EORTC[c] Quality of Life Questionnaire [59]	✓	✓	✓	✓	✓	✓	✓
EORTC Quality of Life Questionnaire breast cancer module [59]	✓	✓	✓	✓	✓	✓	✓
Distress							
Fear of Cancer Recurrence Inventory–short form [60]	✓		✓		✓		✓
Hospital Anxiety and Depression Scale [61]	✓	✓	✓	✓	✓	✓	✓
Positive and Negative Affect Schedule–short form [62]	✓	✓	✓	✓	✓	✓	✓
Distress Thermometer [63]	✓	✓	✓	✓	✓	✓	✓

[a]A checkmark indicates that the assessment tool was administered at the indicated time point.

[b]PTSD: posttraumatic stress disorder.

[c]EORTC: European Organisation for Research and Treatment of Cancer.

Table 2. Sociodemographic and lifestyle assessments.

Variables	Month[a]						
	0	3	6	9	12	15	18
Year of birth	✓						
Level of education	✓						✓
Marital status	✓						✓
Number of children	✓						✓
Employment status	✓	✓	✓	✓	✓	✓	✓
Monthly income	✓						✓
Sick leave days	✓	✓	✓	✓	✓	✓	✓
Employer's support					✓		✓
Return to work							✓
Level of religious faith	✓						✓
Smoke	✓			✓			✓
Drinking habits	✓			✓			✓
Use of drugs	✓		✓		✓		✓
Weight	✓		✓		✓		✓
Height	✓		✓		✓		✓
Diet	✓			✓			✓
Physical exercise	✓		✓		✓		✓
Mental health support		✓	✓	✓	✓	✓	✓
Support activities		✓	✓	✓	✓	✓	✓
Domestic help		✓	✓	✓	✓	✓	✓
Instrumental family support		✓	✓	✓	✓	✓	✓

[a]A checkmark indicates that the information was collected at the indicated time point.

Medical and Treatment Information

The clinical variables, including medical and treatment data, were retrieved from each patient's health record. In particular, the following clinical variables were collected for each participant: classification by the International Statistical Classification of Diseases and Related Health Problems, 10th Revision; tumor biology (ie, primary tumor, regional lymph nodes, histological type, grade, estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 [HER2]); surgery type and side; performance status; ongoing oncological therapy (ie, chemotherapy, endocrine therapy, anti-HER2 therapy, and radiotherapy); menopausal status; genetic risk factors; psychotropic medication; and comorbidity and laboratory tests, including hemoglobin, leukocytes, thrombocytes, neutrophils, and high-sensitivity C-reactive protein (Table 3). Furthermore, data on the patient care pathway were collected. These data were related to three different contexts: oncologic clinic, specialized care unit, and primary care or occupational health care. In particular, we were interested in collecting information regarding the following: the number of consultations with oncologists, nurses, psychiatrists, psychologists, and other health care professionals; the number and dates of treatment visits; the number and dates of inpatient days; the number of visits with regard to emergency care, laboratory visits, and imaging visits; and a list of prescribed medication. Finally, additional medical information was collected at months 12 and 18, regarding local relapse, metastatic disease, and death (Table 3).

Table 3. Medical assessment.

Variables	Month[a]						
	0	3	6	9	12	15	18
Medical information							
Cancer stage	✓						
Comorbidity	✓						
Genetic risk factor	✓						
Menopausal status	✓				✓		
Tumor pathology	✓						
Eastern Cooperative Oncology Group score	✓	✓	✓		✓		
Psychotropic medication	✓	✓	✓		✓		
Hormone replacement treatment	✓						
Laboratory tests	✓				✓		
Treatment information							
Surgery			✓				
Chemotherapy			✓				
Endocrine therapy					✓		✓
Anti–human epidermal growth factor receptor 2					✓		✓
Radiotherapy			✓				
Side effects					✓		
Patient care pathway data		✓	✓	✓	✓		✓

[a]A checkmark indicates that the information was collected at the indicated time point.

Time Point Measurements

Psychosocial, sociodemographic, lifestyle, and clinical variables were measured at different time points (Tables 1-3). There were seven assessment time points over a period of 18 months: baseline (ie, just after the diagnosis, before the start of chemotherapy, or within 2 weeks from the start of endocrine therapy) and every 3 months until month 18. Each assessment time point contains a set of specific measures that are able to capture salient changes in specific domains. Accordingly, variables that are not sensitive to change (eg, tumor biology and personality trait) were collected only at baseline. Data that are expected to change over time because of intervening factors (eg, starting of treatment and associated side effects, as well as adverse life events) were collected periodically.

Recruitment and Follow-Up

A trained researcher identified all eligible patients, evaluating inclusion and exclusion criteria, by checking the patient's health records stored in the electronic database of the hospital. Successively, during the first clinical consultation, the investigator briefly introduced the study to each eligible patient and collected informed consent from those interested in participating. During this first meeting, the investigator gave a short training in Noona and created the patient account. The investigator could use Noona to monitor the response status of questionnaires for each patient and could contact them to stimulate adherence to the study, completion of the questionnaires, and support for any issues with the platform.

Statistical Procedures

Statistical Considerations on the Design

Data collected by Noona are stored centrally by the Foundation for Research and Technology–Hellas (FORTH); the data will be cleaned, homogenized, and shared with the Institute of Communications and Computer Systems (ICCS) for joint conduction of analyses. Interim analyses and quality checks will be conducted on data extracted at different time points during the project (eg, after the month 6 data are complete). Descriptive statistics (ie, mean, SD, median, maximum and minimum, and graphical representation) will be used to summarize the continuous data. Discrete measures will be summarized using counts, percentages, and graphical representations. Bivariate charts will be produced whenever desired. Temporal data mining, time-series prediction, sequence classification methods, clustering time-series data, and temporal association rules will be used to develop and validate the predictive model. Mediation, moderation, and moderated mediation analyses have a central role in the statistical methodology. In order to investigate whether the modality of data collection (ie, paper and pencil or the eHealth platform, Noona) will affect results on self-reported outcomes, analysis will be performed stratifying patients based on the method used to respond. Similarly, patients will be stratified based on sociodemographic (eg, country) and clinical variables (eg, cancer stage).

Sample Size Considerations

In the context of conventional statistical approaches, such as multiple linear regression, that have typically been employed in the existing relevant literature, a minimal sample size (n=500, considering maximal attrition rates of approximately 40%) is sufficient to ensure 85% power at $P<.05$; this will allow detection of the cumulative contribution of up to 30 independent predictors accounting for as little as 5.3% of total variance of each key study outcome. Furthermore, in a regression model with 30 independent variables, this sample size is sufficient to detect the significant added value of each independent variable, assuming a small effect size (Cohen $f^2>0.018$). It should be noted, however, that this study proposed, for the first time, the use of nonconventional computational approaches to assess the hypothesized predictive variables. Given the complexity of the data sets and the fact that interactions between parameters are often difficult to specify—a requirement of conventional methods—supervised machine learning methods are emerging as the approach of choice for identifying hidden patterns among predictor variables. Perhaps the most distinct advantage of these methods is their adaptive capacity (ie, their inherent ability to optimize parameter weights based on known individual outcomes). The clinical accuracy of each optimized prediction model will be tested through various cross-validation techniques.

Data Collection Storage and Security

The multicenter pilot study involves the collection of personal data. Therefore, issues regarding confidentiality, privacy, and protection of data have been addressed so as to be compliant with Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation). All data collected through the questionnaires and all relevant information about participants are stored in Noona electronic databases. The data are processed using a coding system that allows for the identification of patient identity only if and when necessary for the scientific objectives of the research project.

The lists below reflect the partners involved in the project and their respective roles regarding data collection, storage, and security.

Clinical partners are as follows:

- IEO: promoter of the multicenter pilot study and data controller
- HUS: coordinator of the EU BOUNCE project and data processor
- Rabin Medical Center and the Shaare Zedek Medical Center, under HUJI: data processor
- CHAMP: data processor.

Technical partners are as follows:

- FORTH: data analysis and storage
- ICCS: data analysis
- SingularLogic: data analysis and model development
- Nordic Healthcare Group: model development
- Noona: data storage.

Ethics Compliance

Since the IEO is the promoter of the multicenter pilot study, the research protocol of the multicenter clinical study was first submitted for approval to the Ethics Committee of the IEO. Once approved by this Ethics Committee (approval No. R868/18-IEO 916; approval date: October 24, 2018), the protocol was submitted for approval to the Ethics Committees of HUS, the Rabin Medical Center and the Shaare Zedek Medical Center (under HUJI's responsibility), and the CHAMP. In the course of the study, an amendment was submitted to the Ethics Committee of the IEO (amendment version No. 1 date: August 12, 2019; approval date: September 18, 2019) and to the centers in which such process was deemed necessary.

The multicenter pilot study has been devised so as to comply with both national (ie, Good Clinical Practices) and international declarations (ie, the Declaration of Helsinki) regulating proper ethical research involving human subjects, with informed consent obtained from all subjects. Specifically, conduction of the trial is in accordance with the following regulation and norms:

- The Declaration of Helsinki, ethical principles for medical research involving human subjects, revised October 2013
- The Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, Oviedo 1997
- The Council for International Organizations of Medical Sciences in collaboration with the World Health Organization, International Ethical Guidelines for Biomedical Research Involving Human Subjects, revised in 2016
- The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Biomedical and Behavioral Research. Department of Health, Education, and Welfare (DHEW) publication (DHEW-05-78-0012), Washington, DC, 1978.

Results

The recruitment process stared in January 2019 and ended in November 2021. Preliminary results have been published in a scientific journal and are available for consultation on the BOUNCE project website [64]. Data analysis and dissemination of the study results will be performed in 2022.

Discussion

Due to the increasing interest in the role of resilience in cancer recovery, there is a need for evidence regarding the complex paths between resilience, factors affecting resilience, and the interrelated illness outcomes. The study described here has the advantage of firstly assessing the combination of biological, clinical, lifestyle-related, and cognitive-emotional factors. These multiple variables account for systematic fluctuations of resilience across time that, in turn, actually contribute to successful adaptation to and recovery from breast cancer. BOUNCE aspires to move from a biomedical to a

person-centered and biopsychosocial approach, toward growing awareness of the complexity of health and individual responses to illness [64-68]. In particular, we expect that this study will provide a predictive model to describe individual resilience and related factors, with the aim of personalized treatment plans, according to such predictions. In fact, we propose that the identification of individual resilience trajectories along the care process will lead to the development and implementation of tailored interventions, ideally supported by eHealth technologies [69-72]. In addition, it will scale up the knowledge about the interaction between biological, clinical, and psychosocial factors and outcomes, supporting, for example, programs of psychological prevention to support the patient across the disease trajectory.

Data collected from this pilot study could also provide information about cross-cultural differences. Further analyses and research based on BOUNCE data could examine the impact that the various health care systems in different countries could have on breast cancer resilience trajectories. Such possible differences will be of paramount importance, not only for a mere descriptive purpose but also for the development of a culture-based prediction model.

A possible limitation of this study is the large number of self-report scales used to collect the psychosocial variables; this may be perceived as too taxing by patients. However, considering that the general purpose of the study is the early identification of women at risk of poor adaptation, throughout the development of a data-driven quantitative mathematical model, all mentioned variables are needed at this research step to build a unified, multidimensional resilience trajectory predictor tool. This prediction model will encompass the results of the major analyses to be performed within the BOUNCE project; the results will identify potentially different trajectories of psychological adaptation to breast cancer over time, as well as the medical, sociodemographic, and psychosocial variables that may predict these trajectories. Although the final form of this tool is not yet decided and will depend on the actual findings of the study, hopefully it will allow health professionals to have a holistic picture of the patient condition: all the biological, psychological, and social factors together at a glance for a perfectly integrated treatment plan.

Acknowledgments

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Conflicts of Interest

AJOM was the national coordinator for Portugal of a noninterventional study (EDMS-ERI-143085581, 4.0) to characterize a treatment-resistant depression cohort in Europe, sponsored by Janssen-Cilag, Ltd (2019-2020); is the recipient of a grant from Schuhfried GmbH for the norming and validation of cognitive tests; and is the national coordinator for Portugal of trials related to psilocybin therapy for treatment-resistant depression, sponsored by Compass Pathways, Ltd (EudraCT [European Union Drug Regulating Authorities Clinical Trials Database] Nos. 2017-003288-36 and 2020-001348-25), and esketamine for treatment-resistant depression, sponsored by Janssen-Cilag, Ltd (EudraCT No. 2019-002992-33). JS is employed by Varian Medical System Inc, which is the manufacturer of the Noona patient-reported outcomes platform.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel R, Torre L, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018 Nov;68(6):394-424 [FREE Full text] [doi: 10.3322/caac.21492] [Medline: 30207593]
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020 Jan;70(1):7-30 [FREE Full text] [doi: 10.3322/caac.21590] [Medline: 31912902]
3. Rutter M. Implications of resilience concepts for scientific understanding. Ann N Y Acad Sci 2006 Dec;1094:1-12. [doi: 10.1196/annals.1376.002] [Medline: 17347337]
4. Southwick SM, Bonanno GA, Masten AS, Panter-Brick C, Yehuda R. Resilience definitions, theory, and challenges: Interdisciplinary perspectives. Eur J Psychotraumatol 2014;5:25338 [FREE Full text] [doi: 10.3402/ejpt.v5.25338] [Medline: 25317257]
5. Cosco TD, Howse K, Brayne C. Healthy ageing, resilience and wellbeing. Epidemiol Psychiatr Sci 2017 Dec;26(6):579-583 [FREE Full text] [doi: 10.1017/S2045796017000324] [Medline: 28679453]
6. Tramontano D, De Amicis F. Is the secret for a successful aging to keep track of cancer pathways? J Cell Physiol 2018 Nov;233(11):8467-8476. [doi: 10.1002/jcp.26825] [Medline: 29904910]
7. Ben-Shaanan TL, Schiller M, Azulay-Debby H, Korin B, Boshnak N, Koren T, et al. Modulation of anti-tumor immunity by the brain's reward system. Nat Commun 2018 Jul 13;9(1):2723 [FREE Full text] [doi: 10.1038/s41467-018-05283-5] [Medline: 30006573]
8. Felger JC, Li Z, Haroon E, Woolwine BJ, Jung MY, Hu X, et al. Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression. Mol Psychiatry 2016 Oct;21(10):1358-1365 [FREE Full text] [doi: 10.1038/mp.2015.168] [Medline: 26552591]

9. Bruenig D, Morris CP, Mehta D, Harvey W, Lawford B, Young RM, et al. Nitric oxide pathway genes (NOS1AP and NOS1) are involved in PTSD severity, depression, anxiety, stress and resilience. Gene 2017 Aug 20;625:42-48. [doi: 10.1016/j.gene.2017.04.048] [Medline: 28465168]
10. Takeuchi A, Saito T. CD4 CTL, a cytotoxic subset of CD4 T cells, their differentiation and function. Front Immunol 2017;8:194 [FREE Full text] [doi: 10.3389/fimmu.2017.00194] [Medline: 28280496]
11. Walker FR, Pfingst K, Carnevali L, Sgoifo A, Nalivaiko E. In the search for integrative biomarker of resilience to psychological stress. Neurosci Biobehav Rev 2017 Mar;74(Pt B):310-320. [doi: 10.1016/j.neubiorev.2016.05.003] [Medline: 27179452]
12. Bonanno GA, Galea S, Bucciarelli A, Vlahov D. What predicts psychological resilience after disaster? The role of demographics, resources, and life stress. J Consult Clin Psychol 2007 Oct;75(5):671-682. [doi: 10.1037/0022-006X.75.5.671] [Medline: 17907849]
13. Carver CS. Enhancing adaptation during treatment and the role of individual differences. Cancer 2005 Dec 01;104(11 Suppl):2602-2607 [FREE Full text] [doi: 10.1002/cncr.21247] [Medline: 16247785]
14. Molina Y, Yi JC, Martinez-Gutierrez J, Reding KW, Yi-Frazier JP, Rosenberg AR. Resilience among patients across the cancer continuum: Diverse perspectives. Clin J Oncol Nurs 2014 Feb;18(1):93-101 [FREE Full text] [doi: 10.1188/14.CJON.93-101] [Medline: 24476731]
15. Di Giacomo D, Cannita K, Ranieri J, Cocciolone V, Passafiume D, Ficorella C. Breast cancer and psychological resilience among young women. J Psychopathol 2016;22:191-195 [FREE Full text]
16. Pravettoni G, Gorini A. A P5 cancer medicine approach: Why personalized medicine cannot ignore psychology. J Eval Clin Pract 2011 Aug;17(4):594-596. [doi: 10.1111/j.1365-2753.2011.01709.x] [Medline: 21679280]
17. Pravettoni G, Mazzocco K, Gorini A, Curigliano G. Understanding cognitive processes behind acceptance or refusal of phase I trials. Crit Rev Oncol Hematol 2016 Apr;100:69-73. [doi: 10.1016/j.critrevonc.2016.01.023] [Medline: 26852078]
18. Galli F, Scotto L, Ravenda S, Zampino MG, Pravettoni G, Mazzocco K. Personality factors in colorectal cancer: A systematic review. Front Psychol 2021;12:590320 [FREE Full text] [doi: 10.3389/fpsyg.2021.590320] [Medline: 34803785]
19. Garnefski N, Kraaij V, Spinhoven P. Negative life events, cognitive emotion regulation and emotional problems. Pers Individ Dif 2001 Jun;30(8):1311-1327. [doi: 10.1016/S0191-8869(00)00113-6]
20. Li L, Zhu X, Yang Y, He J, Yi J, Wang Y, et al. Cognitive emotion regulation: Characteristics and effect on quality of life in women with breast cancer. Health Qual Life Outcomes 2015 May 06;13:51 [FREE Full text] [doi: 10.1186/s12955-015-0242-4] [Medline: 25944458]
21. Hamama-Raz Y, Pat-Horenczyk R, Perry S, Ziv Y, Bar-Levav R, Stemmer SM. The effectiveness of group intervention on enhancing cognitive emotion regulation strategies in breast cancer patients: A 2-year follow-up. Integr Cancer Ther 2016 Jun;15(2):175-182 [FREE Full text] [doi: 10.1177/1534735415607318] [Medline: 26420778]
22. Nolen-Hoeksema S, Aldao A. Gender and age differences in emotion regulation strategies and their relationship to depressive symptoms. Pers Individ Dif 2011 Oct;51(6):704-708. [doi: 10.1016/j.paid.2011.06.012]
23. Wang Y, Yi J, He J, Chen G, Li L, Yang Y, et al. Cognitive emotion regulation strategies as predictors of depressive symptoms in women newly diagnosed with breast cancer. Psychooncology 2014 Jan;23(1):93-99. [doi: 10.1002/pon.3376] [Medline: 24038706]
24. Mazzocco K, Masiero M, Carriero MC, Pravettoni G. The role of emotions in cancer patients' decision-making. Ecancermedicalscience 2019;13:914 [FREE Full text] [doi: 10.3332/ecancer.2019.914] [Medline: 31123497]
25. Gorini A, Riva S, Marzorati C, Cropley M, Pravettoni G. Rumination in breast and lung cancer patients: Preliminary data within an Italian sample. Psychooncology 2018 Feb;27(2):703-705. [doi: 10.1002/pon.4468] [Medline: 28574170]
26. Novakov I, Popovic-Petrovic S. Personality traits as predictors of the affective state in patients after breast cancer surgery. Arch Oncol 2017;23(1):3-8. [doi: 10.2298/aoo1701003n]
27. BorjAlilu S, Kaviani A, Helmi S, Karbakhsh M, Mazaheri M. Exploring the role of self-efficacy for coping with breast cancer: A systematic review. Arch Breast Cancer 2017 May;4(2):42-57 [FREE Full text] [doi: 10.19187/abc.20174242-57]
28. Wills TA, Bantum EO. Social support, self-regulation, and resilience in two populations: General-population adolescents and adult cancer survivors. J Soc Clin Psychol 2012 Jun;31(6):568-592. [doi: 10.1521/jscp.2012.31.6.568]
29. Rolland JS. Cancer and the family: An integrative model. Cancer 2005 Dec 01;104(11 Suppl):2584-2595 [FREE Full text] [doi: 10.1002/cncr.21489] [Medline: 16270342]
30. Faccio F, Renzi C, Giudice AV, Pravettoni G. Family resilience in the oncology setting: Development of an integrative framework. Front Psychol 2018;9:666 [FREE Full text] [doi: 10.3389/fpsyg.2018.00666] [Medline: 29867644]
31. von Bertalanffy L. General System Theory: Foundations, Development, Applications. New York, NY: George Braziller; 2003.
32. Faccio F, Gandini S, Renzi C, Fioretti C, Crico C, Pravettoni G. Development and validation of the Family Resilience (FaRE) Questionnaire: An observational study in Italy. BMJ Open 2019 Jun 05;9(6):e024670 [FREE Full text] [doi: 10.1136/bmjopen-2018-024670] [Medline: 31171547]
33. Deshields T, Heiland M, Kracen A, Dua P. Resilience in adults with cancer: Development of a conceptual model. Psychooncology 2016 Jan;25(1):11-18. [doi: 10.1002/pon.3800] [Medline: 25787828]

34. Didier F, Radice D, Maldifassi A, Gatti G, Luini A, Leonardi C, et al. Do early breast cancer patients with only sentinel lymph node biopsy experience lower psychological morbidity over time? Breast J 2012;18(6):622-624. [doi: 10.1111/tbj.12024] [Medline: 23057838]
35. Longman AJ, Braden CJ, Mishel MH. Side-effects burden, psychological adjustment, and life quality in women with breast cancer: Pattern of association over time. Oncol Nurs Forum 1999 Jun;26(5):909-915. [Medline: 10382190]
36. Simon AE, Robb KA. Cancer: breast. In: Ayers S, Baum A, McManus C, Newman S, Wallston K, Weinman J, et al, editors. Cambridge Handbook of Psychology, Health and Medicine. Cambridge, UK: Cambridge University Press; 2007:577.
37. Jacobsen PB, Donovan KA. Psychological co-morbidities of cancer. In: Psychological Co-morbidities of Physical Illness. New York, NY: Springer; 2011:163-205.
38. Burgess C, Cornelius V, Love S, Graham J, Richards M, Ramirez A. Depression and anxiety in women with early breast cancer: Five year observational cohort study. BMJ 2005 Mar 26;330(7493):702 [FREE Full text] [doi: 10.1136/bmj.38343.670868.D3] [Medline: 15695497]
39. Antoni MH, Lechner SC, Kazi A, Wimberly SR, Sifre T, Urcuyo KR, et al. How stress management improves quality of life after treatment for breast cancer. J Consult Clin Psychol 2006 Dec;74(6):1143-1152 [FREE Full text] [doi: 10.1037/0022-006X.74.6.1152] [Medline: 17154743]
40. Renzi C, Riva S, Masiero M, Pravettoni G. The choice dilemma in chronic hematological conditions: Why choosing is not only a medical issue? A psycho-cognitive perspective. Crit Rev Oncol Hematol 2016 Mar;99:134-140. [doi: 10.1016/j.critrevonc.2015.12.010] [Medline: 26762858]
41. Thornton LM, Andersen BL, Carson WE. Immune, endocrine, and behavioral precursors to breast cancer recurrence: A case-control analysis. Cancer Immunol Immunother 2008 Oct;57(10):1471-1481 [FREE Full text] [doi: 10.1007/s00262-008-0485-6] [Medline: 18327581]
42. Rogers LQ, Vicari S, Trammell R, Hopkins-Price P, Fogleman A, Spenner A, et al. Biobehavioral factors mediate exercise effects on fatigue in breast cancer survivors. Med Sci Sports Exerc 2014 Jun;46(6):1077-1088 [FREE Full text] [doi: 10.1249/MSS.0000000000000210] [Medline: 24212124]
43. Masiero M, Riva S, Fioretti C, Pravettoni G. Pediatric blood cancer survivors and tobacco use across adolescence and emerging adulthood: A narrative review. Front Psychol 2016;7:392 [FREE Full text] [doi: 10.3389/fpsyg.2016.00392] [Medline: 27047419]
44. Poikonen-Saksela P. Bouncing back from breast cancer. EU Research. 2021. URL: https://issuu.com/euresearcher/docs/bounce_eur29_h_res [accessed 2022-07-12]
45. Chiorri C, Bracco F, Piccinno T, Modafferi C, Battini V. Psychometric properties of a revised version of the Ten Item Personality Inventory. Eur J Psychol Assess 2015 May;31(2):109-119. [doi: 10.1027/1015-5759/a000215]
46. Scheier MF, Carver CS, Bridges MW. Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): A reevaluation of the Life Orientation Test. J Pers Soc Psychol 1994 Dec;67(6):1063-1078. [doi: 10.1037//0022-3514.67.6.1063] [Medline: 7815302]
47. Antonovsky A. The structure and properties of the sense of coherence scale. Soc Sci Med 1993 Mar;36(6):725-733. [doi: 10.1016/0277-9536(93)90033-z] [Medline: 8480217]
48. Weathers FW, Litz BT, Herman DS, Huska JA, Keane TM. The PTSD Checklist (PCL): Reliability, validity, and diagnostic utility. In: Proceedings of the 9th Annual Meeting of the International Society for Traumatic Stress Studies. 1993 Presented at: The 9th Annual Meeting of the International Society for Traumatic Stress Studies; October 24-27, 1993; San Antonio, TX.
49. Bonanno GA, Pat-Horenczyk R, Noll J. Coping flexibility and trauma: The Perceived Ability to Cope With Trauma (PACT) scale. Psychol Trauma 2011;3(2):117-129. [doi: 10.1037/a0020921]
50. Garnefski N, Kraaij V. The Cognitive Emotion Regulation Questionnaire. Eur J Psychol Assess 2007 Jan;23(3):141-149. [doi: 10.1027/1015-5759.23.3.141]
51. Carlson LE, Brown KW. Validation of the Mindful Attention Awareness Scale in a cancer population. J Psychosom Res 2005 Jan;58(1):29-33. [doi: 10.1016/j.jpsychores.2004.04.366] [Medline: 15771867]
52. Moser A, Stuck AE, Silliman RA, Ganz PA, Clough-Gorr KM. The eight-item modified Medical Outcomes Study Social Support Survey: Psychometric evaluation showed excellent performance. J Clin Epidemiol 2012 Oct;65(10):1107-1116 [FREE Full text] [doi: 10.1016/j.jclinepi.2012.04.007] [Medline: 22818947]
53. Connor KM, Davidson JRT. Development of a new resilience scale: The Connor-Davidson Resilience Scale (CD-RISC). Depress Anxiety 2003;18(2):76-82. [doi: 10.1002/da.10113] [Medline: 12964174]
54. Weinman J, Petrie KJ, Moss-morris R, Horne R. The illness perception questionnaire: A new method for assessing the cognitive representation of illness. Psychol Health 1996 Mar;11(3):431-445. [doi: 10.1080/08870449608400270]
55. Broadbent E, Petrie KJ, Main J, Weinman J. The Brief Illness Perception Questionnaire. J Psychosom Res 2006 Jun;60(6):631-637. [doi: 10.1016/j.jpsychores.2005.10.020] [Medline: 16731240]
56. Watson M, Greer S, Young J, Inayat Q, Burgess C, Robertson B. Development of a questionnaire measure of adjustment to cancer: The MAC scale. Psychol Med 1988 Feb;18(1):203-209. [doi: 10.1017/s0033291700002026] [Medline: 3363039]

57. Merluzzi TV, Philip EJ, Heitzmann Ruhf CA, Liu H, Yang M, Conley CC. Self-efficacy for coping with cancer: Revision of the Cancer Behavior Inventory (Version 3.0). Psychol Assess 2018 Apr;30(4):486-499 [FREE Full text] [doi: 10.1037/pas0000483] [Medline: 28504538]
58. Tedeschi R, Calhoun L. The Posttraumatic Growth Inventory: Measuring the positive legacy of trauma. J Trauma Stress 1996;9(3):455-471. [doi: 10.1002/jts.2490090305]
59. Dewolf L, Koller M, Velikova G, Johnson C, Scott N, Bottomley A, EORTC Quality of Life Group. EORTC Quality of Life Group Translation Procedure. Brussels, Belgium: EORTC Quality of Life Group; 2009 Mar. URL: https://abdn.pure.elsevier.com/en/publications/eortc-quality-of-life-group-translation-procedure [accessed 2022-06-10]
60. Simard S, Savard J. Screening and comorbidity of clinical levels of fear of cancer recurrence. J Cancer Surviv 2015 Sep;9(3):481-491. [doi: 10.1007/s11764-015-0424-4] [Medline: 25603948]
61. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983 Jun;67(6):361-370. [doi: 10.1111/j.1600-0447.1983.tb09716.x] [Medline: 6880820]
62. Thompson ER. Development and validation of an internationally reliable short-form of the Positive and Negative Affect Schedule (PANAS). J Cross Cult Psychol 2016 Jul 26;38(2):227-242. [doi: 10.1177/0022022106297301]
63. Roth AJ, Kornblith AB, Batel-Copel L, Peabody E, Scher HI, Holland JC. Rapid screening for psychologic distress in men with prostate carcinoma: A pilot study. Cancer 1998 May 15;82(10):1904-1908. [doi: 10.1002/(sici)1097-0142(19980515)82:10<1904::aid-cncr13>3.0.co;2-x] [Medline: 9587123]
64. BOUNCE Project. URL: https://www.bounce-project.eu/ [accessed 2022-06-10]
65. Engel GL. From biomedical to biopsychosocial. Being scientific in the human domain. Psychosomatics 1997;38(6):521-528. [doi: 10.1016/S0033-3182(97)71396-3] [Medline: 9427848]
66. Berry LL, Seiders K, Wilder SS. Innovations in access to care: A patient-centered approach. Ann Intern Med 2003 Oct 07;139(7):568-574. [doi: 10.7326/0003-4819-139-7-200310070-00009] [Medline: 14530228]
67. McCormack LA, Treiman K, Rupert D, Williams-Piehota P, Nadler E, Arora NK, et al. Measuring patient-centered communication in cancer care: A literature review and the development of a systematic approach. Soc Sci Med 2011 Apr;72(7):1085-1095. [doi: 10.1016/j.socscimed.2011.01.020] [Medline: 21376443]
68. Syrjala KL, Chapko ME. Evidence for a biopsychosocial model of cancer treatment-related pain. Pain 1995 Apr;61(1):69-79. [doi: 10.1016/0304-3959(94)00153-6] [Medline: 7644251]
69. Tramonti F, Giorgi F, Fanali A. Systems thinking and the biopsychosocial approach: A multilevel framework for patient‐centred care. Syst Res Behav Sci 2020 Jul 15;38(2):215-230. [doi: 10.1002/sres.2725]
70. Gorini A, Mazzocco K, Gandini S, Munzone E, McVie G, Pravettoni G. Development and psychometric testing of a breast cancer patient-profiling questionnaire. Breast Cancer 2015 Jun:133. [doi: 10.2147/bctt.s80014]
71. Kondylakis H, Bucur A, Dong F, Renzi C, Manfrinati A, Graf N, et al. iManageCancer: Developing a platform for empowering patients and strengthening self-management in cancer diseases. In: Proceedings of the IEEE 30th International Symposium on Computer-Based Medical Systems. 2017 Presented at: The IEEE 30th International Symposium on Computer-Based Medical Systems; June 22-24, 2017; Thessaloniki, Greece p. 755-760. [doi: 10.1109/cbms.2017.62]
72. Triberti S, Savioni L, Sebri V, Pravettoni G. eHealth for improving quality of life in breast cancer patients: A systematic review. Cancer Treat Rev 2019 Mar;74:1-14. [doi: 10.1016/j.ctrv.2019.01.003] [Medline: 30658289]

Abbreviations

CHAMP: Champalimaud Clinical Centre
DHEW: Department of' Health, Education, and Welfare
EU: European Union
EudraCT: European Union Drug Regulating Authorities Clinical Trials Database
FORTH: Foundation for Research and Technology–Hellas
HER2: human epidermal growth factor receptor 2
HUJI: Hebrew University of Jerusalem
HUS: Helsinki University Hospital
ICCS: Institute of Communications and Computer Systems
IEO: European Institute of Oncology
Noona: Noona Healthcare platform
QOL: quality of life

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Protocol

An Artificial Intelligence–Driven Digital Health Solution to Support Clinical Management of Patients With Long COVID-19: Protocol for a Prospective Multicenter Observational Study

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Abstract

Background: COVID-19 pandemic has revealed the weaknesses of most health systems around the world, collapsing them and depleting their available health care resources. Fortunately, the development and enforcement of specific public health policies, such as vaccination, mask wearing, and social distancing, among others, has reduced the prevalence and complications associated with COVID-19 in its acute phase. However, the aftermath of the global pandemic has called for an efficient approach to manage patients with long COVID-19. This is a great opportunity to leverage on innovative digital health solutions to provide exhausted health care systems with the most cost-effective and efficient tools available to support the clinical management of this population. In this context, the SENSING-AI project is focused on the research toward the implementation of an artificial intelligence–driven digital health solution that supports both the adaptive self-management of people living with long COVID-19 and the health care staff in charge of the management and follow-up of this population.

Objective: The objective of this protocol is the prospective collection of psychometric and biometric data from 10 patients for training algorithms and prediction models to complement the SENSING-AI cohort.

Methods: Publicly available health and lifestyle data registries will be consulted and complemented with a retrospective cohort of anonymized data collected from clinical information of patients diagnosed with long COVID-19. Furthermore, a prospective patient-generated data set will be captured using wearable devices and validated patient-reported outcomes questionnaires to complement the retrospective cohort. Finally, the 'Findability, Accessibility, Interoperability, and Reuse' guiding principles for scientific data management and stewardship will be applied to the resulting data set to encourage the continuous process of discovery, evaluation, and reuse of information for the research community at large.

Results: The SENSING-AI cohort is expected to be completed during 2022. It is expected that sufficient data will be obtained to generate artificial intelligence models based on behavior change and mental well-being techniques to improve patients' self-management, while providing useful and timely clinical decision support services to health care professionals based on risk stratification models and early detection of exacerbations.

Conclusions: SENSING-AI focuses on obtaining high-quality data of patients with long COVID-19 during their daily life. Supporting these patients is of paramount importance in the current pandemic situation, including supporting their health care professionals in a cost-effective and efficient management of long COVID-19.

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KEYWORDS

COVID-19 syndrome; artificial intelligence; AI; primary health care; Postacute COVID-19 syndrome; COVID-19; health system; health care; health care resource; public health policy; long COVID-19; mHealth; digital health solution; patient; clinical information; clinical decision support

Introduction

Definition of Long COVID-19

A percentage of people report prolonged and recurrent symptoms, for weeks or months, after the first episode of COVID-19. Persistent COVID-19 has not yet been precisely defined. It seems clear that it is a disease that affects a large number of people, generating a huge health and social impact in the pandemic [1]. In this context, patient groups, the international scientific community, as well as public health institutions and authorities are making a great effort to improve knowledge, clinical care, and social benefits [2,3]. Numerous Spanish scientific societies alongside patient groups have drawn up a Clinical Guide in which long COVID-19 is defined [2] as follows:

> *"Multiorgan symptomatic complex that affects those patients who have suffered from COVID-19 (with or without diagnosis confirmed by laboratory tests) and who remain with symptomatology once passed the considered acute phase of the disease, after 4 or even 12 weeks, with symptoms persisting over time."*

Incidence of Long COVID-19 and the Most Affected Population

Determining the incidence of long COVID-19 is complicated due to the absence of specific surveillance and a variety of definitions. Another difficulty is that studies are performed in selected groups of patients, which does not allow estimating the true incidence in the population. The UK National Institute of Statistics estimated that 1 in 5 people with COVID-19 had symptoms beyond 5 weeks, and 1 in 10 people had symptoms beyond 12 weeks [4]. In a population-based survey in the United States, the percentage of people with persistent symptoms was 30% at 30 days, 25% at 60 days, and 15% at 90 days [5].

In the UK National Institute of Statistics study [6], a higher incidence was observed in women (23.6%, 95% CI 22.2-25.0) versus men (20.7%, 95% CI 19.3-22.1) and in the middle age. In the US survey, the only factor associated with persistent COVID-19, measured by the number of symptoms, was the initial severity [7].

Long Covid-19 Fatigue and Beyond: Pathophysiology, Symptoms, and Signs

The pathophysiological basis remains unknown, and several theories are put forward: the persistence of the virus in reservoirs, such as the small intestinal epithelium, where it would remain active [8,9]; the presence of an aberrant immune response [10]; the damage produced by the effect of autoantibodies against immunomodulatory proteins [11]; or the hyperactivation of coagulation and platelets [12]. The symptoms and signs are extremely numerous and varied (ie, systemic, neurological, psychiatric, and cardiovascular) [13-19].

It is important to know the people who experience long COVID-19 for a better characterization [20], since it is a characteristically intermittent disease with very varied symptoms, which also involves people who at the time did not have access to a diagnostic test and those affected who felt stigmatized and ignored [21].

A web-based survey by the Spanish Society of General and Family Physicians in 1834 participants reported a variety of more than 200 symptoms. These symptoms included fatigue and general malaise in more than 95% of the patients. Headache, low mood, and muscle aches were observed in more than 80% of them. Dyspnea, joint, chest, and back pain, as well as lack of concentration were detected in more than 75% of them. More than 70% found it difficult to attend their daily duties, and more than 30% reported difficulties even with personal hygiene. Although 52% of the cases were not confirmed by laboratory diagnostic tests, the authors noted that there were no significant differences between the groups with or without diagnostic confirmations [19].

Background and Current Status

COVID-19 caused serious problems to the health system, collapsing it, and depleting the health resources available [20-22]. Fortunately, the development and enforcement of specific public health policies, such as vaccination, mask wearing, and social distancing, among others, has reduced the prevalence and complications associated with COVID-19 in the acute phase [23]. However, the aftermath of the global pandemic requires an efficient approach to manage patients with long COVID-19. It seems a great opportunity to leverage on innovative digital health solutions to provide exhausted health care systems with the most cost-effective and efficient tools

available to support the clinical management of the population experiencing long COVID-19 [24,25].

We can find more than 250 health-labeled apps available on both Google Play and Apple Store, but they are basic products that offer neither the technology nor the advanced approach and services offered to patients with long COVID-19. Adhera Health Fatigue Digital Program for long COVID-19 is built on the principles of patient centricity, and it is guided by the principles of participatory research to promote a meaningful partnership between patients and health care professionals [26]. Furthermore, data mining and artificial intelligence (AI) have been greatly applied lately to health care areas [27]. Data mining is a combination of statistical analysis, algorithms, AI, and database management, with the purpose of extracting intelligence. AI can be defined as the field devoted to build artificial creatures. It is the science and engineering of making intelligent machines, especially intelligent computer programs. In the last years, there has been a growing interest in the application of AI and data mining techniques to clinical data. MEDLINE has seen a sharp 10-fold increase in the number of papers having the term 'data mining' in their title [28]. This AI-driven research is designed toward the improvement of the Adhera Precision Digital Companion platform toward the provision of advanced personalization technologies for adaptive self-management, which is a progress beyond the state of the art [29,30].

The objective of this protocol is the prospective collection of psychometric and biometric data for training algorithms and prediction models to complement the SENSING-AI cohort. Likewise, the final aim of the project is the creation of a digital health solution based on AI and prediction models for a better clinical management of patients with long COVID-19 and to improve self-management of this condition.

Methods

Ethics Approval

This study was approved by the research ethics committee of Primary Care Research Institute Jordi Gol (in Barcelona, Spain) (Código CEIm: 22/010-PCV) and Virgen Macarena University Hospital (Seville, Spain) (1894-N-21). All patients will receive a patient information sheet and will sign an informed consent.

Participation Consent and Protection of Personal Data

This study is registered in Clinicaltrials.gov website (NCT05204615). Data obtained from patients will be pseudo-anonymized by the clinical partner. Only a code, based on an alphanumeric number completely unlinked to any direct patient data, will be included as an identifier of the subjects in the study.

Design

This is a prospective multicenter observational study to complement the SENSING-AI cohort.

Sample Size

Considering that there is no previous experience with long COVID-19, the sample size for the prospective data collection is a small cohort of patients (N=10) to assess the quality of the data and the feasibility of the study. Based on the results obtained, we plan to expand the cohort of patients. In this context, 10 patients with long COVID-19 will be recruited and followed up for 4 weeks at designated primary care centers. Of them, 5 patients will be recruited by the team of the Aljarafe-Seville North Health District of Andalusian Public Foundation for Health Research Management of Seville (FISEVI) and the other 5 by the team of the Primary Care Research Institute (IDIAP) Jordi Gol. The inclusion criteria for participants will be as follows: (1) patients over the age of 18 years; (2) patients diagnosed with persistent COVID-19 in the past year; and (3) having symptoms of fatigue, dyspnea, shortness of breath, anxiety, stress, depression, conduct disorder, or sleep disorder. The exclusion criteria will be as follows: (1) hospital admission during follow-up period motivated by pathology and not related to COVID-19; (2) patients without technological knowledge or unable to use the mobile app; (3) having a known severe psychiatric illness or cognitive impairment; (4) pregnant women; or (5) patients discharged after hospital admission due to COVID-19.

Procedures

AI models will be generated from the following 3 data sources: (1) review of publicly available data sources (eg, OpenAIRE, FAIRsharing, National Sleep Research Resource, DEAP data set, and Kaggle) related to long COVID-19; (2) cohort of anonymized retrospective data (ie, 100 cases) obtained from clinical information from patients with COVID-19, attended by the primary care teams of the Seville North health district; and (3) prospective data collected using Adhera Health Digital Precision Companion platform, which includes clinical, biometric, and psychometric data from 10 patients followed during 1 month by FISEVI and IDIAP Jordi Gol.

Data Collection

Wearable devices will be used to collect data in real time for 1 month to detect physiological and psychological complications.

Biometric information will be collected from wearable devices (Withings Scanwatch) provided to patients. The data to be collected from each patient are classified in Table 1.

The Adhera Health's sensing module will allow the collection of psychometric data using mobile-based validated questionnaires and the integration of wearable data. Based on previous literature [13-19], the most relevant psychometric data for the generation of prediction models were considered to be related to fatigue, dyspnea, anxiety, stress, depression, and sleep disorder. The data to be obtained is classified in Table 2 [31-36].

Table 1. Data collected by wearable devices.

Biometric data	Types of data
Activity data	• Daily distance traveled in meters • Daily number of steps: list of steps per 4-5 minutes approximately • Total daily calories burned in kcal
Training data	• Calories or event in kcal • Distance of the event in meters • Heart rate; minimum, average, and maximum intensity in beats per minute
Sleep data	• Ratio of total sleep time or time spent in bed • Time spent awake in bed after falling asleep for the first time during the night in seconds • REM[a] sleep phase count
Cardiac data	• Atrial fibrillation detected in seconds during an ECG[b] • Detailed ECG signal in µV with 300 Hz sampling rate

[a]REM: rapid eye movement.

[b]ECG: electrocardiogram.

Table 2. Data collected by validated questionnaires using Adhera Precision Digital Companion platform.

Psychometric data	Type of data
Fatigue	Weekly FAS[a] questionnaire
Dyspnea	Weekly MEG DI[b] questionnaire
Anxiety	Weekly GAD[c] questionnaire
Stress	Weekly PSS-10[d] questionnaire
Depression	Weekly PHQ[e] questionnaire
Sleep disorder	Weekly questionnaire

[a]Fatige assessment scale.

[b]Melbourne ENT group dyspnea index.

[c]General anxiety disorder.

[d]Perceived stress scale.

[e]Patient health questionnaire.

Analysis of the Cohort Data

A prediction algorithm based on the nearest neighbor classification method will be used. This method is an instance-based algorithm supervised by machine learning. These algorithms will process the data flows in which the input is presented as a sequence of elements. Therefore, it will allow for searching in the closest observations. This algorithm cannot provide human interpretable models; processing procedures will be applied to make them explainable, based on feature classification. Therefore, this model has the aim of predicting whether the user is having a complication, based on clinical, biometric, and psychometric data.

By the data obtained in the prospective study, an adaptive adjustment of the sampling frequency of the ecological momentary assessments will be made. The objective is to develop a model to predict the most appropriate time to activate the validated questionnaire for the patient. This model will be developed using machine learning algorithms, mainly based on decision trees. These are flowchart-like structures in which each node represents a value in an entity, each branch represents the value, and each leaf represents a class or decision label after calculating all attributes. The model will be measured based on error rates and confusion tables, which will allow measuring accuracy, precision, F1 score, sensitivity, specificity, receiver operating characteristic curve, and area below the hamstring curve.

Another model will be developed to adapt the questionnaires to each patient. It will be focused on the user's history and biometric measurements; the model will decide the number of questions needed for that patient. To develop this model, machine Learning models will be trained, mainly based on artificial neural networks. These are based on a collection of connected units or nodes called artificial neurons, which freely model the neurons in a biological brain. An artificial neuron receives a signal, processes it, and then signals to neurons connected to it. For each question, the input data will be the entities, and the output data will be a predicted answer to the question. If the question is easily predicted, the question will be removed from the test. If not, it has to remain in the test and be answered by the patient. This type of algorithm is not human

interpretable, and therefore, postprocessing models will be applied to make them explainable.

Results

The study is registered in clinical trials, and the SENSING-AI cohort is expected to be completed during 2022.

It is expected that sufficient data will be obtained to generate AI models to enhance the AI-precision digital companion solution toward the provision of adaptive self-management in patients with long COVID-19, while providing useful and timely clinical decision support services to health care professionals based on risk stratification models and early detection of exacerbations.

Discussion

The development of an AI-driven digital health solution based on behavior change techniques will help improve the clinical management of patients with long COVID-19 and improve their well-being and quality of life.

This research focuses on maximizing the usefulness of the information that can be generated by the patient using AI techniques. Once COVID-19 has been controlled in the acute phase through vaccination, it is time to generate new resources focused on long COVID-19. In this context, it is necessary to develop solutions for the detection of exacerbating disease at an early stage, improving patient care, and improving clinical prognosis. It is also necessary to provide AI tools, incorporating monitors to obtain automatic, objective, and easy-to-interpret data for professionals. These tools will be of considerable benefit to professionals, as they will be able to obtain a risk stratification of disease complications in real time, increasing the capacity for case management and aiding in critical decisions.

Technological progress in recent decades has had a great impact on the volume of information. The management of research data is implemented continuously throughout its life cycle. It starts at the planning stage, and it continues with the execution and dissemination of results and the preservation of data. Achieving good data management allows for generating greater innovation and knowledge. In this context, the 4 principles called FAIR arise, oriented to favor maximum performance of the data obtained in research. Applying these principles has significant benefits for the scientific community, improving the flow of information, maximizing the performance of the data obtained, and promoting the improvement of research in patients with long COVID-19. To promote research and reuse of data in future studies, the intention of this project is to make the data FAIR. The data obtained in the study will be discoverable, accessible, interoperable, and reusable.

This study has several limitations. First, the study is focused on a localized population. Even so, one part is representative of a rural population and the other is more urban. Being an innovative study without previous data, once the data are all collected, it is possible that some necessary variables have not been noticed. Likewise, making the data FAIR will help future research to improve this possible limitation. Finally, there may be a sample bias, since the population recruited are adults with different levels of digital skills.

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Conflicts of Interest

LFL, IB, and IACG are employees of Adhera Health Inc.

References

1. Meeting the challenge of long COVID. Nat Med 2020 Dec 07;26(12):1803-1803. [doi: 10.1038/s41591-020-01177-6] [Medline: 33288947]
2. Guía Clínica Para La Atención Al Paciente Long Covid/Covid Persistente. URL: https://www.inmunologia.org/images/site/GUIA_consenso_COVID_persistente.pdf [accessed 2022-09-26]
3. A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October 2021. World Health Organization. URL: https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1 [accessed 2022-09-28]
4. The prevalence of long COVID symptoms and COVID-19 complications. Office for National Statistics. 2020. URL: https://www.ons.gov.uk/news/statementsandletters/theprevalenceoflongcovidsymptomsandcovid19complications [accessed 2021-08-23]
5. Cirulli E, Barrett K, Riffle S, Bolze A, Neveux I, Dabe S. Long-term COVID-19 symptoms in a large unselected population. MedRxiv. Preprint posted online on Dec 1, 2020 . [doi: 10.1101/2020.10.07.20208702]

6. Updated estimates of the prevalence of long COVID symptoms. Office for National Statistics. 2021. URL: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/adhocs/12788updatedestimatesoftheprevalenceoflongcovidsymptoms [accessed 2021-08-23]
7. Davis B, Rothrock AN, Swetland S, Andris H, Davis P, Rothrock SG. Viral and atypical respiratory co-infections in COVID-19: a systematic review and meta-analysis. J Am Coll Emerg Physicians Open 2020 Aug 19;1(4):533-548 [FREE Full text] [doi: 10.1002/emp2.12128] [Medline: 32838380]
8. Patterson B, Guevara-Coto J, Yogendra R, Francisco E, Long E, Pise A. Immune-based prediction of COVID-19 severity and chronicity decoded using machine learning. BioRxiv. Preprint posted online on Dec 22, 2020 . [doi: 10.1101/2020.12.16.423122]
9. Gaebler C, Wang Z, Lorenzi JCC, Muecksch F, Finkin S, Tokuyama M, et al. Evolution of antibody immunity to SARS-CoV-2. Nature 2021 Mar 18;591(7851):639-644 [FREE Full text] [doi: 10.1038/s41586-021-03207-w] [Medline: 33461210]
10. Ong S, Fong S, Young B, Chan Y, Lee B, Amrun S, et al. Persistent symptoms and association with inflammatory cytokine signatures in recovered coronavirus disease 2019 patients. Open Forum Infect Dis 2021 Jun;8(6):ofab156 [FREE Full text] [doi: 10.1093/ofid/ofab156] [Medline: 34095336]
11. Wang E, Mao T, Klein J, Dai Y, Huck J, Liu F, Yale IMPACT Team, et al. Diverse functional autoantibodies in patients with COVID-19. medRxiv 2021 Feb 01;595(7866):283-288 [FREE Full text] [doi: 10.1101/2020.12.10.20247205] [Medline: 33330894]
12. Pretorius E, Vlok M, Venter C, Bezuidenhout JA, Laubscher GJ, Steenkamp J, et al. Persistent clotting protein pathology in Long COVID/post-acute sequelae of COVID-19 (PASC) is accompanied by increased levels of antiplasmin. Cardiovasc Diabetol 2021 Aug 23;20(1):172 [FREE Full text] [doi: 10.1186/s12933-021-01359-7] [Medline: 34425843]
13. Garrigues E, Janvier P, Kherabi Y, Le Bot A, Hamon A, Gouze H, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. J Infect 2020 Dec;81(6):e4-e6 [FREE Full text] [doi: 10.1016/j.jinf.2020.08.029] [Medline: 32853602]
14. Carfì A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. JAMA 2020 Aug 11;324(6):603. [doi: 10.1001/jama.2020.12603]
15. Kosugi EM, Lavinsky J, Romano FR, Fornazieri MA, Luz-Matsumoto GR, Lessa MM, et al. Incomplete and late recovery of sudden olfactory dysfunction in COVID-19. Braz J Otorhinolaryngol 2020 Jul;86(4):490-496 [FREE Full text] [doi: 10.1016/j.bjorl.2020.05.001] [Medline: 32534982]
16. Li J, Long X, Zhu C, Wang H, Wang T, Lin Z, et al. Olfactory dysfunction in recovered coronavirus disease 2019 (COVID-19) patients. Mov Disord 2020 Jul 30;35(7):1100-1101 [FREE Full text] [doi: 10.1002/mds.28172] [Medline: 32468632]
17. Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, Re'em Y, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. SSRN Journal . [doi: 10.2139/ssrn.3820561]
18. Gorna R, MacDermott N, Rayner C, O'Hara M, Evans S, Agyen L, et al. Long COVID guidelines need to reflect lived experience. The Lancet 2021 Feb;397(10273):455-457. [doi: 10.1016/s0140-6736(20)32705-7]
19. Ladds E, Rushforth A, Wieringa S, Taylor S, Rayner C, Husain L, et al. Persistent symptoms after Covid-19: qualitative study of 114 "long Covid" patients and draft quality principles for services. BMC Health Serv Res 2020 Dec 20;20(1):1144 [FREE Full text] [doi: 10.1186/s12913-020-06001-y] [Medline: 33342437]
20. Martinez C, Badia J, Roca J. [What about primary care during the pandemic?]. Aten Primaria 2020 Nov;52(9):598-599 [FREE Full text] [doi: 10.1016/j.aprim.2020.10.001] [Medline: 33190682]
21. Lopez Segui F, Hernandez Guillamet G, Pifarré Arolas H, Marin-Gomez FX, Ruiz Comellas A, Ramirez Morros AM, et al. Characterization and identification of variations in types of primary care visits before and during the COVID-19 pandemic in Catalonia: big data analysis study. J Med Internet Res 2021 Sep 14;23(9):e29622 [FREE Full text] [doi: 10.2196/29622] [Medline: 34313600]
22. Pifarré I Arolas H, Vidal-Alaball J, Gil J, López F, Nicodemo C, Saez M. Missing diagnoses during the COVID-19 pandemic: a year in review. Int J Environ Res Public Health 2021 May 17;18(10):5335 [FREE Full text] [doi: 10.3390/ijerph18105335] [Medline: 34067807]
23. Thanh Le T, Andreadakis Z, Kumar A, Gómez Román R, Tollefsen S, Saville M, et al. The COVID-19 vaccine development landscape. Nat Rev Drug Discov 2020 May 09;19(5):305-306. [doi: 10.1038/d41573-020-00073-5] [Medline: 32273591]
24. Kruse CS, Krowski N, Rodriguez B, Tran L, Vela J, Brooks M. Telehealth and patient satisfaction: a systematic review and narrative analysis. BMJ Open 2017 Aug 03;7(8):e016242 [FREE Full text] [doi: 10.1136/bmjopen-2017-016242] [Medline: 28775188]
25. Sterling R, LeRouge C. Ondemand telemedicine as a disruptive health technology: qualitative study exploring emerging business models and strategies among early adopter organizations in the united states. J Med Internet Res 2019 Nov 15;21(11):e14304 [FREE Full text] [doi: 10.2196/14304] [Medline: 31730038]
26. Healthier you. Adhera Health. URL: https://adherahealth.com/adhera-platform/ [accessed 2022-09-26]
27. Patel VL, Shortliffe EH, Stefanelli M, Szolovits P, Berthold MR, Bellazzi R, et al. The coming of age of artificial intelligence in medicine. Artif Intell Med 2009 May;46(1):5-17 [FREE Full text] [doi: 10.1016/j.artmed.2008.07.017] [Medline: 18790621]

28. Iavindrasana J, Cohen G, Depeursinge A, Müller H, Meyer R, Geissbuhler A. Clinical data mining: a review. Yearb Med Inform 2018 Mar 07;18(01):121-133. [doi: 10.1055/s-0038-1638651]
29. Bokolo AJ. Exploring the adoption of telemedicine and virtual software for care of outpatients during and after COVID-19 pandemic. Ir J Med Sci 2021 Feb 08;190(1):1-10 [FREE Full text] [doi: 10.1007/s11845-020-02299-z] [Medline: 32642981]
30. Pérez Sust P, Solans O, Fajardo JC, Medina Peralta M, Rodenas P, Gabaldà J, et al. Turning the crisis into an opportunity: digital health strategies deployed during the COVID-19 outbreak. JMIR Public Health Surveill 2020 May 04;6(2):e19106 [FREE Full text] [doi: 10.2196/19106] [Medline: 32339998]
31. Fatigue assessment scale (FAS). Ild Care Foundation. URL: https://www.ildcare.nl/index.php/fatigue-assessment-scale-conditions-for-use-and-copyright/ [accessed 2022-09-26]
32. Dyspnoea Index (DI). URL: https://melbentgroup.com.au/wp-content/uploads/2015/10/MEG-Dyspnoea-Index-DI.pdf [accessed 2022-09-28]
33. Generalized Anxiety Disorder 7-Item (GAD-7) Dcale. URL: https://www.hiv.uw.edu/page/mental-health-screening/gad-7 [accessed 2022-09-26]
34. Remor E. Psychometric properties of a European Spanish version of the Perceived Stress Scale (PSS). Span J Psychol 2006 May 10;9(1):86-93. [doi: 10.1017/s1138741600006004] [Medline: 16673626]
35. Uestionario Sobre la Salud del Pacie NTE-9 (PHQ-9). URL: https://www.ons.org/sites/default/files/PatientHealth Questionnaire9_Spanish.pdf [accessed 2022-09-26]
36. Bobes J, García-Portilla González MP, Saiz Martínez PA, Bascarán Fernández MT, Iglesias Álvarez C, Fernández Domínguez JM. Propiedades psicométricas del cuestionario Oviedo de sueño. Psicothema 2000;12(1):107-112 [FREE Full text]

Abbreviations

FAIR: Findability, Accessibility, Interoperability, and Reuse
FISEVI: Fundación Pública Andaluza para la Gestión en la Investigación en Salud de Sevilla (Andalusian Public Foundation for Health Research Management of Seville)
IDIAP: Primary Health Care Research Institute

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Protocol

Mixed Reality Prototype of Multimodal Screening for Early Detection of Cognitive Impairments in Older Adults: Protocol Development and Usability Study

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Abstract

Background: The early diagnosis of cognitive impairments is an important step in the adequate management of dementia. The project “Smart Cognition & Behaviour Screening powered by Augmented Reality” (SCOBES-AR) aims to develop a multimodal screening tool (MST) for the early detection of cognitive impairments using augmented and virtual reality. The first project phase selected validated assessments for combination with the MST and tested it in 300 healthy older adults.

Objective: This study established a protocol for the implementation and usability of a mixed reality (MR)–enhanced multidisciplinary screening tool for the early detection of cognitive impairments in older adults. The developed MST will be partially enhanced by MR, which is a combination of augmented reality (AR) and virtual reality (VR). This MR-enhanced prototype of the screening tool (MR-MST) will be tested and compared to the previously developed MST. The usability of the prototype will also be examined.

Methods: This single-center observational crossover design study screens 100 healthy participants (aged 60-75 years) for cognitive decline using a specially developed MST (assessment of cognitive functions, olfactory sensitivity, nutritional preferences, gait parameters, reaction times, and activities of daily living) and an MR-enhanced MST in which the assessments of cognitive functions, reaction time, activities of daily living, and gait will be performed using tailor-made software and AR and VR hardware. The results of the MR-enhanced MST will be compared to those without MR. The usability of the developed MR-enhanced MST will be tested on 10 investigators and 10 test participants using observed summative evaluation and the codiscovery method, and on 2 usability experts using the codiscovery and cognitive walkthrough methods.

Results: This study was funded by the Austrian Research Promotion Agency (grant 866873) and received approval from the ethics committee of the Medical University of Graz. The MR-MST and the experimental protocol for this study were developed.

All participants gave written informed consent. As of July 15, 2022, a total of 70 participants have been screened. Data analysis and dissemination are scheduled for completion by September 2023.

Conclusions: The development and testing of the MR-MST is an important step toward the establishment of the best practice procedure for the implementation of AR and VR in the screening of cognitive declines in older adults. It will help improve our knowledge of the usability and applicability of the developed prototype and promote further advancement in AR and VR technologies to be used in therapeutic settings.

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KEYWORDS

augmented reality; virtual reality; multimodal screening; cognitive impairment; smart cognition; elderly; usability; dementia; aging; screening tool; digital health; digital health intervention

Introduction

Human neurocognitive functions decline with advanced age, but this decline may often exceed physiological cognitive aging and progress to dementia. The prevalence of dementia worldwide is expected to almost double every 20 years, from 46.8 million in 2015 to 131.5 million in 2050 [1], which poses an increasing challenge for health and social systems. On the way from normal cognitive decline to dementia, mild cognitive impairment (MCI) is regarded as a decline in the ability to learn new information or recall stored information [2]. MCI was detected in 10%-15% of the population older than 65 years and is regarded as a "window" in which suitable interventions may delay progression to dementia [3]. The possibility of slowing dementia raises awareness of this global health problem in the scientific and health communities, which involve a large spectrum of clinicians, neuropsychologists, dietologists, speech therapists, physiotherapists, and occupational therapists. Combating dementia has become a public health priority. In accordance with the global action plan of the World Health Organization against dementia [4], international research has focused on the identification and reduction of risk factors, development of prevention and therapeutic interventions, and early detection of cognitive decline [5].

Because of the complexity of dementia diseases, predicting the course of MCI is not always successful. However, the efforts of clinicians and health providers are focused on screening, early diagnosis, and identification of risk factors. Very early diagnosis of MCI enables health care providers to manage these factors or ideally to decrease the potential progression to dementia. Notably, the early detection of MCI signs increases patient awareness and self-management and encourages participation in clinical studies or prevention programs. Although the diagnosis of early dementia initially causes uncertainty [6], people affected by this diagnosis and their family caregivers report benefits of early detection [7]. Healthy populations, and especially people 60 years or older, tend to show increased intention and willingness to be screened for cognitive decline [8-11].

Screenings and preventive interventions among older at-risk individuals that target several modifiable risk factors were effective [12,13]. Current clinical diagnostic procedures, such as liquor diagnostics and imaging techniques [14-18], are highly important but are not suitable for population-based early detection. Therefore, alternative screening tools that provide a low-threshold, safe, and valid way are needed to detect subtle cognitive changes in the earliest clinical phase. Notably, the manifestation of MCI includes cognitive, motor, sensory, and behavioral domains. These complex characteristics require a miscellaneous assessment approach.

The screening tools for cognitive impairments are controversial because of their limitations when they are performed using pen and paper [19]. For example, the written form does not allow direct digitalization for further and automatic processing, and these tests do not resemble real-life situations. Therefore, the performance of screening tests using augmented reality (AR) and virtual reality (VR) technologies facilitate data recording and processing while simultaneously enabling multisensory interaction of the subject with a real environment. AR superimposes 3D virtual objects into the real environment, typically using a tablet or a smartphone [20], but VR offers the user a multisensory experience of a simulated 3D virtual world via head-mounted displays, such as Oculus Quest screening tools [21]. For screening tests that aim for the early detection of cognitive decline, an integration of multiple domains with smart technology solutions must be developed and examined to prove their usability and validity.

The rationale for the Smart Cognition & Behaviour Screening powered by Augmented Reality (SCOBES-AR) project [22] is based on evidence-based predictors and protective factors for cognitive decline to establish a suitable assessment instrument that may be easily implemented in a nonclinical environment. Therefore, a combination of validated assessments of cognitive, motor, and behavioral functions was tested in the first phase of the project on 300 individuals aged 60-75 years. The multimodal screening tool (MST) includes assessments of olfactory functions [23], specificity of nutritional behavior [24], changes in gait pattern [25] and reaction time [26], cognitive functions [27], and instrumental activities of daily living [28]. As a next step, the developed MST will be enhanced with mixed reality (MR) technologies (AR and VR), which will require the establishment and testing of the developed prototype. Some of the assessments in the MR-enhanced screening tool will be performed using specially developed software and suitable AR and VR hardware, such as smartphones mounted in Haori headsets (AR) and Oculus Quest 2 (VR) headsets. This single-center observational crossover design study aims to

establish a protocol for the implementation and usability of a prototype screening tool for the early detection of cognitive impairments in older adults using an MR environment.

Methods

Study Design, Participants, and Recruitment Procedure

This study developed a protocol for a single-center observational crossover design study. Male and female volunteers (N=100) aged 60 to 75 years were recruited from the pool of participants who had participated in the previous phase of the project. The volunteers were invited to a second visit at the Health Perception Lab, FH JOANNEUM University of Applied Sciences. Assuming that the effects were larger than the previous project phase, an effect size of 0.35 was selected. Therefore, with α=.05 and β=.95, a sample size of approximately 100 participants was considered sufficient for this study. Feasibility reasons and recruitment experience were also considered for the laboratory setting and geographical region. The recruitment and enrolment process for participants with stringent inclusion criteria (ie, age 60-75 years; absence of movement; and visual, auditory, neurocognitive, and psychiatric disorders) lasted from March 2022 to April 2022. For recruitment, participants were contacted by email or telephone to obtain consent and make preliminary agreements for participation. The study procedure, including the application of the respective information and technology devices, was presented to the volunteers. Participants were excluded from the study if they developed 1 or more of the conditions described in Textbox 1.

Textbox 1. Study exclusion criteria.

- Clinical diagnosis of mild cognitive impairment or dementia
- Clinical diagnosis of mental illness (eg, depression, psychosis)
- Reduced mobility (eg, walking aid, wheelchair)
- Aided hearing or visual impairment
- Participation in any other cognitive training study within the last 6 months
- Present guardianship according to the provisions of the Austrian adult protection law

All selected volunteers are tested once with the MST and once with the MR-MST in a randomized order. An independent investigator executed the randomization plan using a computer-generated random numbers table.

Ethics Approval

The study is performed in accordance with the Helsinki Declaration and its later amendments, and all procedures involving human participants have been approved and accepted by the local ethics committee of the Medical University of Graz (EC No. 32016 ex 19/20, 14-17 2019). The participants are informed in detail verbally and in writing about the procedure and aim of the study. Participation in the study is ensured by signing a written informed consent form. As compensation for the time spent in the study, participants receive a voucher (equivalent to €15 or US $14.80). Access to the generated data is restricted to the immediate research team, and only coded data stored on a secure internal server of the FH JOANNEUM, University of Applied Sciences, are used for analyses.

Indemnity

This study is not an intervention study and poses a low risk to participants. For some attendees, the test results may indicate a deviation in cognitive abilities, which suggests early cognitive decline. When this occurs, we provide a comprehensive medical consultation with the study's clinical investigator to ensure further medical care and possibly determine a further diagnostic plan. Participants may report slight fatigue when participating in the different assessments. A short preventive break is taken after approximately half of the testing procedure.

Part of the screening procedure involves wearing a head-mounted display with VR, which may cause cybersickness [29]. Cybersickness is triggered by visual stimuli during exposure to the virtual environment and shares similar symptoms with motion sickness, including nausea, sweating, dizziness, and fatigue. To minimize the risk of cybersickness, the participants undergo screening in a static (sitting or standing) position. The participants could withdraw from the screening in case of cybersickness. Except for these considerations, no health risks or side effects are expected for the participants.

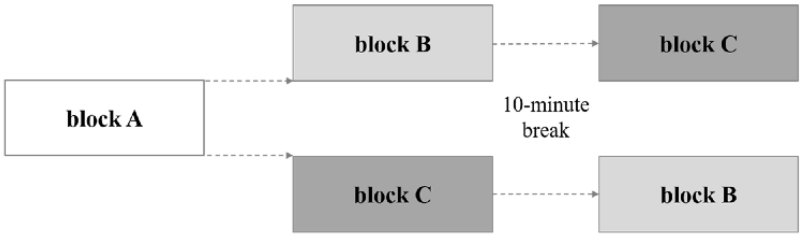
Study Procedure

At the beginning of the study, the investigator clarifies in detail the screening procedure and COVID-19–related hygiene measures and obtains signed written informed consent from the volunteers. The screening procedure for each participant consists of 3 blocks (see Figure 1). Anthropometric, sociodemographic, and risk factor data are collected in the first block (A). The Brief Smell Identification Test (B-SIT) [23], Food Frequency Index (FFI) [30], and Dementia Detection Test (DemTect) are also performed in block A using a laptop computer as well as pen and paper. The Dual-Task Assessment (DTA) [25,31,32], Trail-Making Test (TMT) [33], Reaction Time Test "Match 4 Point Test" [34], and Erlangen Test of Activities of Daily Living in Persons With Mild Dementia or Mild Cognitive Impairment (ETAM; parts transport and finances) [34] are performed in the second block (block B) using software as well as pen and paper. The same assessments from block B are performed in the third block (block C) using MR technologies, tailor-made MR software, and suitable AR and VR hardware. Prior randomization determines the order in which participants perform blocks B and C.

The entire testing procedure lasts approximately 130 minutes, including a 10-minute break between blocks B and C. Trained

project staff conduct the study. A medical doctor acting as the clinical investigator is available to the participants for consultation to answer questions related to their cognitive health.

Figure 1. Experimental design. AR: augmented reality; B-SIT: Brief Smell Identification Test; DemTect: Dementia Detection Test, DTA: Dual-Task Assessment; ETAM: Erlangen Test of Activities of Daily Living in Persons With Mild Dementia or Mild Cognitive Impairment; FFI: Food Frequency Index; RTT: Reaction Time Test; TMT: Trail-Making Test; VR: virtual reality.



block A: anthropometric and sociodemographic data; dementia risk factors; B-SIT, FFI, DemTect
block B: DTA, TMT, RTT, and ETAM performed using lap top as well as pen and paper
block C: DTA, TMT, RTT, and ETAM performed using AR- and VR

Methods of Measurement in the MST

The selection of the assessments included in this screening tool was based on the results of a systematic review process, focus groups, and an observational study (unpublished data), which were performed in the first phase of the SCOBES-AR project. The assessments were evaluated based on predefined criteria related to their quality and applicability for the purpose of the project. Assessments from cognitive, motor, sensory, and behavioral domains with proven validity and reliability were chosen for this study.

B-SIT Procedure

A decrease in olfactory perception is a predictive factor for the development of neurocognitive impairment [35,36]. The B-SIT [23] is a screening test for odor recognition, and it is a short version of the widely distributed University of Pennsylvania Smell Identification Test. Different versions of the B-SIT have shown validation sensitivity/specificity ratios between 83.1%/79.5% and 96.5%/51.8% [37]. For the test, 12 different microcapsulated fragrances were painted over with a pencil for release in a standardized quantity (scratch-and-sniff test). The person undergoing the test must detect the released odor and extract it from a 4-step multiple choice question. A total odor score results from the number of correctly identified fragrances, with higher values indicating better olfactory performance (>9 detected fragrances).

FFI Determination

A healthy diet helps reduce the risk of cognitive impairment and dementia [38]. Observational studies showed that omega-3 polyunsaturated fatty acids and vitamins, such as the B-complex (vitamins B6, B12, and folate), antioxidants (vitamins A, C, and E), and vitamin D, have a protective effect against brain aging [39]. Therefore, the assessment of nutrition quality and patterns shows a much broader picture of dietary behavior than individual nutrients [24,40]. The FFI is a 10-item index for the assessment of dietary behavior in Austrian adults. The index is based on the Austrian recommendations for food intake [30]. For each food group, 8 frequency expressions are available, and a maximum of 7 points may be achieved. Nutritional behavior is classified as poor (FFI<32), moderate (FFI=32-34), good (FFI=35-39), and very good (FFI>39). The FFI was validated with biochemical indicators. Higher FFI scores were associated with mean nutrient intakes closer to current nutrient-based dietary guidelines (ie, lower intakes of fat and cholesterol and higher intakes of total carbohydrate, fiber, and micronutrients). Significant correlations between FFI levels and the intake of saturated fat (P=.004), vitamin C (P=.02), and vitamin B6 (P=.04) were reported [30]. The test is implemented using a laptop computer.

DemTect Screening

The DemTect was designed as a highly sensitive psychometric screening process to identify patients with MCI and patients with dementia in the early stages of the disease. Compared to the known Minimental State Examination [41], classification rates of the DemTect were superior for the MCI and dementia groups, with high sensitivities of 80% and 100%, respectively, especially in incipient and only slightly advanced cognitive disorders [42,43]. The DemTect includes 5 short easy-to-administer cognitive tasks that are sensitive for the early diagnosis of dementia (immediate recall of word lists, number transcoding, semantic word fluency task, and digit span reverse delayed recall of word lists). The test is implemented using a laptop computer. A score is determined for each task of the test, which is then converted to a test score using a conversion table. The test values are ultimately summed and evaluated using a scale that indicates the presence and severity of cognitive impairment.

DTA Procedure

Walking while performing a secondary cognitive task (dual-task paradigm) has become a classic way to assess the relationship between cognition and gait. Performance in a dual task has been associated with global cognitive function in older individuals with preserved cognition [44,45] and with MCIs [46-48], and it significantly correlates with the progression of dementia. DTA [25,31] measures the influence of the cognitive task on the gait pattern. DTA has demonstrated high test-retest reliability and

strong criterion-related validity in older adults with MCI and high sensitivity (effect size=0.9) in detecting MCI [49]. For this study, a walking distance of 10 meters and an additional 2 meters for acceleration and deceleration were chosen. Participants in block B are asked to walk the distance at a self-paced speed (single task). They are then asked to walk the 10-meter track and count backward loudly from 100 in increments of 3 (ie, dual task). Spatial and temporal gait parameters are measured using a stopwatch and a mechanical counter. Based on the walked distance, the needed time, performed steps, and spatial and temporal gait parameters are calculated (eg, walking speed, cadence, and stride length). From the single- and dual-task results, a percentage difference, which is defined as cognitive cost, is calculated [50]. DTA in block C is performed using a Google Pixel 6 smartphone (Google) mounted in a Haori headset (Shenzen Haori Technology Co, Ltd). Tailored AR software provides instructions to the participants and measures spatial and temporal gait parameters. Gait parameters are measured by detecting the walked distance and counting the time using Google ARCore [51]. The unity asset called Android StepCounter enables access to smartphone sensors and software algorithms to detect steps. The procedure is identical to that used for block B.

TMT Procedure

TMT may be used for the identification of attention disorders and executive dysfunctions [52], and screening for cognitive dysfunction [53]. Discrimination validity of TMT in dementia versus nondementia participants indicated sensitivity/specificity ratios of 75%/62.6% (TMT-A) and 62.5%/76.4% (TMT-B) [54]. TMT evaluates cognitive abilities and consists of two parts: (1) connecting numbers and (2) connecting numbers and letters in ascending order. The test is completed using pen and paper in block B. The MR-enhanced TMT in block C is performed using a Google Pixel 6 smartphone mounted in a Haori headset to enrich the real world with virtual objects (Figure 2). The virtual objects are spheres, labeled with numbers and letters. These spheres are anchored in real space. Participants select the spheres in the correct sequence by looking at them and pressing a real button with their hand. The completion times in seconds are separately recorded for both test parts (numbers, and numbers and letters) in blocks B and C. A maximum of 100 seconds is provided for the test part “numbers” and 300 seconds for the test part “numbers and letters.”

Figure 2. Trail-Making Test using Haori headset.

Reaction Time Test: Match 4 Point Test

Studies on reaction time demonstrated that a slowing of the reaction time and an increasing intraindividual performance variability represented an important marker for the presence of dementia and MCI [55-57]. The Match 4 Point Test evaluates the complex reactions (eye-hand, eye-leg, and eye-hand-leg reactions) in response to visual signals displayed in a randomized order. Studies on the reliability and validity of the test demonstrated good test-retest reliability (r=0.82) and an acceptable correlation for convergent validity (r=0.61) compared to the results of the visual reaction test S1 by Schuhfried [58,59]. The test in block B is performed using the Talent Diagnose System (Werthner Sport Consulting) [25]. The Talent Diagnose System implements 3 contact plates (2 for the hands and 1 ground contact plate marked for the right and left foot), placed on a table (hands) and under a table (feet). A laptop computer displays 20 visual signals. The test participant is in a standing position and is instructed to touch the relevant contact plates as fast as possible using the left/right hand/foot in response to the given visual signal. The MR-enhanced “Match 4 Point Test” is performed in block C using a Google Pixel 6 smartphone by running a tailor-made mobile app and using 4 Flic 2 (Shortcut Labs) buttons, which are connected with the smartphone via Bluetooth. This app displays visual signals in the form of black and white shapes. Depending on the color and position of the signal, participants push the Flic 2 buttons with their left/right hand/foot. The time taken to complete the task is recorded.

ETAM Procedure

Activities of daily living are restricted in individuals with mild cognitive declines [28,60,61] compared to healthy controls.

ETAM is a valid and reliable instrument for assessing activities of daily living in persons with MCI or mild dementia [62]. ETAM provides satisfactory discrimination between healthy individuals and persons with MCI or mild dementia [28,34] with test-retest reliability (r=0.78) and interrater reliability (r=0.97) [34]. The ETAM consists of six items that cover the following domains according to the Classification of Functioning, Disability and Health: communication, mobility, self-care, domestic life, and major life areas (specifically, the economic life subcategory referred to as finances). The items mobility and finances are implemented using pen and paper in block B and VR in block C.

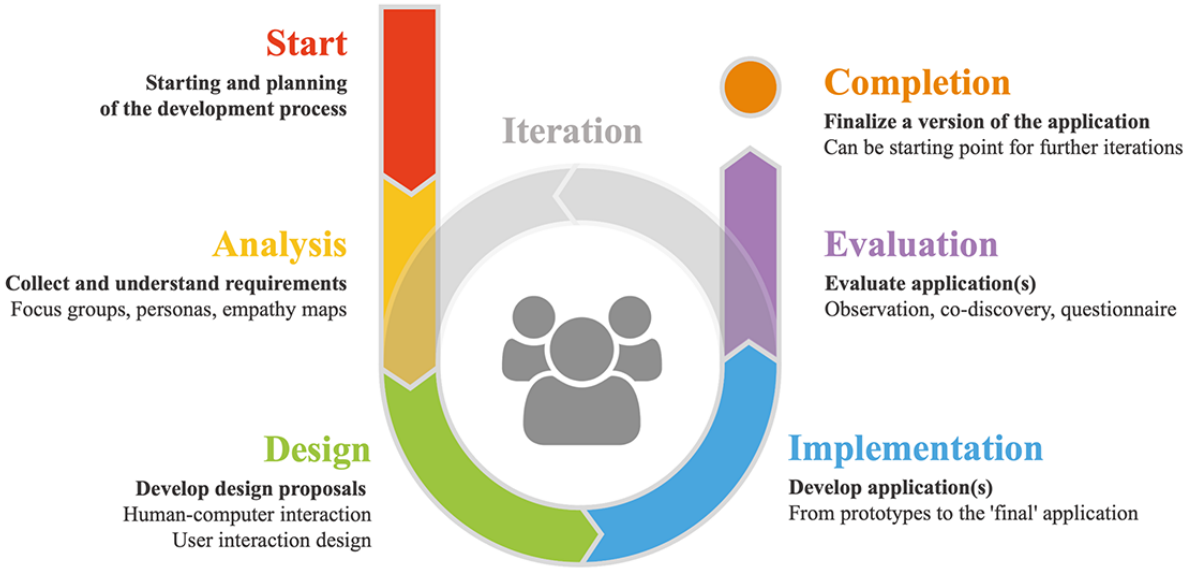
The task "traffic" (mobility) is related to understanding basic rules in road traffic situations and is tested based on 6 everyday traffic scenarios (eg, traffic lights). Participants in block B are shown photographs of 6 different traffic situations and asked to proceed and behave accordingly. The task "finances" (economic life) includes skills to compare offers, sum amounts, and count money. Participants receive three advertising leaflets and a stack of coins and are asked to buy the following grocery items: 1 pack of butter, 1 liter of milk, and 1 bread roll. They are supposed to pick the cheapest offer for butter from the 3 leaflets and calculate the total amount they need for all 3 products. Finally, they should take the necessary amount from the stack of coins in front of them. Performance in both tasks is evaluated using the ETAM scoring system. The same tasks are performed in block C using an Oculus Quest 2 VR headset (Figure 3). For the traffic task, participants are virtually "placed" in a spherical 360° video-recorded street environment and asked to navigate from a starting point to the pharmacy. Their behavior with respect to the traffic situations is documented automatically. Navigation within the 360° videos is performed in a standing position, using rotations, tilting of the body, and head and hand gestures. For the finances task, the participants are "placed" in a 3D grocery store. They interact with the virtual environment using hand gestures. Similar to the pen and paper version of ETAM, participants need to recognize the correct goods, calculate spending, and handle money in the virtual shop. The performance is scored based on the ETAM scoring system and automatically recorded.

Figure 3. Erlangen Test of Activities of Daily Living in Persons With Mild Dementia or Mild Cognitive Impairment using Oculus Quest 2 virtual reality headset.

Software Development of the MR Screening Tool Prototype

The MR-enhanced MST is implemented using information and communication technologies. After analyses of the available hardware and software technologies and interfaces, technical and data management concepts were established for the project domain of SCOBES-AR. Selected tests from the screening tool were implemented using a Google Pixel 6 smartphone (Google) mounted in a Haori headset, an Oculus Quest 2 VR headset (Facebook Technologies, LLC), Flic 2 buttons, and tablets or computers for monitoring and annotation. Multiple software prototypes were developed by a team of digital media specialists and customized to meet the users' needs when operating the devices. Therefore, we adapted a user-centered design process [63,64] and applied it iteratively in the software development. The process of software planning, development, design, analysis, evaluation, and final application is illustrated in Figure 4.

Figure 4. User-centered design process of prototype development.



To obtain a deep understanding of the users of the screening tool prototype, target groups of older adults and therapists were identified at the start of the study, and the context of use was clarified [65]. The older adults and therapists separately participated in 2 focus groups [66], in which the study purpose and the user's risks, problems, and benefits were discussed in detail. Based on the gathered information, personas [63,65,66] and empathy maps [65] were generated. These tools provided important feedback for the development process. Screenings of the test battery were conducted in the design phase for transformation into software applications. Selection and transformation of the screenings occurred in cooperation with health professionals with the help of early functional prototypes. The key features of the software for MR-MST were defined in group discussions in the focus groups. The implementation of the software prototypes occurred in the cross-platform development environment of Unity (Unity Software Inc) [67], assisted by plugins for Google ARCore [68] and Oculus Quest 2 [69,70]. The software prototype itself was designed as multiple mobile apps that could be installed on the target platforms, namely, smartphones with an Android operating system [71] and Oculus Quest 2 [70].

Usability of the MR-Enhanced Screening Tool Prototype

The usability evaluation is performed to estimate the ease, efficiency, and satisfaction of using the prototype. The usability of the MR-enhanced screening tool prototype is evaluated by 2 testing groups implementing different methods. The usability tests focused on the assessments included in block C (MR-MST).

The first testing group includes 10 investigators and 10 participants in the screening procedure, acting as users (therapist/client). They evaluate the usability of the overall process, including all software applications and hardware devices used in block C. Traditionally conducted subscreenings will be assessed via observed summative evaluation [63,72] using the codiscovery [63] method. Using this method, both users act as they would in the performance of conventional screening without any interruption by the test supervisor during the test procedure. No additional tasks will be presented to them. These observations may be seen as unmoderated [73] usability tests, where usual screening occurs to provide qualitative (eg, behavior analysis afterward) and quantitative (eg, task completion times) feedback. The test supervisor will perform follow-up questionnaires after each observation to gain deeper insights into the interaction with the user interface. The questions will be personalized for each target group (ie, investigator and participant). A total of 10 screenings will then be observed with multiple video cameras, microphones, and screen recording apps for tablets. Afterward, usability experts will analyze the observations and questionnaires. This usability evaluation should deliver findings related to the organization of the complete process in block C and the user's interaction with all software components.

The second testing group will include 2 usability experts, who will gain deeper insights into the usability of the complete system in the form of codiscovery using the cognitive walkthrough method [74,75]. During a cognitive walkthrough usability analysis, experts will look at action sequences using a product (eg, hardware, software, or both) through the user's eyes. They will try to accomplish common action sequences that the target group will perform and detect as many usability problems as possible.

Data Management

This study is performed by a multidisciplinary team of psychologists, speech therapists, occupational therapists and physiotherapists, dieticians, nursing scientists, information managers, software engineers, and biomedical analysts. All data will be saved and processed in a pseudonymized form using automatically generated alphanumeric codes. The list for identification is securely stored in a password-protected document in the study center and may be accessed only by the principal investigators. When published, all data will be anonymized. The collection, processing, and storage of the data follows the legal provisions of the General Data Protection Regulation (Regulation EU 2016/679) and requires signed

informed consent. The data gathered from the test methodology (questionnaires) are collected and stored on a telehealth platform [76] provided by the Austrian Institute of Technology GmbH (subcontractor). The telehealth platform provides standardized data collection and interfaces based on Fast Health Interoperability Resources questionnaires [77] and on user interfaces for the medical personnel within the SCOBES-AR project.

Outcome Parameters and Data Analysis

Statistical analyses will be performed to identify possible correlations between the different components of the MST and MR-enhanced MST. Spearman rank correlations (Spearman ρ) or product-moment correlations (Pearson correlations) will be calculated, depending on the distribution of the collected data. Multiple regression analyses will be conducted for cases of strong effects in the correlation between the MST and MR-enhanced MST. Descriptive statistics of the data will be presented as means and SDs. The level of significance is set at α=.05. The statistical data will be evaluated using SPSS (IBM Corp).

For usability assessment, usability experts will collect and analyze data from the video observations and questionnaires. The video observations will be evaluated using "Eisenhower's Urgent/Important Principle" [78], in which items are classified as "not urgent" to "urgent" and as "not important" to "important." The "urgent" and "important" items indicate higher needs of improvement. The questionnaires addressing the personal experiences with the screening procedure are based on a 5-point Likert scale, where 1 indicates "very good usability."

Results

This study was funded by the Austrian Research Promotion Agency (FFG, grant 866873) and was approved by the ethics committee of the Medical University of Graz, Austria. The funding body and funding source are not involved in performing the research and do not play any role in the execution of the study, data analyses, or result interpretation. All described procedures related to the equipment and software development, preliminary tests, study organization, and recruitment plans were completed. The investigators involved in the test procedure were trained to use the MR prototype and perform the entire screening procedure in joint and separate sessions. As of July 15, 2022, a total of 70 participants have been screened. Because this study describes the protocol for the implementation of the MR-enhanced multimodal screening tool, no results are currently available. Data analyses and result dissemination will be completed by September 2023.

Discussion

Overview

The increasing availability of AR and VR technologies provides an opportunity to translate available screening tools from the laboratory to the real world. This translation is challenging because of the current limited evidence in clinical research. Therefore, the development and testing of prototypes and research protocols are important steps in the successful application of these novel technologies in health care practice. This study described the development process and research protocol for the implementation and usability of an MR-enhanced MST for the early detection of cognitive decline in older adults.

Selection of the single assessments included in this MST was based on their validity and reliability in detecting cognitive changes in healthy older adults and individuals with diagnosed cognitive impairments. The screening tool was tested in the previous phase of the SCOBES-AR project. Some of these assessments are performed for the first time in this way using MR technologies, which require integrated multidisciplinary knowledge and the development and testing of several software models.

The user-centered approach for the development of the software prototype was based on the collaboration between engineers (digital media specialists, information and communication specialists, and software developers) and end users (therapists and researchers with different expertise areas as well as older adults). Common challenges during the software design process were related to appropriate implementation of the different assessments with the MR technologies, documentation of results, and provision of guidelines for the therapists on how to use the different software and hardware products. The extensive exchange between engineers and users enabled the development of easy-to-use AR and VR software with reliable technical quality and attractive designs. This exchange enables a smooth transition from technical to clinical research settings, where the developed prototype will be applied for screening older adult test participants and further evaluated.

Strengths and Limitations

We designed this study to compare the results of the MST (block B) to those of the MR-MST (block C). The performance in the first block may facilitate the performance in the second block. To minimize the "learning effect," these blocks were randomized among participants. As the entire screening procedure has a duration of approximately 130 minutes, participants may experience cognitive fatigue, which could influence the results of the tests. The effect of possible cognitive fatigue was minimized by providing a resting break between the blocks and frequently obtaining feedback from participants. The order of assessments in blocks B and C was selected to ensure maximum convenience and time efficiency when changing from assessments performed using AR to those performed using VR in block C.

Another limitation of this study protocol is related to the fact that the experiments are performed at different times of the day (eg, in the morning and afternoon) and by different investigators. To reduce the impact of circadian rhythms on cognitive performance, we avoided testing in the early morning and late afternoon. To ensure standard testing conditions, all involved investigators obtained the same training using the AR and VR technologies and performed the screening procedure.

One strength of this study is that the assessments performed with VR included familiar situations and daily life activities

(eg, crossing a street, shopping in a grocery store) in which immersion into the virtual world created a cognitive experience that aligned with real-life demands. The MR-enhanced assessments were designed to resemble the assessments performed with pen and paper as much as possible. We are aware that the results of MR-enhanced MST may not be directly comparable to those of the MST because of the specificity of the AR and VR equipment and environment. These findings will shed more light on the extent, art, and origin of possible differences, which will enable further adaptations and optimizations of the prototype.

Usability is another important consideration in establishing screening tools involving novel technologies. Therefore, this study describes the usability evaluation of the developed MR prototype. Feedback will be collected from the users (investigators and clients) via observations (video observations of the screening procedure) and questionnaires. Usability experts will focus on the users' cognitive activities related to their specific goals and understanding when executing screening using the MR prototype. This approach should reveal possible limitations and user disadvantages. Notably, outlining the particular needs of improvement will encourage further optimization to enable further application of the MR-enhanced screening tool in therapeutic settings.

Conclusions

The development and application of the described MR-enhanced prototype for the screening of early cognitive decline in older adults is an innovative and demanding process. Establishment of the respective methodological procedures is a saliant step toward identifying the best practices. The results of the study will provide more information on the usability, utility, and applicability of AR- and VR-enhanced screening tools, which may encourage further development of these models and their use in therapeutic settings.

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Data Availability

The data sets that will be generated and analyzed during this study will not be publicly available because the generated experimental data are only usable in the given context of the project and its aims, but they are available from the corresponding author upon reasonable request.

Authors' Contributions

MC was involved in organizing and writing the manuscript. RS led the software development process, developed parts of the software prototypes, designed and performed the usability study, and wrote the parts of the manuscript related to these aspects. SS and AN developed parts of the software for the prototype and participated in planning and performing the usability study. GS participated in planning the usability study and 3D design. BG, BF-N, TD, WS, HS, and BL-F were involved in the study design and writing of the manuscript. RP was involved in the statistical analyses. All authors were involved in the final revisions to the manuscript.

Conflicts of Interest

None declared.

References

1. Prince M, Wimo A, Guerchet M. The global impact of dementia: an analysis of prevalence, incidence, cost and trends. World Alzheimer Report 2015. London, United Kingdom: Alzheimer's Disease International; 2015. URL: https://www.alzint.org/u/WorldAlzheimerReport2015.pdf [accessed 2022-09-27]
2. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999 Mar;56(3):303-308. [doi: 10.1001/archneur.56.3.303] [Medline: 10190820]
3. Anderson ND. State of the science on mild cognitive impairment (MCI). CNS Spectr 2019 Feb;24(1):78-87. [doi: 10.1017/S1092852918001347] [Medline: 30651152]
4. Global action plan on the public health response to dementia 2017-2025. World Health Organization. Geneva, Switzerland; 2017. URL: https://apps.who.int/iris/bitstream/handle/10665/259615/9789241513487-eng.pdf?sequence=1 [accessed 2022-09-27]
5. Shah H, Albanese E, Duggan C, Rudan I, Langa KM, Carrillo MC, et al. Research priorities to reduce the global burden of dementia by 2025. Lancet Neurol 2016 Nov;15(12):1285-1294. [doi: 10.1016/S1474-4422(16)30235-6] [Medline: 27751558]

6. Gomersall T, Smith SK, Blewett C, Astell A. 'It's definitely not Alzheimer's': perceived benefits and drawbacks of a mild cognitive impairment diagnosis. Br J Health Psychol 2017 Nov;22(4):786-804. [doi: 10.1111/bjhp.12255] [Medline: 28628736]
7. Lohmeyer JL, Alpinar-Sencan Z, Schicktanz S. Attitudes towards prediction and early diagnosis of late-onset dementia: a comparison of tested persons and family caregivers. Aging Ment Health 2021 May;25(5):832-843. [doi: 10.1080/13607863.2020.1727851] [Medline: 32091238]
8. Holsinger T, Boustani M, Abbot D, Williams JW. Acceptability of dementia screening in primary care patients. Int J Geriatr Psychiatry 2011 Apr;26(4):373-379. [doi: 10.1002/gps.2536] [Medline: 20845398]
9. Tang W, Kannaley K, Friedman DB, Edwards VJ, Wilcox S, Levkoff SE, et al. Concern about developing Alzheimer's disease or dementia and intention to be screened: an analysis of national survey data. Arch Gerontol Geriatr 2017 Jul;71:43-49 [FREE Full text] [doi: 10.1016/j.archger.2017.02.013] [Medline: 28279898]
10. Takeda S, Ota M, Taniguchi T. Factors affecting intention to undergo dementia screening. Yonago Acta Med 2017 Mar;60(1):47-51 [FREE Full text] [Medline: 28331421]
11. Aihara Y, Maeda K. Intention to undergo dementia screening in primary care settings among community-dwelling older people. Int J Geriatr Psychiatry 2020 Sep;35(9):1036-1042. [doi: 10.1002/gps.5326] [Medline: 32383788]
12. Ngandu T, Lehtisalo J, Solomon A, Levälahti E, Ahtiluoto S, Antikainen R, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. The Lancet 2015 Jun;385(9984):2255-2263. [doi: 10.1016/S0140-6736(15)60461-5] [Medline: 25771249]
13. Kivipelto M, Mangialasche F, Ngandu T. Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. Nat Rev Neurol 2018 Nov;14(11):653-666. [doi: 10.1038/s41582-018-0070-3] [Medline: 30291317]
14. Mitchell AJ. CSF phosphorylated tau in the diagnosis and prognosis of mild cognitive impairment and Alzheimer's disease: a meta-analysis of 51 studies. J Neurol Neurosurg Psychiatry 2009 Sep;80(9):966-975. [doi: 10.1136/jnnp.2008.167791] [Medline: 19465413]
15. Ferreira D, Perestelo-Pérez L, Westman E, Wahlund L, Sarría A, Serrano-Aguilar P. Meta-review of CSF core biomarkers in Alzheimer's disease: the state-of-the-art after the new revised diagnostic criteria. Front Aging Neurosci 2014 Mar;6:47 [FREE Full text] [doi: 10.3389/fnagi.2014.00047] [Medline: 24715863]
16. Staffaroni A, Elahi F, McDermott D, Marton K, Karageorgiou E, Sacco S, et al. Neuroimaging in dementia. Semin Neurol 2017 Oct;37(5):510-537 [FREE Full text] [doi: 10.1055/s-0037-1608808] [Medline: 29207412]
17. Young PNE, Estarellas M, Coomans E, Srikrishna M, Beaumont H, Maass A, et al. Imaging biomarkers in neurodegeneration: current and future practices. Alzheimers Res Ther 2020 Apr;12(1):49 [FREE Full text] [doi: 10.1186/s13195-020-00612-7] [Medline: 32340618]
18. Hameed S, Fuh J, Senanarong V, Ebenezer EGM, Looi I, Dominguez JC, et al. Role of fluid biomarkers and PET imaging in early diagnosis and its clinical implication in the management of Alzheimer's disease. J Alzheimers Dis Rep 2020 Feb;4(1):21-37 [FREE Full text] [doi: 10.3233/ADR-190143] [Medline: 32206755]
19. Niemann M, Prange A, Sonntag D. Towards a multimodal multisensory cognitive assessment framework. 2018 Presented at: 2018 IEEE 31st International Symposium on Computer-Based Medical Systems (CBMS); June 18-21, 2018; Karlstad, Sweden p. 18-21. [doi: 10.1109/cbms.2018.00012]
20. Azuma R, Baillot Y, Behringer R, Feiner S, Julier S, MacIntyre B. Recent advances in augmented reality. IEEE Comput Grap Appl 2001 Nov;21(6):34-47. [doi: 10.1109/38.963459]
21. Chirico A, Lucidi F, De LM, Milanese C, Napoli A, Giordano A. Virtual reality in health system: beyond entertainment. A mini-review on the efficacy of VR during cancer treatment. J Cell Physiol 2016 Feb;231(2):275-287. [doi: 10.1002/jcp.25117] [Medline: 26238976]
22. SCOBES-AR. Smart cognition and behaviour screening powered by augmented reality. URL: https://scobes-ar.fh-joanneum.at/en/ [accessed 2022-07-15]
23. Doty RL, Marcus A, Lee WW. Development of the 12-item Cross-Cultural Smell Identification Test (CC-SIT). Laryngoscope 1996 Mar;106(3 Pt 1):353-356. [doi: 10.1097/00005537-199603000-00021] [Medline: 8614203]
24. Allès B, Samieri C, Féart C, Jutand M, Laurin D, Barberger-Gateau P. Dietary patterns: a novel approach to examine the link between nutrition and cognitive function in older individuals. Nutr Res Rev 2012 Dec;25(2):207-222. [doi: 10.1017/S0954422412000133] [Medline: 22874455]
25. Tseng B, Cullum C, Zhang R. Older adults with amnestic mild cognitive impairment exhibit exacerbated gait slowing under dual-task challenges. Curr Alzheimer Res 2014 Jun;11(5):494-500 [FREE Full text] [doi: 10.2174/1567205011666140505110828] [Medline: 24801217]
26. Test your talent. Talent Diagnose System. URL: http://www.werthner.at/tds/tds-german/index.html [accessed 2022-07-15]
27. Jahn T, Hessler J. Handanweisung zum Test-Set Kognitive Funktionen Demenz (CFD) im Wiener Testsystem (WTS). Mödling, Austria: Schuhfried GmbH; 2017.
28. Jekel K, Damian M, Wattmo C, Hausner L, Bullock R, Connelly PJ, et al. Mild cognitive impairment and deficits in instrumental activities of daily living: a systematic review. Alzheimers Res Ther 2015 Mar;7(1):17 [FREE Full text] [doi: 10.1186/s13195-015-0099-0] [Medline: 25815063]

29. Jerald J. The VR Book: Human-Centered Design for Virtual Reality. San Rafael, CA: Association for Computing Machinery and Morgan & Claypool; 2016.
30. Freisling H, Elmadfa I. Food frequency index as a measure of diet quality in non-frail older adults. Ann Nutr Metab 2008 Mar;52(Suppl 1):43-46 [FREE Full text] [doi: 10.1159/000115348] [Medline: 18382078]
31. Gillain S, Dramé M, Lekeu F, Wojtasik V, Ricour C, Croisier J, et al. Gait speed or gait variability, which one to use as a marker of risk to develop Alzheimer disease? a pilot study. Aging Clin Exp Res 2016 Apr;28(2):249-255. [doi: 10.1007/s40520-015-0392-6] [Medline: 26076908]
32. Lin K, Wu Y, Chen I, Tsai P, Wu C, Chen C. Dual-task performance involving hand dexterity and cognitive tasks and daily functioning in people with schizophrenia: a pilot study. Am J Occup Ther 2015 May;69(3):1-7. [doi: 10.5014/ajot.2014.014738] [Medline: 25871598]
33. Reitan RM, Wolfson D. Category test and trail making test as measures of frontal lobe functions. Clin Neuropsychol 1995 Feb;9(1):50-56. [doi: 10.1080/13854049508402057]
34. Luttenberger K, Reppermund S, Schmiedeberg-Sohn A, Book S, Graessel E. Validation of the Erlangen Test of Activities of Daily Living in Persons with Mild Dementia or Mild Cognitive Impairment (ETAM). BMC Geriatr 2016 May;16:111 [FREE Full text] [doi: 10.1186/s12877-016-0271-9] [Medline: 27229937]
35. Behrman S, Chouliaras L, Ebmeier KP. Considering the senses in the diagnosis and management of dementia. Maturitas 2014 Apr;77(4):305-310. [doi: 10.1016/j.maturitas.2014.01.003] [Medline: 24495787]
36. Gopinath B, Anstey KJ, Kifley A, Mitchell P. Olfactory impairment is associated with functional disability and reduced independence among older adults. Maturitas 2012 May;72(1):50-55. [doi: 10.1016/j.maturitas.2012.01.009] [Medline: 22321638]
37. Joseph T, Auger SD, Peress L, Rack D, Cuzick J, Giovannoni G, et al. Screening performance of abbreviated versions of the UPSIT smell test. J Neurol 2019 Aug;266(8):1897-1906 [FREE Full text] [doi: 10.1007/s00415-019-09340-x] [Medline: 31053960]
38. Scarmeas N, Anastasiou CA, Yannakoulia M. Nutrition and prevention of cognitive impairment. Lancet Neurol 2018 Nov;17(11):1006-1015. [doi: 10.1016/S1474-4422(18)30338-7] [Medline: 30244829]
39. Hooshmand B, Mangialasche F, Kalpouzos G, Solomon A, Kåreholt I, Smith AD, et al. Association of vitamin B12, folate, and sulfur amino acids with brain magnetic resonance imaging measures in older adults: a longitudinal population-based study. JAMA Psychiatry 2016 Jun;73(6):606-613. [doi: 10.1001/jamapsychiatry.2016.0274] [Medline: 27120188]
40. Zuniga K, McAuley E. Considerations in selection of diet assessment methods for examining the effect of nutrition on cognition. J Nutr Health Aging 2015 Mar;19(3):333-340 [FREE Full text] [doi: 10.1007/s12603-014-0566-5] [Medline: 25732219]
41. Creavin ST, Wisniewski S, Noel-Storr AH, Trevelyan CM, Hampton T, Rayment D, et al. Mini-Mental State Examination (MMSE) for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations. Cochrane Database Syst Rev 2016 Jan;2016(1):CD011145. [doi: 10.1002/14651858.CD011145.pub2] [Medline: 26760674]
42. Kohn N, Kalbe E, Georg H, Kessler J. Vergleich MMST und DemTect: Spezifität und Sensitivität bei primär kognitiven Störungen. Akt Neurol 2007;34(S 2):P672. [doi: 10.1055/s-2007-987943]
43. Kalbe E, Kessler J, Calabrese P, Smith R, Passmore AP, Brand M, et al. DemTect: a new, sensitive cognitive screening test to support the diagnosis of mild cognitive impairment and early dementia. Int J Geriatr Psychiatry 2004 Feb;19(2):136-143. [doi: 10.1002/gps.1042] [Medline: 14758579]
44. Ansai JH, Aurichio TR, Rebelatto JR. Relationship between dual task walking, cognition, and depression in oldest old people. Int Psychogeriatr 2016 Jan;28(1):31-38. [doi: 10.1017/S1041610215000915] [Medline: 26132488]
45. Venema D, Bartels E, Siu KC. Tasks matter: a cross-sectional study of the relationship of cognition and dual-task performance in older adults. J Geriatr Phys Ther 2013 Jul;36(3):115-122. [doi: 10.1519/JPT.0b013e31827bc36f] [Medline: 23249724]
46. Doi T, Shimada H, Makizako H, Tsutsumimoto K, Uemura K, Anan Y, et al. Cognitive function and gait speed under normal and dual-task walking among older adults with mild cognitive impairment. BMC Neurol 2014 Apr 01;14:67 [FREE Full text] [doi: 10.1186/1471-2377-14-67] [Medline: 24694100]
47. Montero-Odasso MM, Sarquis-Adamson Y, Speechley M, Borrie MJ, Hachinski VC, Wells J, et al. Association of dual-task gait with incident dementia in mild cognitive impairment: results from the gait and brain study. JAMA Neurol 2017 Jul;74(7):857-865 [FREE Full text] [doi: 10.1001/jamaneurol.2017.0643] [Medline: 28505243]
48. Ansai JH, Andrade LPD, Rossi PG, Almeida ML, Carvalho Vale FA, Rebelatto JR. Association between gait and dual task with cognitive domains in older people with cognitive impairment. J Mot Behav 2018 Jul;50(4):409-415. [doi: 10.1080/00222895.2017.1363702] [Medline: 28901834]
49. Yang Q, Tian C, Tseng B, Zhang B, Huang S, Jin S, et al. Gait change in dual task as a behavioral marker to detect mild cognitive impairment in elderly persons: a systematic review and meta-analysis. Arch Phys Med Rehabil 2020 Oct;101(10):1813-1821. [doi: 10.1016/j.apmr.2020.05.020] [Medline: 32553899]
50. Hunter SW, Divine A, Frengopoulos C, Montero Odasso M. A framework for secondary cognitive and motor tasks in dual-task gait testing in people with mild cognitive impairment. BMC Geriatr 2018 Sep;18(1):202 [FREE Full text] [doi: 10.1186/s12877-018-0894-0] [Medline: 30176796]

51. Guggenberger B, Jocham AJ, Jocham B, Nischelwitzer A, Ritschl H. Instrumental validity of the motion detection accuracy of a smartphone-based training game. Int J Environ Res Public Health 2021 Aug;18(16):8410 [FREE Full text] [doi: 10.3390/ijerph18168410] [Medline: 34444160]
52. Tischler L, Petermann F. Trail Making Test (TMT). Zeitschrift für Psychiatrie, Psychologie und Psychotherapie 2010 Jan;58(1):79-81. [doi: 10.1024/1661-4747.a000009]
53. Rasmusson XD, Zonderman AB, Kawas C, Resnick SM. Effects of age and dementia on the Trail Making Test. Clinical Neuropsychol 2010 Aug;12(2):169-178. [doi: 10.1076/clin.12.2.169.2005]
54. Ramlall S, Chipps J, Bhigjee AI, Pillay BJ. Sensitivity and specificity of neuropsychological tests for dementia and mild cognitive impairment in a sample of residential elderly in South Africa. S Afr J Psych 2014 Nov;20(4):7. [doi: 10.4102/sajpsychiatry.v20i4.558]
55. Christensen H, Dear KBG, Anstey KJ, Parslow RA, Sachdev P, Jorm AF. Within-occasion intraindividual variability and preclinical diagnostic status: Is intraindividual variability an indicator of mild cognitive impairment? Neuropsychology 2005 May;19(3):309-317. [doi: 10.1037/0894-4105.19.3.309] [Medline: 15910117]
56. Hultsch DF, MacDonald SWS, Dixon RA. Variability in reaction time performance of younger and older adults. J Gerontol B Psychol Sci Soc Sci 2002 Mar;57(2):P101-P115. [doi: 10.1093/geronb/57.2.p101] [Medline: 11867658]
57. Hultsch DF, MacDonald SWS, Hunter MA, Levy-Bencheton J, Strauss E. Intraindividual variability in cognitive performance in older adults: comparison of adults with mild dementia, adults with arthritis, and healthy adults. Neuropsychology 2000 Oct;14(4):588-598. [doi: 10.1037/0894-4105.14.4.588] [Medline: 11055261]
58. Simi H, Holler P, Pilz R, Zöhrer D, Staubmann W. The visual hand reaction test and complex hand-foot-reaction test from Werthner's talent diagnostic system-construct validity and test-retest reliability in healthy older adults. In: Proceedings of the 17th Annual Convention and International Conference of the International Network of Sport and Health Science. Alicante, Spain: Journal of Human Sport and Exercise; 2021 Presented at: 17th Annual Convention and International Conference of the International Network of Sport and Health Science; May 27-29, 2021; St Petersburg, Russia. [doi: 10.14198/jhse.2021.16.Proc4.54]
59. Schuhfried G. Manual Reaktionstest (RT) im Wiener Testsystem (WTS). Mödling, Austria: Schuhfried GmbH; 1996.
60. Marshall GA, Amariglio RE, Sperling RA, Rentz DM. Activities of daily living: Where do they fit in the diagnosis of Alzheimer's disease? Neurodegener Dis Manag 2012 Oct;2(5):483-491 [FREE Full text] [doi: 10.2217/nmt.12.55] [Medline: 23585777]
61. Reppermund S, Brodaty H, Crawford JD, Kochan NA, Draper B, Slavin MJ, et al. Impairment in instrumental activities of daily living with high cognitive demand is an early marker of mild cognitive impairment: the Sydney Memory and Ageing Study. Psychol Med 2013 Jan;43(11):2437-2445. [doi: 10.1017/s003329171200308x] [Medline: 23308393]
62. Book S, Luttenberger K, Stemmler M, Meyer S, Graessel E. The Erlangen test of activities of daily living in persons with mild dementia or mild cognitive impairment (ETAM) - an extended validation. BMC Psychiatry 2018 Sep;18(1):308 [FREE Full text] [doi: 10.1186/s12888-018-1886-5] [Medline: 30249231]
63. Barnum C. Usability Testing Essentials (Second Edition). Amsterdam, The Netherlands: Morgan Kaufmann, Elsevier; 2021.
64. Vredenburg K, Mao J, Smith P, Carey T. A survey of user-centered design practice. In: CHI '02: Proceedings of the SIGCHI Conference on Human Factors in Computing Systems. New York, NY: Association for Computing Machinery; 2002 Presented at: SIGCHI Conference on Human Factors in Computing Systems; April 20-25, 2002; Minneapolis, MN p. 471-478. [doi: 10.1145/503376.503460]
65. Thesmann S. Interface Design. Usability, User Experience und Accessibility im Web gestalten. Wiesbaden, Germany: Springer Fachmedien Wiesbaden GmbH; 2016.
66. Richter M, Flückiger M. Usability und UX kompakt. Heidelberg, Germany: Springer Vieweg Berlin, Heidelberg; 2016.
67. Unity Technologies. URL: https://unity.com/ [accessed 2022-01-13]
68. Unity manual: ARCore XR plugin. Unity Technologies. URL: https://docs.unity3d.com/Manual/com.unity.xr.arcore.html [accessed 2022-01-13]
69. Unity manual: Oculus XR plugin. Unity Technologies. URL: https://docs.unity3d.com/Manual/com.unity.xr.oculus.html [accessed 2022-01-13]
70. Oculus Quest 2: Unser bisher bestes, neues all-in-one VR-headset | Oculus. Meta. URL: https://www.oculus.com/quest-2/?locale=de_DE [accessed 2022-01-13]
71. Android. URL: https://www.android.com/ [accessed 2022-01-13]
72. Geisen E, Bergstrom J. Usability Testing for Survey Research. Amsterdam, The Netherlands: Morgan Kaufmann, Elsevier; 2017.
73. Morten H. Usability Testing?: A Practitioner's Guide to Evaluating the User Experience. San Rafael, CA: Morgan & Claypool Publishers; 2020.
74. Sutcliffe AG, Kaur KD. Evaluating the usability of virtual reality user interfaces. Behav Inf Technol 2000 Jan;19(6):415-426. [doi: 10.1080/014492900750052679]
75. Doumanis I, Economou D. Using cognitive walkthrough and hybrid prototyping to gather user requirements in early design virtual reality prototypes. In: Beck D, Peña-Rios A, Ogle T, Economou D, Mentzelopoulos M, Morgado L, et al, editors.

Immersive Learning Research Network. iLRN 2019. Communications in Computer and Information Science, vol 1044. Cham, Switzerland: Springer; 2019:234-246.
76. KIT telehealth solutions. Austrian Institute of Technology. URL: https://kit.ait.ac.at/home/ [accessed 2022-07-15]
77. HL7 FHIR questionnaire. HL7 FHIR Foundation. URL: https://www.hl7.org/fhir/questionnaire.html [accessed 2022-07-15]
78. Dwight D. Eisenhower, Address at the Second Assembly of the World Council of Churches, Evanston, Illinois. The American Presidency Project. URL: https://www.presidency.ucsb.edu/node/232572 [accessed 2022-07-15]

Abbreviations

AR: augmented reality
B-SIT: Brief Smell Identification Test
DemTect: Dementia Detection Test
DTA: Dual-Task Assessment
ETAM: Erlangen Test of Activities of Daily Living in Persons with Mild Dementia or Mild Cognitive Impairment
FFI: Food Frequency Index
MCI: mild cognitive impairment
MR: mixed reality
MST: multimodal screening tool
SCOBES AR: Smart Cognition & Behaviour Screening powered by Augmented Reality
TMT: Trail-Making Test
VR: virtual reality

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Protocol

Understanding the Influence of Web-Based Information, Misinformation, Disinformation, and Reinformation on COVID-19 Vaccine Acceptance: Protocol for a Multicomponent Study

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Abstract

Background: The COVID-19 pandemic has generated an explosion in the amount of information shared on the internet, including false and misleading information on SARS-CoV-2 and recommended protective behaviors. Prior to the pandemic, web-based misinformation and disinformation were already identified as having an impact on people's decision to refuse or delay recommended vaccination for themselves or their children.

Objective: The overall aims of our study are to better understand the influence of web-based misinformation and disinformation on COVID-19 vaccine decisions and investigate potential solutions to reduce the impact of web-based misinformation and disinformation about vaccines.

Methods: Based on different research approaches, the study will involve (1) the use of artificial intelligence techniques, (2) a web-based survey, (3) interviews, and (4) a scoping review and an environmental scan of the literature.

Results: As of September 1, 2022, data collection has been completed for all objectives. The analysis is being conducted, and results should be disseminated in the upcoming months.

Conclusions: The findings from this study will help with understanding the underlying determinants of vaccine hesitancy among Canadian individuals and identifying effective, tailored interventions to improve vaccine acceptance among them.

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KEYWORDS

vaccine hesitancy; COVID-19; misinformation; vaccine decisions; disinformation; online; vaccine; vaccination

Introduction

Background

Prior to the pandemic, web-based misinformation and disinformation were identified as key issues that negatively impact vaccine acceptance [1,2]. The COVID-19 pandemic has heightened these issues to a point where the World Health Organization director noted that the world was not just fighting a pandemic but also an infodemic [3]. For example, *reinformation* [4] is a form of disinformation that could have contributed to COVID-19 vaccine hesitancy [5]. Hyper-partisan news is not false per se—the events reported may be real—but their claim to be informative conceals the intention to manipulate readers into adopting the organization's viewpoints [6,7]. For example, in Canada, the Rebel News and Global Research media outlets publish controversial news, and their coverage is often qualified as misleading [8]. Fact-checking devices are already being used in journalism, policy making, and education to limit the detrimental effects of disinformation. However, checking facts has proven to be insufficient for countering reinformation and is less efficient with information that is not false per se but is biased and emotionally loaded in its presentation. Textbox 1 presents the definitions of some of the key concepts used in our study.

Textbox 1. Definitions of key concepts.

Key concepts

- Infodemic: overabundance of information—true, false or misleading—that makes it harder for people to know what to do [9]
- Misinformation: false information that is not created with the intention of causing harm [10]
- Disinformation: false information that is deliberately created to cause harm [10]
- Malinformation: information that is based on reality and used to inflict harm [10]
- Reinformation: hyper-partisan information created by groups that are self-proclaimed alternative news organizations [4]

The COVID-19 vaccination campaign is unprecedented not only in terms of scale and the public's attention toward the safety and effectiveness of the different vaccines but also in terms of misinformation and disinformation about COVID-19 vaccination, which were already prominent even before the first vaccines were approved for use [11,12]. In Canada, high rates of COVID-19 vaccine uptake were reached overall in adults, but these rates have been lower among equity-deserving groups, such as racialized people, newcomers, and Indigenous people [13,14]. Moreover, among those who accepted initial doses, there is lower uptake or willingness with regard to completing their initial series of vaccines or accepting additional or booster doses [15]. Studies have shown that parents, even those who are vaccinated themselves, are more hesitant toward vaccinating their children [16,17].

Experts often attribute lower than expected vaccine uptake rates to the negative impact of false or antivaccine information shared on the internet [18]. However, the role that web-based misinformation and disinformation play in individual and community COVID-19 vaccine decision-making in real-life settings remains poorly understood, particularly among equity-deserving groups. Most studies are descriptive (ie, content analyses of antivaccine websites and social media) or have tested the impact of experimentally created fictitious websites [1,19,20], leaving important questions unanswered. For example, there is little known on the influence of the writing style of alleged facts about COVID-19 vaccination or the characteristics of web-based content on people's attitudes toward COVID-19 vaccines. It is unclear if information-seeking practices differ between vaccine-hesitant parents and vaccine-confident parents and to what extent vaccine-hesitant parents are being led into echo chambers by social media algorithms. The consequences of experiences of inequity and systemic racism within the health system on trust in official sources of COVID-19 vaccine information (eg, governments and public health or health systems) remain unclear. Finally, research into interventions to address misinformation and disinformation is growing rapidly, but there is a need to identify effective interventions that could be easily and rapidly implemented within public health practices to reduce the impact of misinformation and disinformation on vaccine acceptance [21].

Objective

The overall aims of our study are to better understand the influence of web-based misinformation and disinformation on COVID-19 vaccine decisions and investigate potential solutions to reduce the impact of web-based misinformation and disinformation about vaccines.

Specifically, the study has the following four objectives: (1) describe the infodemic and web-based discourses related to the generation and spread of misinformation and disinformation on COVID-19 vaccines in Canada by evaluating the quality of content with presumed journalistic value in the digital environment and modeling the different characteristics of social network conversations following COVID-19 news items; (2) examine the impact of web-based misinformation and

disinformation and the infodemic on COVID-19 vaccine decisions by using a web-based randomized controlled experimental survey; (3) explore attitudes, values, risk perceptions, beliefs, behaviors, and information seeking about COVID-19 vaccination in an ethnically diverse sample of vaccine-hesitant, Canadian parents of children aged 12 to 17 years; and (4) investigate potential solutions to address COVID-19 vaccine hesitancy in Canada and reduce the impact of web-based misinformation and disinformation about vaccines by reviewing gamified digital tools for enhancing vaccine acceptance and uptake.

Methods

This is a protocol for a multicomponent study that will involve several research approaches. Each objective's methodological approach is described below.

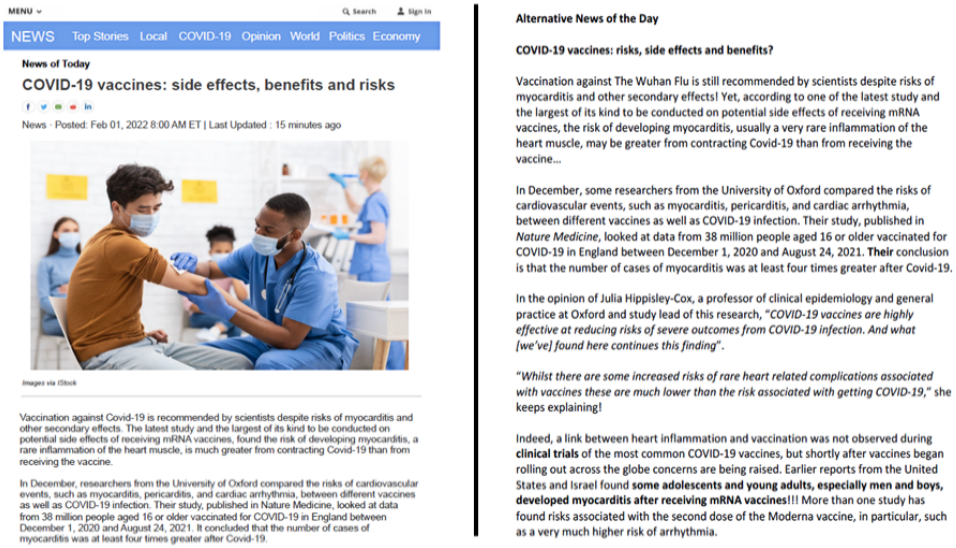
Understanding the Potential Impact of Web-Based Misinformation and Disinformation on Vaccine Acceptance and Their Characteristics

Objective 1 is concerned with the *production sphere of reinformation news*. A machine learning algorithm will be trained to identify and detect reinformation content about COVID-19. The writing styles of mainstream news articles will be assessed to determine whether the nature of neutral and objective storytelling is in line with traditional media guidelines. This will include an assessment of visual (eg, the layout of a page), linguistic (eg, the choice of words), narrative, journalistic (eg, identifying fundamental questions that every news article is supposed to answer), and structural characteristics (eg, the type of content goes in the initial, middle, or final paragraphs) [22]. The procedure for analyzing mainstream media news articles will be repeated on alternative media websites to determine their enunciative and storytelling characteristics and identify how they differ from traditional news. In addition, we are developing a corpus of real and reinformation news from more than 55,000 web-based news and reinformation articles. This corpus will be used to train algorithms to rank the quality of news articles based on their style. Objective 1 also focuses on social media that allow readers to submit comments and express their viewpoints on news articles, providing a window into audiences' reception of content in a more dialogic way. The stylistic attributes, semantic attributes, and meta-attributes of the messages will be identified via a machine learning algorithm to study the course of conversations following news about COVID-19 vaccines. These attributes will then be used to define classes of messages (eg, comments, jokes, questions, answers, and attacks). We will also train a hidden Markov model on social media conversations to discover their flows and impacts on readership and identify critical messages that may affect a conversation in different ways.

Objective 2 focuses explicitly on *audiences of reinformation*. The aim is to better understand how readers perceive information about COVID-19 based on the writing style in which such content is conveyed. In an infodemic context where the quality of information available about the COVID-19 pandemic varies across media, the enunciation of discourse may have a negative effect on readers' attitudes toward vaccination against COVID-19. Accordingly, one strategy behind reinformation and disinformation is to mimic traditional media writing styles while rejecting traditional media [23]. However, there is evidence that readers who perceive information as tentative often rate such information as less credible [24]. Using the Qualtrics panel system (Qualtrics International Inc), we will conduct a web-based survey (n=500) to distinguish the effect of ideologically biased material from that of journalistic style–based material. In collaboration with a journalist from a major Canadian Anglophone newspaper, we developed a news article on the potential side effects of vaccination against COVID-19. The news article that we developed will serve as a basis for comparing different styles (ie, journalistic style–based material vs ideologically biased material) and visual layouts (ie, journalistic layout with colored graphs vs nonjournalistic layout) within a 2-by-2 factorial (between-group) design (Figure 1).

In news articles 2 (ideologically biased style and journalistic layout) and 4 (ideologically biased style without a journalistic layout), the original text from a media story was edited to match modalities that bias the style of text [25]. For example, if terms such as *Wuhan flu*, instead of *COVID-19*, are used, the ideology and attitude of the information provider is encoded and may be shared by and to readers. The use of an ideologically biased style could be one of the drivers of vaccine hesitancy.

Figure 1. Examples of news article 1 (journalistic style and journalistic layout) and news article 4 (ideologically biased style without a journalistic layout). mRNA: messenger RNA.



Exploring the Role of Web-Based Misinformation and Disinformation About COVID-19 in Parental Vaccine Hesitancy

With objective 3, we aim to gain a better understanding of the factors that result in COVID-19 vaccine hesitancy, including the potential influence of web-based content and other information sources. We will conduct semistructured interviews with an ethnically diverse sample of Canadian parents of children aged 12 to 17 years (n=50). We will focus on adolescent vaccination, as the COVID-19 vaccine uptake rate of 12- to 17-year-olds in Canada is among the lowest in the country [15]. Previous studies have also shown that parents can make vaccination decisions for their children that are different from those they make for themselves [16,26]. Although Canadian adolescents can provide consent for vaccination (the age of medical consent ranges from 14 to 16 years in some provinces, while others have not set any specific age), many studies have shown that these decisions are often aligned with parental views and values [27,28]. A better understanding of the reasons why parents hesitate to accept a full course of vaccines for their children can provide a basis for the development of public health interventions, as these parents' attitudes may be more amenable to change than the attitudes of those who are strongly opposed to vaccination for themselves and their children. The recruitment of parents will be facilitated through previous surveys by our research team, in which some participants agreed to be contacted for subsequent qualitative studies. Two pan-Canadian surveys were conducted among the general public and equity-deserving groups (ie, racialized people, newcomers, Indigenous people, and persons whose first language is not English or French) within Canada in December 2020 and in October and November 2021 [29]. We will use the results of the latest survey to identify parents who were unsure about having, or were unwilling to have, their 12- to 17-year-old children vaccinated against COVID-19 and invite them to participate in individual interviews. We will also use sociodemographic information, including gender, location, age, and education status, to ensure that we recruit a diverse sample of vaccine-hesitant parents. This purposive recruitment will allow us to explore how social location affects vaccine hesitancy. The interviews will elicit information from the parents about rationales behind COVID-19 vaccination decisions and hesitation for themselves and their adolescents, including the extent to which participants feel that web-based information has influenced their decisions about COVID-19 vaccination. The interviews will be conducted in English or French and transcribed verbatim. A thematic analysis will be performed with NVivo software (QSR International). The interviews will allow us to situate the findings for objectives 1 and 2 in the real world of local knowledge systems (vaccine stories and experiences) that are used by diverse, vaccine-hesitant parents.

Identifying Potential Web-Based Solutions to Counter Misinformation and Disinformation About Vaccines

Although it is often suggested that web-based misinformation and disinformation about vaccines negatively influence vaccine acceptance and uptake, very few web-based interventions that promote vaccination have been shown to be effective [30]. Previous reviews suggested that gamification can have positive effects on health-related behaviors and their determinants and may be a promising vehicle for inoculating the public against misinformation and disinformation, but limited data exist with regard to applying gaming interventions for vaccination [31]. With objective 4, we aim to review the existing, gamified, digital tools that have been implemented or evaluated across various populations and encourage vaccination uptake. We will conduct a scoping review and environmental scan, using relevant keywords in 9 databases and on Google. Individual interviews with experts in the field (eg, game developers and experts in gamification and health behaviors) will be conducted to complement the web-based searches and identify other tools. We will undertake a content analysis to assess the gamification elements and modalities and behavior change techniques that were used in the tools [32]. More information on this objective methodology is available on the Center for Open Science website [33]. We will triangulate this analysis with the findings of the other parts of our study to explore whether the content

and writing style of games are likely to positively influence peoples' views and attitudes toward vaccines (identified via objectives 1 and 2) and identify which of these games are aligned with the information needs and preferences of vaccine-hesitant parents (identified via objective 3).

Ethics Approval

The study was approved by the Research Ethics Committee of CHU de Québec-Université Laval. Participants' data will be stored on secure servers.

Results

As of writing this paper (September 1, 2022), data collection has been completed. The research team is performing quantitative and qualitative analyses. The dissemination of findings and conclusions through scientific papers and conference abstracts will occur in the upcoming months.

Discussion

Although the scientific consensus on the public health benefits of vaccination is unequivocal, there is no such agreement on how best to address vaccine hesitancy and combat web-based misinformation and disinformation about COVID-19 vaccines. Our study relies on an interdisciplinary team of researchers with extensive research expertise in understanding vaccine decision-making in Canada [34-37]. Our previous work has shown that technical, psychological, cultural, and societal factors can affect vaccine decision-making [34,35], and education interventions or information-based interventions for promoting vaccine acceptance can be unsuccessful if they are not grounded in the multiple ways in which knowledge is shared and heard within the communities of our increasingly interconnected world [38-40] Vaccine acceptance requires the public's trust in health care providers, public health agencies, and health systems, which play a critical role in both communicating accurate information and dispelling misinformation and disinformation. Our study will contribute to the development of tailored strategies that are tested, are informed by evidence, and take into account the complex and context-specific nature of vaccine acceptance [41,42].

This protocol presents the methods that we will apply to better understand the influence of web-based information on COVID-19 vaccine decisions. The findings of our study will contribute to a better understanding of how people use current web functionalities, how such usage influences expectations about information sources and vaccination decision-making processes, and the implications for health authorities' communication strategies [43]. As additional doses of COVID-19 vaccines are recommended, our study will identify promising solutions to address the influence of misinformation and disinformation regarding vaccines. In the current infodemic context, our study will identify tools and solutions that align with how people access and use information in their vaccination decision-making processes. Given the amount of financial and human resources that are invested in developing and diffusing communication materials about vaccination, it is critical to understand how to optimize these tools to ensure that they work as intended.

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Authors' Contributions

All authors provided substantial contributions to this paper's conception and edits, and approved the final version of the manuscript.

Conflicts of Interest

None declared.

References

1. Betsch C, Renkewitz F, Betsch T, Ulshöfer C. The influence of vaccine-critical websites on perceiving vaccination risks. J Health Psychol 2010 Apr;15(3):446-455. [doi: 10.1177/1359105309353647] [Medline: 20348365]
2. Kata A. Anti-vaccine activists, Web 2.0, and the postmodern paradigm--an overview of tactics and tropes used online by the anti-vaccination movement. Vaccine 2012 May 28;30(25):3778-3789. [doi: 10.1016/j.vaccine.2011.11.112] [Medline: 22172504]
3. World Health Organization. An ad hoc WHO technical consultation managing the COVID-19 infodemic: call for action, 7-8 April 2020. World Health Organization. 2020. URL: https://www.who.int/publications/i/item/9789240010314 [accessed 2022-03-21]
4. Pyrhönen N, Bauvois G. Conspiracies beyond fake news. Produsing reinformation on presidential elections in the transnational hybrid media system. Sociol Inq 2019 Oct 30;90(4):705-731 [FREE Full text] [doi: 10.1111/soin.12339]
5. Tagliabue F, Galassi L, Mariani P. The "Pandemic" of disinformation in COVID-19. SN Compr Clin Med 2020;2(9):1287-1289 [FREE Full text] [doi: 10.1007/s42399-020-00439-1] [Medline: 32838179]
6. Blanc C. Théories et praxis de la «réinformation»: Militantisme catholique traditionaliste et pratiques info-communicationnelles sur Internet. Laboratoire de recherche MICA. 2018. URL: https://mica.u-bordeaux-montaigne.fr/wp-content/uploads/2018/10/BLANC.C-resume-these.pdf [accessed 2022-10-05]

7. Palau-Sampio D. Pseudo-media sites, polarization, and pandemic skepticism in Spain. Front Polit Sci 2021 Jul 21;3:685295 [FREE Full text] [doi: 10.3389/fpos.2021.685295]
8. Al-Rawi A, Fakida A. The methodological challenges of studying “Fake News”. Journalism Practice 2021 Sep 23:1-20. [doi: 10.1080/17512786.2021.1981147]
9. Zielinski C. Infodemics and infodemiology: a short history, a long future. Rev Panam Salud Publica 2021 May 12;45:e40 [FREE Full text] [doi: 10.26633/RPSP.2021.40] [Medline: 33995517]
10. Wardle C, Derakhshan H. Information disorder: Toward an interdisciplinary framework for research and policymaking. Council of Europe. 2017 Sep 27. URL: https://rm.coe.int/information-disorder-toward-an-interdisciplinary-framework-for-researc/168076277c [accessed 2022-10-05]
11. Loomba S, de Figueiredo A, Piatek SJ, de Graaf K, Larson HJ. Measuring the impact of COVID-19 vaccine misinformation on vaccination intent in the UK and USA. Nat Hum Behav 2021 Mar;5(3):337-348. [doi: 10.1038/s41562-021-01056-1] [Medline: 33547453]
12. Roozenbeek J, Schneider CR, Dryhurst S, Kerr J, Freeman ALJ, Recchia G, et al. Susceptibility to misinformation about COVID-19 around the world. R Soc Open Sci 2020 Oct 14;7(10):201199 [FREE Full text] [doi: 10.1098/rsos.201199] [Medline: 33204475]
13. Ismail SJ, Tunis MC, Zhao L, Quach C. Navigating inequities: a roadmap out of the pandemic. BMJ Glob Health 2021 Jan;6(1):e004087 [FREE Full text] [doi: 10.1136/bmjgh-2020-004087] [Medline: 33479019]
14. McKinnon B, Quach C, Dubé È, Nguyen CT, Zinszer K. Social inequalities in COVID-19 vaccine acceptance and uptake for children and adolescents in Montreal, Canada. Vaccine 2021 Dec 03;39(49):7140-7145 [FREE Full text] [doi: 10.1016/j.vaccine.2021.10.077] [Medline: 34763947]
15. COVID-19 vaccination in Canada. Government of Canada. URL: https://health-infobase.canada.ca/covid-19/vaccination-coverage/ [accessed 2022-03-21]
16. Dubé E, Gagnon D, Pelletier C. COVID-19 vaccination in 5-11 years old children: Drivers of vaccine hesitancy among parents in Quebec. Hum Vaccin Immunother 2022 Dec 31;18(1):2028516 [FREE Full text] [doi: 10.1080/21645515.2022.2028516] [Medline: 35103550]
17. Humble RM, Sell H, Dubé E, MacDonald NE, Robinson J, Driedger SM, et al. Canadian parents' perceptions of COVID-19 vaccination and intention to vaccinate their children: Results from a cross-sectional national survey. Vaccine 2021 Dec 20;39(52):7669-7676 [FREE Full text] [doi: 10.1016/j.vaccine.2021.10.002] [Medline: 34688500]
18. Puri N, Coomes EA, Haghbayan H, Gunaratne K. Social media and vaccine hesitancy: new updates for the era of COVID-19 and globalized infectious diseases. Hum Vaccin Immunother 2020 Nov 01;16(11):2586-2593 [FREE Full text] [doi: 10.1080/21645515.2020.1780846] [Medline: 32693678]
19. Haase N, Schmid P, Betsch C. Impact of disease risk on the narrative bias in vaccination risk perceptions. Psychol Health 2020 Mar;35(3):346-365. [doi: 10.1080/08870446.2019.1630561] [Medline: 31480866]
20. Johnson NF, Velásquez N, Restrepo NJ, Leahy R, Gabriel N, El Oud S, et al. The online competition between pro- and anti-vaccination views. Nature 2020 Jun;582(7811):230-233. [doi: 10.1038/s41586-020-2281-1] [Medline: 32499650]
21. Lewandowsky S, Cook J, Schmid P, Holford DL, Finn A, Leask J, et al. The COVID-19 vaccine communication handbook. A practical guide for improving vaccine communication and fighting misinformation. HackMD. 2021. URL: https://sks.to/c19vax [accessed 2022-03-21]
22. Ireton C, Posetti J. Journalism, fake news and disinformation: handbook for journalism education and training. UNESCO Digital Library. 2018. URL: https://unesdoc.unesco.org/ark:/48223/pf0000265552 [accessed 2022-03-21]
23. Nygaard S. On the mainstream/alternative continuum: Mainstream media reactions to right-wing alternative news media. Digital Journalism 2021 Mar 10:1-17 [FREE Full text] [doi: 10.1080/21670811.2021.1894962]
24. Kimmerle J, Flemming D, Feinkohl I, Cress U. How laypeople understand the tentativeness of medical research news in the media: An experimental study on the perception of information about deep brain stimulation. Sci Commun 2014 Nov 12;37(2):173-189. [doi: 10.1177/1075547014556541]
25. Sarfati GE. Eléments d'analyse du discours, 3rd Edition. Paris, France: Armand Colin; 2019.
26. COVID-19 - sondages sur les attitudes et comportements des adultes québécois. Institut national de santé publique du Québec. URL: https://www.inspq.qc.ca/covid-19/sondages-attitudes-comportements-quebecois [accessed 2022-03-21]
27. Karafillakis E, Peretti-Watel P, Verger P, Chantler T, Larson H. 'I trust them because my mum trusts them': Exploring the role of trust in HPV vaccination decision-making among adolescent girls and their mothers in France. Vaccine 2022 Feb 16;40(8):1090-1097 [FREE Full text] [doi: 10.1016/j.vaccine.2022.01.028] [Medline: 35090776]
28. Perez S, Restle H, Naz A, Tatar O, Shapiro GK, Rosberger Z. Parents' involvement in the human papillomavirus vaccination decision for their sons. Sex Reprod Healthc 2017 Dec;14:33-39. [doi: 10.1016/j.srhc.2017.08.005] [Medline: 29195632]
29. Reifferscheid L, Marfo E, Assi A, Dubé E, MacDonald NE, Meyer SB, et al. COVID-19 vaccine uptake and intention during pregnancy in Canada. Can J Public Health 2022 Aug;113(4):547-558 [FREE Full text] [doi: 10.17269/s41997-022-00641-9] [Medline: 35476258]
30. Odone A, Ferrari A, Spagnoli F, Visciarelli S, Shefer A, Pasquarella C, et al. Effectiveness of interventions that apply new media to improve vaccine uptake and vaccine coverage. Hum Vaccin Immunother 2015;11(1):72-82 [FREE Full text] [doi: 10.4161/hv.34313] [Medline: 25483518]

31. Montagni I, Mabchour I, Tzourio C. Digital gamification to enhance vaccine knowledge and uptake: Scoping review. JMIR Serious Games 2020 May 18;8(2):e16983 [FREE Full text] [doi: 10.2196/16983] [Medline: 32348271]
32. Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. Ann Behav Med 2013 Aug;46(1):81-95. [doi: 10.1007/s12160-013-9486-6] [Medline: 23512568]
33. Hakim H. Gamification tool - Enviromental scan. Center for Open Science. URL: https://osf.io/nv8af [accessed 2022-03-21]
34. Dubé E, Gagnon D, Ouakki M, Bettinger JA, Guay M, Halperin S, Canadian Immunization Research Network. Understanding vaccine hesitancy in Canada: Results of a consultation study by the Canadian Immunization Research Network. PLoS One 2016 Jun 03;11(6):e0156118 [FREE Full text] [doi: 10.1371/journal.pone.0156118] [Medline: 27257809]
35. Dubé E, Gagnon D, Ouakki M, Bettinger JA, Witteman HO, MacDonald S, Canadian Immunization Research Network. Measuring vaccine acceptance among Canadian parents: A survey of the Canadian Immunization Research Network. Vaccine 2018 Jan 25;36(4):545-552. [doi: 10.1016/j.vaccine.2017.12.005] [Medline: 29233605]
36. Manca TA, Graham JE, Dubé È, Kervin M, Castillo E, Crowcroft NS, Canadian Vaccine Product Monograph Working Group. Developing product label information to support evidence-informed use of vaccines in pregnancy. Vaccine 2019 Nov 15;37(48):7138-7146 [FREE Full text] [doi: 10.1016/j.vaccine.2019.09.063] [Medline: 31594709]
37. Sell H, Assi A, Driedger SM, Dubé È, Gagneur A, Meyer SB, et al. Continuity of routine immunization programs in Canada during the COVID-19 pandemic. Vaccine 2021 Sep 15;39(39):5532-5537 [FREE Full text] [doi: 10.1016/j.vaccine.2021.08.044] [Medline: 34426028]
38. CPSTF findings for increasing vaccination. The Community Guide. URL: https://www.thecommunityguide.org/content/task-force-findings-increasing-vaccination [accessed 2022-10-05]
39. Fu LY, Bonhomme LA, Cooper SC, Joseph JG, Zimet GD. Educational interventions to increase HPV vaccination acceptance: a systematic review. Vaccine 2014 Apr 07;32(17):1901-1920 [FREE Full text] [doi: 10.1016/j.vaccine.2014.01.091] [Medline: 24530401]
40. Kaufman J, Synnot A, Ryan R, Hill S, Horey D, Willis N, et al. Face to face interventions for informing or educating parents about early childhood vaccination. Cochrane Database Syst Rev 2013 May 31(5):CD010038. [doi: 10.1002/14651858.CD010038.pub2] [Medline: 23728698]
41. Dubé E, Gagnon D, MacDonald NE, SAGE Working Group on Vaccine Hesitancy. Strategies intended to address vaccine hesitancy: Review of published reviews. Vaccine 2015 Aug 14;33(34):4191-4203 [FREE Full text] [doi: 10.1016/j.vaccine.2015.04.041] [Medline: 25896385]
42. MacDonald NE, Dube E, Comeau JL. Have vaccine hesitancy models oversimplified a complex problem to our detriment? The Adapted Royal Society of Canada vaccine uptake framework. Vaccine 2022 Jun 23;40(29):3927-3930 [FREE Full text] [doi: 10.1016/j.vaccine.2022.05.052] [Medline: 35637069]
43. van der Linden S. Misinformation: susceptibility, spread, and interventions to immunize the public. Nat Med 2022 Mar;28(3):460-467. [doi: 10.1038/s41591-022-01713-6] [Medline: 35273402]

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Protocol

Effectiveness of an Ambient Assisted Living (HomeAssist) Platform for Supporting Aging in Place of Older Adults With Frailty: Protocol for a Quasi-Experimental Study

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Abstract

Background: Ambient assisted living (AAL) technologies are viewed as a promising way to prolong aging in place, particularly when they are designed as closely as possible to the needs of the end users. However, very few evidence-based results have been provided to support its real value, notably for frail older adults who have a high risk of autonomy loss as well as entering a nursing home.

Objective: We hypothesized that the benefit from an AAL with a user-centered design is effective for aging in place for frail older adults in terms of everyday functioning (instrumental activities of daily-life scale). In addition, our secondary hypotheses are that such an AAL decreases or neutralizes the frailty process and reduces the rates of institutionalization and hospitalization and that it improves the psychosocial health of participants and their caregivers when compared with the control condition. We also assume that a large proportion of equipped participants will have a satisfactory experience and will accept a subscription to an internet connection to prolong their participation.

Methods: HomeAssist (HA) is an AAL platform offering a large set of apps for 3 main age-related need domains (activities of daily-living, safety, and social participation), relying on a basic set of entities (sensors, actuators, tablets, etc). The HA intervention involves monitoring based on assistive services to support activities related to independent living at home. The study design is quasi-experimental with a duration of 12 months, optionally extensible to 24 months. Follow-up assessments occurred at 0, 12, and 24 months. The primary outcome measures are related to everyday functioning. Secondary outcome measures include indices of frailty, cognitive functioning, and psychosocial health of the participants and their caregivers. Every 6 months, user experience and attitudes toward HA are also collected from equipped participants. Concomitantly, data on HA use will be collected. All measures of the study will be tested based on an intention-to-treat approach using a 2-tailed level of significance set at α=.05, concerning our primary and secondary efficacy outcomes.

Results: Descriptive analyses were conducted to characterize the recruited equipped participants compared with the others (excluded and refusals) on the data available at the eligibility visit, to describe the characteristics of the recruited sample at baseline, as well as those of the dropouts. Finally, recruitment at 12 months included equipped participants (n=73), matched with control participants (n=474, from pre-existing cohorts). The results of this study will be disseminated through scientific publications and conferences. This will provide a solid basis for the creation of a start-up to market the technology.

Conclusions: This trial will inform the real-life efficacy of HA in prolonging aging in place for frail older adults and yield an informed analysis of AAL use and adoption in frail older individuals.

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KEYWORDS

ambient assisted living technology; AAL; Internet-of-Things; IoT; aging and frailty; independent living; effectiveness study

Introduction

Background

Frailty is a common geriatric syndrome characterized by age-related declines in both physical and cognitive reserves, as well as physiological function, leading to increased vulnerability to adverse health outcomes (eg, [1]). According to the physical phenotype proposed by Fried et al [2], frailty refers to individuals meeting at least three of the following 5 criteria: weakness, slowness, low level of physical activity, self-reported exhaustion, and unintentional weight loss. In the community-dwelling older population, frail and prefrail individuals represent approximately 40% of people aged >65 years [3]. Frail individuals (FI) are at a higher risk of disability, hospitalization, and institutionalization [4,5] and are recognized as an optimal target population for the implementation of effective programs to prevent dependency [3] or even to reach a successful aging path [6]. As highlighted by the World Health Organization in its healthy aging concept, environments and their interactions with intrinsic capabilities play a substantial role in developing or maintaining functional abilities that enable well-being in older age [6]. In this FI population, environmental support can be a relevant approach to encourage and facilitate the instrumental activities of daily life (IADLs). In turn, this contributes to reducing or delaying functional degradation and fostering and extending aging under good conditions [7].

Assistive technologies (ATs) for activities of daily life (ADLs) refer to all technical forms of environmental support that provide an adaptation of the environment to make it more accommodating for persons with impairments [8]. Despite enthusiasm for ATs, several issues remain to be resolved. First, all the studies published so far on AT lack empirical evidence of their efficacy, mostly because of shortcomings related to study design (small sample size, irrelevant or nonstandardized measures, short follow-up duration, no control group, etc) [9,10]. Second, despite the many technological innovations available to assist older adults in their daily life [9], their silo-based nature (one technology per need) makes them challenging to integrate, as older adults require more services to assist an increasing number of ADLs because of multiple, various, and evolving task needs, particularly in the frailty context [11]. Indeed, the restricted capability to perform ADL remains extremely patient-dependent (individual and need variability) [6]. Therefore, personalized multiple intervention programs are more efficient in reducing the impact of frailty progression (cognition, autonomy, and quality of life) than the usual intervention programs [12]. A third limitation related to the silo-based approach is context awareness of assistive services that are too restricted. Hence, such services are not flexible and are delivered irrespective of the actual person's needs in a given situation, rendering them unsuitable or even obstructive for performing ADL [13]. Finally, informal and formal caregivers are important resources for community-dwelling FI, acting as *human support for ADLs* [14,15]. Thus, the assessment of ambient assisted living (AAL) benefits should integrate measures related to caregiver efficiency [16].

To advance the field of ATs, we designed a clinical trial assessing AAL-based multiservice assistance, called HomeAssist (HA), dedicated to supporting FI in their 3 main needs domains: ADL, safety, and social participation. We expected that HA use would result in better everyday functioning (main efficacy criterion: IADL scale score) compared with older adults living in the community not benefiting from HA. This paper describes the clinical trial design.

Primary and Secondary Objectives

The objectives of the HA trial will be to perform a 12-month field study for testing in real conditions the use the HA-AAL in a sample of older persons (frail or not) living alone at home and then, to assess the impact and efficacy of HA in terms of aging in place and the efficiency of the caregiving environment.

Consequently, the primary outcome will be aging in place-related measures through functional status (IADL scale measure). Secondary criteria of HA efficacy will also be studied, including institutionalization and hospitalization as well as measures of health scales (self-efficacy, quality of life, routinization, etc), general cognitive status, memory, and executive functioning. In addition, caregiver-related measures will be used to assess the impact of HA on the daily delivery of services (eg, feeling of burden assessment and psychological health of caregivers) and reassurance regarding the situation of the older person.

Therefore, we mainly hypothesize that (1) the benefit of an AAL with a user-centered design is effective for aging in place of frail older adults in terms of everyday functioning (IADL scale score). As previously observed in pilot studies [17-20], we anticipate that the intervention group will maintain or improve their IADL scale score, whereas the control group will decline significantly. In addition, our secondary hypotheses are that (2) such an AAL decreases or neutralizes the frailty process and reduces the rates of institutionalization and hospitalization and that (3) it improves the psychosocial health of participants and their caregivers when compared with the control condition. Given these assumptions, we also assume that a large proportion of participants will want to continue the study at 24 months, despite the HA subscription fees.

Methods

Overview of the HA Study

Overview of the Functions of HA Services

HA is an implementation of general principles highlighted by an ecosystemic approach of human factors applied to the context of environmental gerontology that stresses environment-aging relations and encourages the synergy of multiple disciplines

and professionals (eg, psychologists, epidemiologists, technologists, allied health professionals, community planners, and social policy makers). The common goal is the development of preventive and ameliorative interventions, targeting both individual and environmental factors to provide a better "fit" between FI and their home, thus supporting aging in place as well as good quality of life. Therefore, HA aims to provide services related primarily to promoting aging in place (independent living) and secondarily, improving the efficiency of the caregiving environment.

Accordingly, HA services support the autonomous realization of daily tasks, including social activities, which are known to be related to independent living capabilities and older adult well-being. Originally, applications support self-regulation and self-determination in helping users conform to their daily routines via sensor-based activity monitoring and assistive support (eg, activity reminders according to notification feedback from monitoring services customized according to user preferences).

The web-based HA catalog also offers applications materializing a caregiving proxy for several actions, including mutualizing the planning of care services, gathering information on older adult activities, reminding activities and appointments, and monitoring potentially unsafe activities and situations. The HA catalog and user interface designs have been primarily based on a human factor–centered approach to designing, introducing, and assessing an AAL platform among the FI.

Study Design

To test the impact and efficacy of HA, we designed a quasi-experimental study for a 12-month duration, which started in 2017, including older adults, ranging from autonomous to frail (ie, cognitive or physical frailty or both) equipped with HA, and matched controls recruited in Aquitaine territories (not equipped with HA), forming part of an existing population-based cohort on aging (The Three-City; 3C; study [21] and the aging multidisciplinary investigation [AMI] cohort [22]). Follow-up assessments for clinical outcomes (effectiveness on aging in place and caregiver burden measures) were performed at 0 (T0) and 12 months (T12).

In the HA condition, older adults and their families or formal caregivers had the option to participate in our proposed field study for an additional period of 12 months, only if they paid an HA subscription (corresponding to the cost of an internet subscription amounting to €20 or US $ 20 a month). This "paid" aspect of the study design allows for evaluation of the perceived usefulness of HA by the participants leading to its purchase and long-term adoption. Hence, follow-up assessments for equipped participants occurred at 0 and 12 months and optionally at 24 months. Follow-up assessments for user experience, attitudes, and HA use were also collected every 6 months (0, 6, and 12 months and optionally at 18 and 24 months).

Eligibility Criteria

First, the participants had to be aged ≥65 years of age or older; live alone in an independent community setting (with an equal selection in urban, semiurban, and rural locations); have a Mini-Mental State Evaluation (MMSE) score >23 [23]; be able to understand the use of applications and devices included in the HA platform; be ambulatory (either without support or with a cane or a walker); have an available, reliable formal and informal caregiver (contact frequency>4-5 hours per week); and be able to understand and sign informed consent.

In addition, they had to have prefrailty or frailty syndrome according to the Short Emergency Geriatric Assessment scale [24].

The exclusion criteria were as follows: living in an institution (nursing home), living with a partner, having an upcoming relocation project, having from dementia, having visual or hearing loss or any other conditions limiting HA use, or having ongoing serious or unstable medical conditions or any personal condition that may limit follow-up visits.

Constitution of the HA and Control Groups

For HA conditions, several recruitment methods have been used, such as advertisements in local media, interactions with home services for aging in place, and attendance at older adult associations. Analysis of the recruitment data indicated that home services specialized for older adults were the most fruitful recruitment process. These home services were equally located in rural, semirural, and urban areas. The recruitment duration was 12 months.

The best way to assess the efficacy of an AAL is to compare the individual evolution while being equipped with an AAL compared with nonequipped persons. To do so, a control group has been constituted from 2 existing epidemiological population-based cohorts on aging: the 3C study [21] and the AMI cohort [22]. Briefly, 9294 participants of the 3C study, aged ≥65, initially noninstitutionalized, were selected from the electoral rolls in 3 French cities (Bordeaux, Dijon, and Montpellier; N=2104) and included from 1999 to 2000. The AMI cohort included 1002 retired farmers, aged ≥65 years, randomly selected from the Farmer Health Insurance System and followed up since 2007. In each cohort, several follow-up examinations were performed every 2 to 3 years with visits conducted at home by trained psychologists.

The control group of this trial has been constituted from the sample of 3C participants living in the Bordeaux site, not equipped with the HA solution, and interviewed at both the 10-year and T12 follow-ups and from the AMI sample, using the baseline and T12 follow-ups. Following the HA eligibility criteria, the control group included ≥70 older persons living alone in an independent community setting. Comparisons between the 2 groups (intervention vs control) are possible because of similar assessment tools between studies regarding the primary and secondary outcomes, for IADL scale, cognitive performance, depressive symptomology, hospitalization, and institutionalization.

Description of the HA Intervention

The HA Platform

HA services are apps developed using the DiaSuiteBox technology [25], except for some services for social participation where existing apps are used (see further sections). HA is an AAL platform based on pervasive computing leveraged from

the Internet-of-Things (IoT). As a result of previous user-centered design studies [18,26-33], HA proposes many assistive apps in the 3 key domains of everyday life, as follows:

- *Daily activities*, including circadian activity monitoring (getting up from or going to bed according to sleep habits declared by the user and toilet activity), daily routine monitoring (3 meal preparations: breakfast, lunch, and dinner; getting dressed; and bathing or showering) with the option of asking the activity reminder to issue a notification when the activity is not performed in the desired time slot by the user [29,30], appointment, and event reminders using a simplified diary app, shared with the informal caregiver. Indeed, a simplified diary application has been specially developed so that both family caregivers and techno-clinicians can quickly and easily enter the activities and events and their recurrence to be recalled.
- *Home or personal safety*, including entrance monitoring (entrance door left open, daytime outings, or abnormal night outings), electric appliance alerts (fridge, stove, or coffee maker monitoring), a light path for night getting-ups, and no activity alert to the caregiver when the user does not answer.
- *Social participation*, included internet browsers, photo sharing with family, collaborative games (cards games, Scrabble, arrows and crosswords, puzzles, etc), videoconferencing (Skype), simplified mailing systems (eg, voice recording to send messages and speech synthesizers to read the messages out loud [28], simplified email information about local events, television programs, bank service, etc) [18].

Assisted by a specifically trained techno-clinician, older adults and their caregivers were asked to determine what and how activities should be assisted by selecting the appropriate assistive applications and configuring them with respect to the person's needs and preferences. The resulting set of applications provides personalized assistive support for an individual while respecting the self-determination of the older person [18]. In addition, to respond to evolving needs, our platform allows to stop or remove applications easily and to install new ones from the web-based catalog. Figure 1 represents a more typical app pack chosen by older adults and their caregivers.

Figure 1. Examples of assistive applications from our web-based catalog.

It is noteworthy that both the activity and the daily routine monitoring services are systematically deployed in each home, as they are at the heart of the HA system, while the assistive apps and caregiver alerts can be optionally selected for personalized assistance. Indeed, the situational awareness provided by a monitoring service (ie, passive user interactions) is a key property of HA for ensuring relevant assistive services by Belloum et al [33]: (1) answering queries such as "is the person asleep?" (2) recognizing ADLs; (3) automatically detecting alerting situations such as door opening during the night; and (4) identifying specific behavior changes that may indicate, for instance, a decline in health status such as changes in ADL routine or a reduction in the number of times going out of the home [29,30]. Abnormal behaviors are detected according to the classification by Tran et al [34], who have defined four types of abnormal behaviors: (1) known behavior in a deviating spatial context (eg, sleeping in the living room), (2) known behavior occurring at a deviating moment in time (eg, leaving home at an abnormal time or having dinner unusually late), (3) known behavior with an abnormal duration or occurrence (eg, sleeping until noon or going to the toilet twice as many times as before), and (4) behavior resulting in abnormal or unexpected sensor firing patterns (eg, a fall resulting in an extended period of mute sensors).

The minimal HA setup included at least a daily routine monitoring service with no activity reminder notification, 1 to 2 security applications (most often, door alerts and no daytime activity alerts), 2 to 3 social activity applications (simplified mailer, internet browser, and games), and photo sharing on the main tablet. Table 1 summarizes the main HA and its commercial apps deployed or potentially deployed in homes.

Table 1. Summary of apps included in the HomeAssist (HA) platform assistive technologies (ATs).

Tablet support and activity domain	Apps developed into the HA platform	Features		
		Home service	Installation	Type
Main tablet (I)				
Daily activity				
Circadian activity	Getting up from or going to bed	Monitoring	✓	HA
Circadian activity	Reminder	AT	Optional	HA
Continence activity	Toilet activity	Monitoring	Optional	HA
Continence activity	Reminder	AT	Optional	HA
Dressing activity	Clothing furniture's activities	Monitoring	Optional	HA
Dressing activity	Reminder	AT	Optional	HA
Bathing or showering activity	Bathroom activity	Monitoring	Optional	HA
Bathing or showering activity	Reminder	AT	Optional	HA
Meal preparations	breakfast, lunch, and dinner	Monitoring	Optional	HA
Meal preparation	Reminder	AT	Optional	HA
Daily routine	Three meal preparations and circadian activity	Monitoring	✓	HA
Daily routine	Report	AT	✓	HA
Simplified diary	Appointment and event reminders	AT	✓	HA
Safety				
Entrance door	Door left open, daytime outings, or abnormal night outings	Monitoring	✓	HA
Entrance door	Reminder or alert	AT	✓	HA
Electric appliances	Fridge, stove, or coffee maker (end user: frail individual)	Monitoring	✓	HA
Appliance	Reminder or alert	AT	✓	HA
Light path	Night getting-ups	AT	Optional	HA
No-activity alert	No daytime activity from any sensor (end user: frail individual or also caregiver)	AT	✓	HA
Social participation				
Photo sharing	With family or automatic pushing according to person's interests	AT	✓	HA
Email notification	New received email	AT	✓	HA
Secondary tablet (II): social participation				
Internet	Internet browser (Google)	AT	Optional	Commercial app
Asynchronous communication	Simplified email (relatives and local public services for leisure and social activities)	AT	✓	HA
Synchronous communication	Video conferencing (Skype) and social network (Facebook)	AT	Optional	Commercial app
Financial or administrative activities	Bank and government apps (regular administrative procedures, incomes taxes, etc); collaborative and non-collaborative games (cards games, Scrabble, arrows and crosswords, puzzles, etc); video player (YouTube); television programs	AT	Optional	Commercial app

Sensors and Actuators

Technically, monitoring and assistive applications rely on the infrastructure of the devices and web services deployed at the home of each user. The HA platform relies on a set of sensors and actuators, as well as 2 touch screen tablets (Figure 2). Indeed, several entities are required for running HA services: (1) wireless sensors (motion and contact sensors and smart electric switches) and 2 tablets and (2) software services (agenda, address book, mail agent, and photo agent). Three types of sensors were used in our platform: contact sensors that enable detection when a door or drawer is opened or closed,

electric meters that sense the electric consumption of electric appliances and enable them to remotely turn it on or off, and motion sensors that collect timed information when motion is detected in their sensing range. These sensors were chosen because they are small, wireless, and cheap, and they respect users' privacy.

Sensors are placed in strategic locations: kitchen, bedroom, bathroom, toilet, and near the entrance. Figure 3 shows a typical HA kit that is deployed.

Figure 2. Content of HomeAssist platform—a set of sensors, a web-based catalog of assistive applications, and two touch screen tablets (main and secondary). ADL: activities of daily life.

Figure 3. Typical HomeAssist (HA) kit deployed, with apartment layout with sensors (left) and the HA sensors and their locations and functions (right).

Room	Sensor ID	Function
Kitchen	EMeter_Coffeemaker	Coffee maker in use
	EMeter_Microwave	Microwave in use
	ContactS_Cupboard	Cabinet door open
	ContactS_Fridge	Fridge door open
	MotionD_K	Kitchen presence
Entrance	ContactS_E	Door open
	MotionD_E	Entrance presence
Bedroom	EMeter_L	Bedside lamp in use
	MotionD_B	Bedroom presence
Bathroom	MotionD_Ba	Bathroom presence
	MotionD_S	Shower/Bathtub presence
Toilet	MotionD_T	Toilet presence
Living room	MotionD_L	Living room presence

Two Touch Screen Tablets

Regarding active user interactions, users interacted with the platform via 2 similar touch screen tablets operating under Android OS, which we configured following the guidelines for older population (eg, International Standardization Organization/TR 22,411 [35]; Accessibility World Wide Web Consortium [36,37]) and prior user testing relative to objective and subjective measures of usability, use learning, and self-reported user experience [18,28,31,32]. Importantly, HA services revolve around a unifying and simplified interface suitable for older adults [31]. Having 2 tablets allows the person to associate each tablet with a type of service (assistive apps for daily activities and safety on the main tablet vs social activity apps on the secondary tablet). In addition, this approach also brings two levels of security: (1) assistive services guarantee for users—the main tablet remains stationary and always under electric power ensuring the nominal delivery of the notifications, while the secondary tablet is used freely in the space, and if it

turns off in case of empty batteries, it does not have critical consequences for the person and (2) HA service reliability—all the apps on the main tablet are specially developed into the HA platform, where we controlled the security process of the data collected while the secondary tablet included commercial apps for which it is not possible to have a fully secure control.

For the main tablet where the assistance notifications are displayed, the notification system exploits the preference of older adults for simple interactions and optimizes their cognitive resources using multimodal coding of notifications (tones, shapes, colors, and text). All assistive applications are required to interact with the user via either a critical or noncritical notification, depending on the risk level of the situation. Each type of notification uses a specific multimodal coding, as illustrated in Figures 4A and 4B, displaying a critical and noncritical notification, respectively. This approach makes it easier to discriminate among the notification types. Furthermore, the user follows a dedicated procedure for each notification type. Critical notifications (Figure 4A) use a loud volume and only disappear when the situation is resolved; they can contact a caregiver via an SMS text message after a predefined period to seek help. By contrast, noncritical notifications (Figure 4B) use a soft tone; they disappear after being displayed for a set period and are added to a list of unattended (noncritical) notifications. An example of such a list is shown in Figure 4C. This mechanism allows the user to disregard a notification if it occurs while performing another task. If the condition that raises a noncritical notification does not hold (eg, the door of the fridge is closed), then this notification is suppressed from the list of unattended notifications. To respect user self-determination [18], the notification system can be deactivated by the users themselves for a predefined period, for example, when someone visits the user, as depicted in Figure 4D. When no notification is delivered, the main tablet turns into a photo display shared with the person's relatives, allowing discreet and nonstigmatizing assistance.

The secondary tablet provides social participation services (except for the photo-sharing app). A simplified application launcher was developed to make it easier to use these services (Figure 5). This launcher displays applications as a page listing 3 applications. A simple click on the icon of the application opens it. A total of 5 pages can be created, and the user navigates from page to page with a simple gesture of the finger, mimicking leafing through a book. The launcher updates itself as it is used and lists the applications on the pages according to their use frequency so that the user finds the applications that are used most often more quickly.

A video presentation of the HA is available to provide a concrete idea of the HA platform [38].

Figure 4. Critical notification (A), noncritical notification (B), list of unattended notifications (C), and pause feature of the notification system (D).

Figure 5. Secondary tablet with its simplified app launcher.

Protocol and Time Line Procedure

For each participant, several visits were planned: 1 for eligibility, 2 for personalized installation of HA services, 4 to 6 for training, and 1 to 2 for each follow-up.

Eligibility and Baseline Assessment

Eligibility criteria were screened in 2 steps. First, the participants who were interested in participating contacted the study coordinator, who screened the first eligibility criteria (age, independent home, living arrangements, and geographic area of residence). Then, an eligibility visit was conducted at the participant's home with a techno-clinician to apply all the eligibility criteria (cognitive and functional status, frailty level, etc) and the procedure for obtaining informed consent. For this eligibility visit, the person was advised to be accompanied by a person of trust or by a close person who frequently assists them (family, neighbor, friend, etc). The presence of a relative had a 3-fold objective: to reassure the older person; to help the older person, if necessary, to make their decision to participate in the study; and finally, to invite this relative to participate. A period of 7 days of reflection was given to each pair of participants to formulate their own decisions. When the eligibility visit was successful, the other visits were scheduled.

HA Service Selection

First, the techno-clinician carried out the steps to subscribe to the internet for each participant. The costs of this subscription were covered by the research program, and the participant had nothing to pay for 12 months, but its renewal for another 12 months was at the participant's expense if they wanted to continue the experiment.

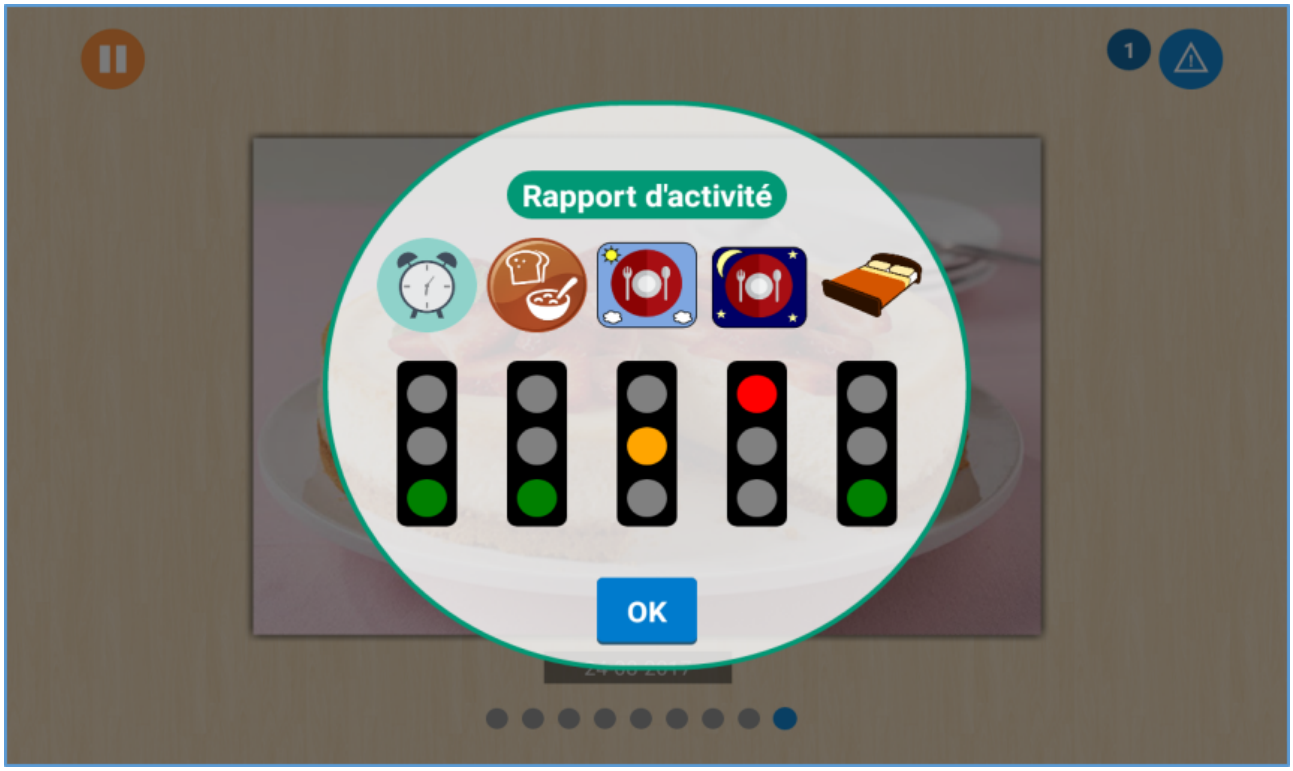
The clinician's goal was to make explicit and record older adults' everyday routines, desired assistive services, and preferences, notably in terms of both critical and noncritical notifications and notification sharing with a caregiver. The presence of a caregiver (family, friend, or home care professional) was greatly advised, both to reduce older adult's stress and to help the older adult declare their preferences.

The choice of assistive services was based on a needs questionnaire, in which each need was associated with a pictorial description of the corresponding HA service. The questionnaire was divided into 2 parts.

The first part assessed the needs in terms of daily routine, everyday activities, and safety, for which assistive services are provided on the main tablet.

For daily routine, 4 types of activities were systematically monitored (getting up and going to bed, the 3 meal activities, bathing activities, and dressing activities), the performance of which was monitored every day, and an assessment was reported to the person in a pictorial way, where each activity was evaluated in the form of traffic lights (green: 80% of the activity has been performed; orange: 50%-79% of the activity has been performed; red: <50% of the expected activity has been performed; Figure 6). Each participant can then choose to have a reminder of each of their routine activities on the main tablet and send the daily activity report to the caregiver of their choice.

Figure 6. Example of a daily routine report provided to the user on the main tablet.



Moreover, reminder services (simplified diary application) were dedicated to medication intake or reminders of any activities (medical appointments, hairdresser appointments, leisure activities, etc) or events (relatives' birthdays, a television show, local social events, etc).

For safety, several notification services are offered: monitoring household appliances, the unintentional opening of the front door or fridge, abnormal absence of activities in the home during the day, and repeated nighttime getting-ups. In addition, a service for activating a light path during nighttime rise is offered. For each notification or reminder-based service, the participants decided whether the notification was critical. If the notification had a critical status, the participant could choose whether the notification was sent via SMS text message to the phone of their informal caregiver. The first part of the questionnaire ended with the participant's choice of photos displayed on the main tablet and the schedule of their updates. To do this, the participant indicated which relatives could send photos, and if no relatives were present, the participant indicated their interests, from which photos were extracted from free photo libraries.

The second part of the questionnaire referred to services dedicated to social participation activities provided by the secondary tablets. These services include internet browsers, communication applications (videoconferencing or a simplified mailer), and various applications such as television program guides, simple games (card games, puzzles, crossword puzzles, etc) and interactive ones (scrabble, card games, etc), shopping services (food, clothing, etc), and banking or public services applications (income tax, social assistance, etc). Overall, each HA service setup was personalized. The minimal setup included at least a daily routine monitoring service with no activity reminder notification, 1 to 2 security applications (most often, door alerts and no daytime activity alerts), 2 to 3 social activity applications (simplified mailer, internet browser, and games), and photo sharing on the main tablet.

The questionnaire-based service selection could be updated every 6 weeks during the home visit by the techno-clinician.

HA Installation

When the services were chosen, the second home visit was organized with a home automation technician to install the HA platform in the participant's home and test whether the platform was working properly. Each participant's home in the HA condition was equipped with an HA kit, including sensors, actuators, and 2 tablets, as described previously. All participants also had a stylus available to interact with the tablets as needed (according to our pilot study, some very old participants had fingertips that did not allow effective interaction with the tablet). From a technical point of view, the necessary steps included setting and personalizing the assistive apps (eg, filling the calendar or adding family contacts) and testing the platform. Simultaneously, the techno-clinician initiated the training phase.

Training and Practice of HA Services

Again, the presence of a caregiver was advised to learn from the techno-clinician and later to offer support on technical issues. The training phase for using the HA services was gradual. During the training phase, the techno-clinician introduced the different features of the platform on a step-by-step basis during 4 monthly sessions of 75 minutes based on concrete scenario use. This instructional strategy was successfully used in other studies (eg, [38]). The use of services offered by the main tablet (daily activities and safety-related services) was first targeted. Essentially, simulations of assistance scenarios lasting 10 minutes placed the participant in a situation of active interaction with the notification (critical vs noncritical) and pause features

of HA [18,29]. The techno-clinician was provided with a scale to evaluate the quality of the response (time taken and number of errors, omissions, and commissions), and if this was unsatisfactory, the simulations were repeated. A maximum of 3 repetitions was sufficient to obtain and understand the appropriate interactions from the participants. The techno-clinician left a pictorial user manual of the services, especially designed for the participants, on which a dedicated space allowed the participant to write comments and difficulties encountered with the services provided by the main tablet. During the first training phase, only the main tablet support services chosen by the participants were active. A week later, a third visit was arranged by the techno-clinician who checked the user manual to see if any difficulties had been encountered with HA. If so, the first phase of training was repeated. If this was not the case, the second phase of training began, which focused on the use of social participation services on a secondary tablet. Here again, scenario simulations were proposed in the spirit of the first training phase, aiming at the proper use of the application launcher, the opening of an application, and its use. This second phase lasted longer, 20 to 30 minutes, because for the email and videoconference applications, the techno-clinician entered the person's desired contacts and carried out numerous tests with them. For services from the main tablet, a picture-based user manual for the secondary tablet was provided to each participant (a usability expert initially designed both user manuals). At present, all the social participation services on the secondary tablet were active. At the fourth visit, the techno-clinician checked to see if the person had difficulty with the secondary tablet. As the interfaces of the selected applications (especially the applications not designed by us, eg, game) had very heterogeneous designs; often the second training phase had to be replayed during this fourth visit. When this was not the case, the third phase of training was initiated. This phase always consisted of simulated use scenarios but mixed the services of the main tablet with those of the secondary tablet. If the participant's interactions with the platform were appropriate, the training ended. Otherwise, the fifth visit was scheduled. Hence, HA training took a minimum of 4 sessions (1 per week) and a maximum of 6 sessions.

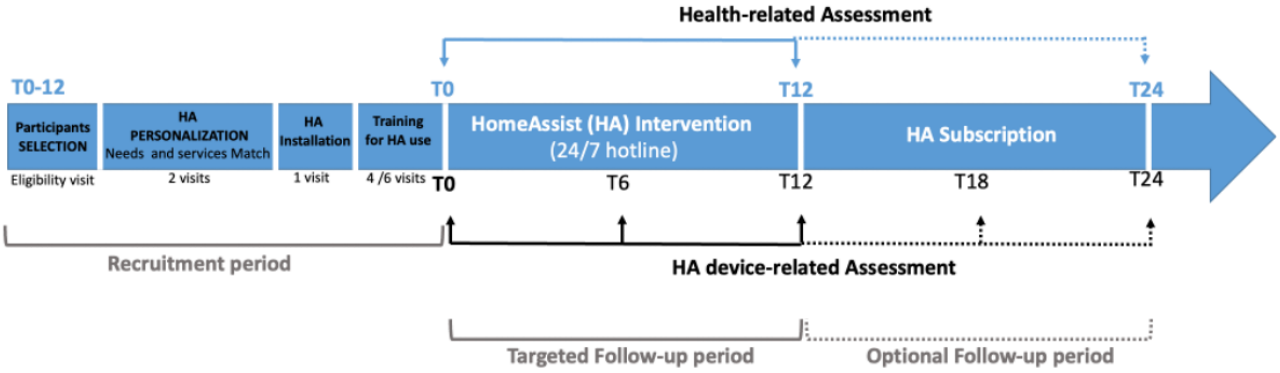
A Support Hotline

Throughout the training and study duration, a 24/7 support hotline was available to all participants. Thus, problems were solved remotely, but some required personal visits for issues such as changing sensor batteries, the loss of internet connection, and the participants' incorrect use of the tablet, leading to malfunctions. In all cases, participants received a "check-in" call at 1 week, 1 month, 6 months, 12 months, 18 months, and 24 months.

Assessment of the HA Intervention

The assessment is divided into 2 parts: health (Multimedia Appendix 1 [22,38-59]) and HA device (Multimedia Appendix 2 [17,18,60-73]) parts (Figure 7).

Figure 7. Time line of recruitment and follow-up for the HomeAssist (HA) condition.



Health-Related Part of the Assessment

Initially, the participants completed a *screening questionnaire* that assessed their basic demographic information and living home conditions. These measures will serve as potential moderating variables in our analyses.

They also completed the efficacy follow-up battery, including independent living capabilities, frailty-related ratings, and self-perceived health for the participant and the informal caregiver. The primary outcome measures for the trial include changes at 12 months (and optionally at 24 months) in everyday functioning (self-perceived and perceived by informal caregivers measured using the IADL scale [39]). The other measures were the secondary outcomes.

This health-related assessment is already part of the 3C and AMI cohorts, from which the control group is formed.

HA Device Part of the Assessment

An additional set of measures is provided to the participants equipped with the HA system. This additional assessment aims to study across time (at 0, 6, 12 months, and optionally at 18 and 24 months) the user's HA needs, the user's HA perception, the HA uses and usages, and their possible relationships and the evolution over time. HA uses and usages are assessed through active interactions with the HA platform to which passive interactions are added, particularly the monitoring of activity in the home via motion sensors or door or drawer contactors. These latter measures are called HA-related measures.

Treatment Fidelity and Data Collection

For the HA condition, an external trial monitoring board has been specifically set up and met once a year or as needed. It

included 12 members gathering multiple expertise (gerontology and geriatrics, clinical trials for behavioral interventions, home services, public services for older adults, user-centered gerontechnology, IoT and software orchestration, epidemiology and statistics, and innovation transfer). This board provided trial oversight and monitored participant safety and well-being for the entire trial duration.

A detailed manual of operations has been developed for all study protocols, and HA-related implementation and training protocols have been scripted. All study activities are discussed at weekly HA coordinating team meetings with the project coordinators, the data management team, and technical staff around issues related to data collection, transfer, or HA technology.

Statistical Treatments

Descriptive analyses were conducted to characterize the recruited HA sample compared with the others (excluded and refusals) on the data available at the eligibility visit and to describe the characteristics of the recruited sample at baseline as well as those of the dropouts. We also performed group comparisons to obtain a baseline description of the HA and control groups for the primary and secondary outcomes.

To test our main and secondary hypotheses, all measures of the study will be tested based on an intention-to-treat approach using a 2-tailed level of significance set at α=.05. The quasi-experimental study design will allow the comparison of primary and secondary efficacy outcomes in HA and control conditions. The 12-month follow-up data being not available for the control sample, imputations will be performed according to a linear hypothesis of the evolution of the scores between T0 and T24. For each outcome, we will compare the mean score at T12 between the HA and control groups. In addition, to control for confounders, three successive linear regression models will be used: (1) Model 1: $Y_{(at\ T12)}$ = DomAssist (vs control) + age + Sex, (2) Model 2: $Y_{(at\ T12)}$ = Model 1 + dependent variable at T0 ($Y_{(à\ T0)}$), and (3) Model 3: $Y_{(at\ T12)}$ = Model 2 + MMSE T0.

Finally, we will also describe the evolution of the primary and secondary efficacy outcomes over 12 months of HA use and conduct comparisons by age, gender, initial level of technology acceptance, and user satisfaction with HA technology (collected after 6 months of use).

Ethics Approval

For the HA condition, the French Southwest and Overseas Protection of Persons Committee deemed the study to be outside the scope of the provisions governing biomedical research and routine care (DC 2015/2066). The study protocol was also approved by the National Commission of Informatics and Liberty (Comission Nationale Informatique & Libertés-French name) and the Ethics COERLE (Comité Operationel d'Evaluation des Risques Légaux et Ethiques) committee of the French National Institute of Informatics and Mathematics (Inria), as protecting participants and data accordingly. For the control group from the 2 cohorts, an ethics committee approved the research according to the principles embodied in the Declaration of Helsinki: for 3C, the Ethical Committee of the University Hospital of Kremlin-Bicêtre (Paris, France) and Sud-Méditerranée 3 (Nîmes, France) and for AMI, the committee of the University Hospital of Bordeaux (France). All the participants provided written informed consent.

Results

The HA project is funded for a 5-year period (2016-2021), and the full HA intervention (24 months) was completed in 2020 before the COVID-19 crisis.

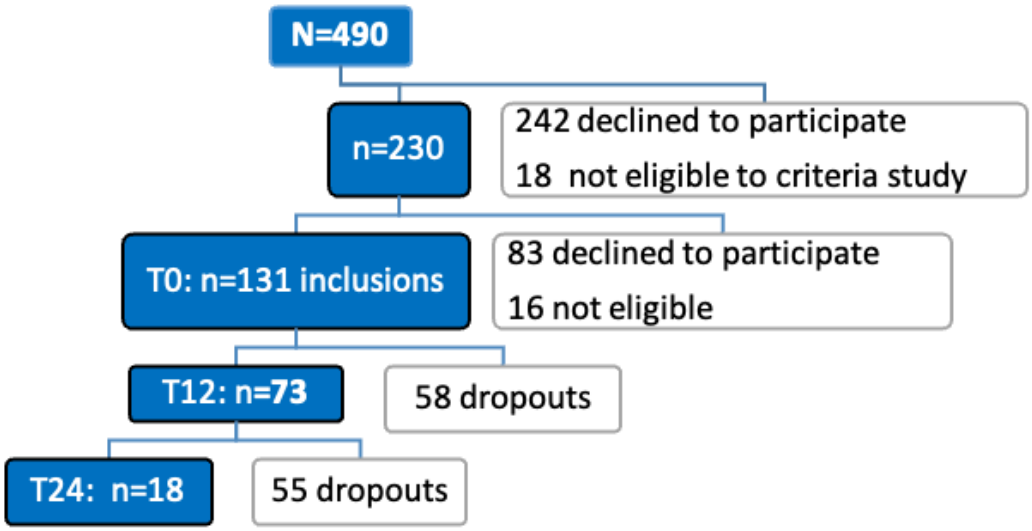
Participants Recruitment

As indicated in Figure 5, a total of 490 individuals received a prescreening visit for the HA condition. Of these 490 individuals, 260 (53%) were excluded because of ineligibility (n=18) or a lack of interest in participating (n=242). A total of 230 older adults underwent the baseline assessment, of which 99 (43%) were excluded (16 ineligible; 83 refusals). Finally, 56.9% (131/230) of individuals were enrolled: more than half of the participants completed the 12-month follow-up (73/131, 55.7%), from whom one-third of participants (24/73, 33%) were requested to continue the experiment for 6 additional months (18 months), and 18 participants were enrolled for 12 additional months (24 months). Figure 8 illustrates the recruitment flowchart for the 24-month duration of the HA condition.

The HA sample (n=131) at T0 is primarily female (114/131, 87%) and ranges in age from 70 to 93 (mean 81.9, SD 6.0) years. The participants enrolled in the HA condition have varied living spaces: 35.1% (46/131) individuals in rural areas, 27.4% (36/131) in semirural areas, and 37.4% (49/131) in urban areas. Of the 131 participants, 63 (48.1%) do not have a senior high school degree, and 57 (43.5%) do not have a junior high school degree. The MMSE scores range from 23 to 30 (mean 25.9, SD 2.4).

Of the 131 participants, 58 (44.3%) dropped out before T12. Compared with T12 completers (73/131, 55.7%), these individuals were slightly older (26/58, 47% were over 85 years vs 16/58, 22% of T12 completers; *P*=.004) and less educated (mean 8.2, SD 3.2 vs mean 9.8, SD 2.3; *P*=.005), while no significant difference was observed in gender (*P*=.80), living environment (*P*=.26), frailty-Short Emergency Geriatric Assessment score (*P*=.10), and MMSE score (*P*=.18).

Figure 8. Recruitment diagram for HomeAssist condition.



Baseline Description of HA and Control Group

From the 3C and AMI cohorts, 474 control participants were selected according to the eligibility criteria (Figure 9).

When comparing baseline characteristics between the HA sample and the control group, we observed no differences in terms of age, education, living condition (all living alone), IADL disability, depressive symptoms, and cognition. For the MMSE test, the control group tended to have a higher mean score, but this difference was not significant (*P*=.08). However, as indicated in Table 2, participants in the HA condition were more often women (63/75, 88% vs 372/474, 78.4%; *P*=.054).

Regarding our 2 primary outcomes, the sample size provides a reliable statistical power of 0.80 with a significance level set at .05, attesting to a significant difference in means of the IADL scale score between the 2 groups for a difference >0.87 units.

Figure 9. Flow of the study. 3C: Three-City; AMI: aging multidisciplinary investigation.

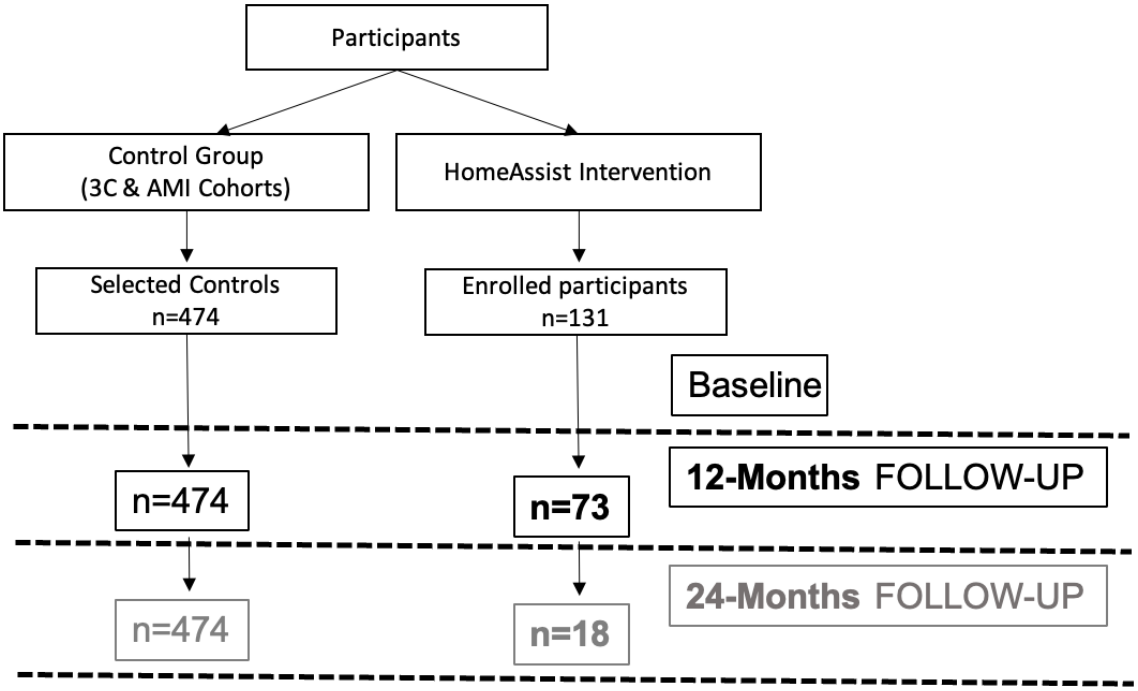


Table 2. Sample description and group comparisons for baseline measures of primary and secondary outcomes.

	HA[a] (n=73)		Control (n=474)		*P* value
	Sample size (n)	Value	Sample size (n)	Value	
Age (years), mean (SD)	73	81.2 (5.1)	474	81.3 (4.3)	.84
Age (≥80 years), n (%)	73	43 (58.9)	474	303 (63.4)	.46
Sex (female), n (%)	73	64 (87.7)	474	372 (77.8)	.05
Lower level of education, n (%)	62	27 (43.5)	474	229 (48.3)	.48
Living alone, n (%)	73	73 (100)	474	474 (100)	—[b]
IADL[c] disability, n (%)	67	21 (31.3)	473	137 (29)	.68
IADL score, mean (SD)	64	6.4 (2.2)	473	6.4 (2.5)	.92
CESD[d] score, mean (SD)	73	10.0 (6.7)	427	9.1 (8.9)	.38
MMSE[e] score, mean (SD)	66	26.0 (2.4)	474	26.6 (2.6)	.08
Benton score, mean (SD)[f]	68	10.8 (2.2)	318	11.2 (2.3)	.12
Isaac[g] 15-s score, mean (SD)	72	26.3 (6.1)	459	26.2 (6.4)	.94
Isaac 30-s score, mean (SD)	72	40.6 (8.5)	459	40.1 (10.4)	.68

[a]HA: HomeAssist.

[b]Not available.

[c]IADL: instrumental activities of daily life.

[d]CESD: Center for Epidemiologic Studies—Depression Scale [41].

[e]MMSE: Mini-Mental State Evaluation.

[f]Benton test [40] was not available for the aging multidisciplinary investigation cohort.

[g]Isaac fluency test [74] (see Multimedia Appendix 1 for details).

Discussion

Principal Findings

The HA project proposes an ecosystemic human-centered approach for introducing a personalized AAL platform dedicated to FI and their caregivers. Hence, our main outcome is to observe the benefit of our HA approach on this capability (improvement or nondeterioration) due to IADL follow-ups performed at 0 and 12 months. Our secondary expectation is to observe a positive effect of HA intervention for prolonging aging in place of FI living alone through improved cognitive and mental health, leading to reduced institutionalization and hospitalization. We also anticipate a positive effect on caregivers' health. In addition, owing to the personalization of HA services and their user-centered design, we also expect that equipped persons will have a positive user experience on pragmatic criteria (perceived usability, usefulness, ease of use, learnability, etc) and hedonic criteria (pleasure, satisfaction, perceived attractiveness, etc). These expectations are directly based on our previous pilot study involving 17 HA-equipped FI compared with 17 nonequipped FI to assess the feasibility of the HA concept and collect preliminary results regarding its acceptance and elicited user experience. The results showed that HA was well adopted (highly accepted and usable) by FI and their families or caregivers [18]. Moreover, after 6 and 9 months of follow-up, the benefits of measures of self-determination behaviors and IADL scale scores [9,19] were higher in equipped FI [18-20]. For instance, with normalized scores, at 9 months, the equipped group did not change its IADL scale score, whereas the control group lost 1 SD. In addition, the objective burden of caregivers to support care receivers' ADL increased in the control group after the follow-up period, while it did not increase in the equipped group, even though the subjective burden remained unchanged [19,20].

Comparison With Previous Work

A total of 131 users and their families or formal caregivers participated in our proposed field study, and 73 accepted to continue the experience until 12 months. Such a clinical validation study is rare in the field of AAL-based interventions in terms of experimental design quality. Indeed, most studies in the AAL field remain at the prototype level (because of technological and usability or acceptability challenges) or at best pilot studies (because of the challenges of a field study) with small samples that do not provide the onset of the ground truth of AAL-based interventions [75].

Technological barriers include issues related to the deployment of the technologies, such as inaccurate sensors; battery power or bandwidth reliability issues, restricting users within the monitoring area; and lack of interoperability [76]. The lack of user-centered design approaches in AAL development also contributes to the low usability observed in some instances because of very limited experience for older adults in using advanced technologies [77,78], and even more for FI with physical or cognitive exhaustion leading to a lack of motivation to accept actively interacting with such technologies [79]. Taken

together, these barriers have led field studies with large sample sizes to adopt a silo approach offering specialized services in one domain of need for older adults. For instance, the Personal Reminder Information and Social Management system only provides services for communication and leisure [80], and the platforms designed by Rantz et al [81] and Tomita et al [17] focus on activity monitoring. In addition, the efficacy of such specialized AAL is always estimated by a focus on older adults, without involving an impact evaluation of caregivers' well-being. However, as highlighted by Fadrique et al [76], AAL benefits must be measured for the social care environment while protecting (near and far stakeholders) against risks in privacy and security related to data sharing in the AAL scope.

Therefore, multidomain AAL is still only in the design phase, as recently proposed with the next system study protocol [82].

Strengths and Limitations

The HA platform has already completed all the design, user testing, and pilot study phases to reach the empirical evidence step based on this study. Furthermore, our field study includes evaluations that cover other critical indicators for home care more broadly, such as the rate of institutionalization in nursing homes, the impact on mental and physical health, and data reported by HA (actimetrics, use, and use of services). For the equipped group, we gathered data on the factors that influence usability, technology acceptance, and use. These multiple secondary indicators aim to respond to the needs expressed by all the project's stakeholders (aging policy makers, home service organizations, caregivers, older adults, and researchers from different domains) for successful participatory achievements while also moving on to more daring, innovative plans; for example, new research areas such as the study of relationships between AAL acceptance and AAL effectiveness for aging in place. In addition, the field and participatory nature of this study imply combining a traditional top-down approach (ie, expectation relative to specific primary criteria for a prescriptive purpose) with a bottom-up approach definitively driven by the field expertise of the main stakeholders of aging in place. The growth of citizen science supports that this combined approach (albeit risky) is a successful way to bridge science and practices with the result of rapid societal impact for targeted people and for emerging new research issues [83].

From our combined approaches, the study consortium encountered a few issues that reinforced study-related challenges, especially with older adults and with technology-based intervention. First, major challenges are related to the quasi-experimental study design, where the HA condition is compared with the control condition of a subsample of an existing population-based cohort on aging. We paid great attention to matching as well as possible the 2 groups with respect of the factors known to influence the IADL scale score (main criteria outcome). These factors include demographic factors, frailty scores, and cognitive status. Nonetheless, we are aware that such a matching method does not neutralize possible biases related to differences in recruitment methods, the number of home visits on 1-year deployment, or the minimal level of technology acceptance that is probably shared by the participants in the HA condition. It should be remembered that out of almost 500 older adults contacted, only 46.9% (230/490) met our selection criteria, and only 26.7% (131/490) agreed to participate in the study. Half of the participants dropped out after 12 months of experimentation, notably regarding technology-related challenges.

A second challenge is a great variability in participants' technological skills in the HA condition. As recommended [84,85], we set up a standardized training phase for the use of HA, and each participant was guaranteed to keep the 2 tablets provided for the study after the experiment to boost their interest in such technology training. In addition, the interoperability of HA with a variety of technologies (Bluetooth, UPnP, ZWave, Web services, etc) and its unique point of user interaction are major assets for ensuring the acceptance of HA at the organizational level (bypassing the technical disparities across territories) and the individual level (reducing the demand on cognitive or learning resources for using assistive services).

Another study challenge is to provide 24/7 technology interventions requiring reliable internet access and good-quality bandwidth in areas offering disparate digital infrastructure. Technologically, any elaborate assistance service is based on the internet, and it is impossible to guarantee its continuous operation. To minimize service interruptions, we ensured the use of a single internet operator to avoid multiple service interruptions owing to operator-dependent updates. Covering a wide spectrum of needs and their evolution relies critically on the ability to populate the HA service catalog with a range of applications that match these needs. To do so, the HA leverages a dedicated integrated development environment while relying on needs analysis and human-centered design. This strategy is of paramount importance to ensure that the proposed assistive support is personalized to fulfill the needs of the participants and caregivers.

Despite these challenges, the outcomes of the HA study will yield significant insights into the benefits of AAL in frail older adults. It will also yield some insights into the factors influencing technology acceptance and use in FI. Indeed, it will be possible to explore how they vary according to participant characteristics, such as gender, age, cognitive abilities, and frailty level. The study will also inform the feasibility of technology-based personalization of multidomain assistive services and will probably teach some useful lessons for future technology-based field studies.

Dissemination Plan

The results of this study will be disseminated through scientific publications and conferences. In addition, as we previously included in the HA design phases, the decision makers of the French public policy of assistance to the autonomy of older adults ensured that the solution is financially sustainable (<€ or US $1200 per home) by the public services so that a gain of only 1 month of aging in place produced by HA is more profitable than the monthly cost of a nursing home (>€ or US $1800 in France). This will provide a solid foundation for a business model when there is a start-up to market the technology.

Conclusions and Future Directions

Although further research is needed, the findings of the HA project will provide the very first evidence-based study in IoT-based AAL in-home environments involving user-centered design for frail and nonfrail older adults.

To move forward with evidence robustness, it will be necessary to go further and consider conducting a trial using strict randomized controlled trial methods. Similarly, there is the question of scaling up for large-scale intervention. As also mentioned, our ecosystemic and participatory approach has led us to work directly with the key stakeholders in frailty and home care for older adults in each territory, to both design an upstream HA and evaluate it downstream. Consequently, scaling up other territories for the evaluation of HA will be required thereafter for better proof of the interest of an AAL system such as HA.

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Authors' Contributions

HA was involved in the conceptualization, methodology, validation, investigation, data curation, and paper writing. AE was involved in the formal analysis, data curation, and paper writing. CC was involved in software development, acquiring resources, project administration, and funding acquisition. KP was involved in the conceptualization, methodology, formal analysis, data curation, and paper writing. HS was involved in the conceptualization, methodology, validation, investigation, resources, data curation, supervision, project administration, funding acquisition, and paper writing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Health-related part of the assessment.
[DOCX File , 22 KB - resprot_v11i10e33351_app1.docx]

Multimedia Appendix 2
HomeAssist device part of the assessment.
[DOCX File , 24 KB - resprot_v11i10e33351_app2.docx]

References

1. Aguilar-Navarro S, Gutiérrez-Robledo LM, García-Lara JM, Payette H, Amieva H, Avila-Funes JA. The phenotype of frailty predicts disability and mortality among mexican community-dwelling elderly. J Frailty Aging 2012;1(3):111-117. [doi: 10.14283/jfa.2012.18] [Medline: 27093198]
2. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. J Gerontol A Biol Sci Med Sci 2004 Mar 01;59(3):255-263. [doi: 10.1093/gerona/59.3.m255] [Medline: 15031310]
3. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013 Mar;381(9868):752-762. [doi: 10.1016/S0140-6736(12)62167-9]
4. Avila-Funes JA, Helmer C, Amieva H, Barberger-Gateau P, Le Goff M, Ritchie K, et al. Frailty among community-dwelling elderly people in France: the three-city study. J Gerontol A Biol Sci Med Sci 2008 Oct 01;63(10):1089-1096 [FREE Full text] [doi: 10.1093/gerona/63.10.1089] [Medline: 18948560]
5. Cesari M, Gambassi G, van Kan GA, Vellas B. The frailty phenotype and the frailty index: different instruments for different purposes. Age Ageing 2014 Jan 16;43(1):10-12. [doi: 10.1093/ageing/aft160] [Medline: 24132852]

6. Beard JR, Officer A, de Carvalho IA, Sadana R, Pot AM, Michel J, et al. The World report on ageing and health: a policy framework for healthy ageing. Lancet 2016 May;387(10033):2145-2154. [doi: 10.1016/S0140-6736(15)00516-4]
7. Mann W, Ottenbacher KJ, Fraas L, Tomita M, Granger CV. Effectiveness of assistive technology and environmental interventions in maintaining independence and reducing home care costs for the frail elderly. A randomized controlled trial. Arch Fam Med 1999;8(3):210-217. [doi: 10.1001/archfami.8.3.210] [Medline: 10333815]
8. Gillespie A, Best C, O'Neill B. Cognitive function and assistive technology for cognition: a systematic review. J Int Neuropsychol Soc 2011 Dec 12;18(1):1-19. [doi: 10.1017/s1355617711001548]
9. Song Y, van der Cammen TJ. Electronic assistive technology for community-dwelling solo-living older adults: a systematic review. Maturitas 2019 Jul;125:50-56. [doi: 10.1016/j.maturitas.2019.04.211] [Medline: 31133218]
10. Connelly K, ur Rehman Laghari K, Mokhtari M, Falk TH. Approaches to understanding the impact of technologies for aging in place: a mini-review. Gerontology 2014;60(3):282-288 [FREE Full text] [doi: 10.1159/000355644] [Medline: 24457288]
11. Scherer M. Assistive Technologies and Other Supports for People With Brain Impairment. Cham: Springer Publishing Company; 2011.
12. Fairhall N, Sherrington C, Kurrle SE, Lord SR, Lockwood K, Howard K, et al. Economic evaluation of a multifactorial, interdisciplinary intervention versus usual care to reduce frailty in frail older people. J Am Med Dir Assoc 2015 Jan;16(1):41-48. [doi: 10.1016/j.jamda.2014.07.006] [Medline: 25239014]
13. Caroux L, Consel C, Merciol M, Sauzéon H. Acceptability of notifications delivered to older adults by technology-based assisted living services. Univ Access Inf Soc 2019 Jul 6;19(3):675-683. [doi: 10.1007/s10209-019-00665-y]
14. O'Neill B, Gillespie A. Simulating naturalistic instruction: the case for a voice mediated interface for assistive technology for cognition. J Assistive Technologies 2008 Jun;2(2):22-31. [doi: 10.1108/17549450200800015]
15. Lopez-Hartmann M, Wens J, Verhoeven V, Remmen R. The effect of caregiver support interventions for informal caregivers of community-dwelling frail elderly: a systematic review. Int J Integr Care 2012;12(5):e133 [FREE Full text] [doi: 10.5334/ijic.845] [Medline: 23593047]
16. Liu L, Stroulia E, Nikolaidis I, Miguel-Cruz A, Rios Rincon A. Smart homes and home health monitoring technologies for older adults: a systematic review. Int J Med Inform 2016 Jul;91:44-59. [doi: 10.1016/j.ijmedinf.2016.04.007] [Medline: 27185508]
17. Tomita MR, Mann WC, Stanton K, Tomita AD, Sundar V. Use of currently available smart home technology by frail elders. Topic Geriatr Rehabil 2007;23(1):24-34. [doi: 10.1097/00013614-200701000-00005]
18. Dupuy L, Consel C, Sauzéon H. Self determination-based design to achieve acceptance of assisted living technologies for older adults. Comput Human Behav 2016 Dec;65:508-521. [doi: 10.1016/j.chb.2016.07.042]
19. Dupuy L, Froger C, Consel C, Sauzéon H. Everyday functioning benefits from an assisted living platform amongst frail older adults and their caregivers. Front Aging Neurosci 2017 Sep 28;9:302 [FREE Full text] [doi: 10.3389/fnagi.2017.00302] [Medline: 29033826]
20. Dupuy L, Sauzéon H. Effects of an assisted living platform amongst frail older adults and their caregivers: 6 months vs. 9 months follow-up across a pilot field study. Gerontechnology 2020 Mar 01;19(1):16-27. [doi: 10.4017/gt.2020.19.1.003.00]
21. 3C Study Group. Vascular factors and risk of dementia: design of the Three-City Study and baseline characteristics of the study population. Neuroepidemiology 2003 Oct 21;22(6):316-325. [doi: 10.1159/000072920] [Medline: 14598854]
22. Pérès K, Matharan F, Allard M, Amieva H, Baldi I, Barberger-Gateau P, et al. Health and aging in elderly farmers: the AMI cohort. BMC Public Health 2012 Jul 27;12(1):558 [FREE Full text] [doi: 10.1186/1471-2458-12-558] [Medline: 22839764]
23. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. J Psychiatric Res 1975 Nov;12(3):189-198. [doi: 10.1016/0022-3956(75)90026-6]
24. Tardieu, Mahmoudi R, Novella J, Oubaya N, Blanchard F, Jolly D, et al. [External validation of the short emergency geriatric assessment (SEGA) instrument on the SAFES cohort]. Geriatr Psychol Neuropsychiatr Vieil 2016 Mar;14(1):49-55. [doi: 10.1684/pnv.2016.0592] [Medline: 27005336]
25. Kabáč M, Consel C, Volanschi N. Designing parallel data processing for enabling large-scale sensor applications. Pers Ubiquit Comput 2017 Feb 20;21(3):457-473. [doi: 10.1007/s00779-017-1009-1]
26. Aguilova L, Sauzéon H, Balland É, Consel C, N'Kaoua B. [AGGIR scale: a contribution to specifying the needs of disabled elders]. Rev Neurol (Paris) 2014 Mar;170(3):216-221. [doi: 10.1016/j.neurol.2014.01.039] [Medline: 24630760]
27. Dupuy L, Sauzéon H, Consel C. Perceived needs for assistive technologies in older adults and their caregivers. In: Proceedings of the WomENcourage'15. 2015 Presented at: WomENcourage'15; Sep, 2015; Uppsala, Sweden URL: http://womencourage.acm.org/archive/2015/pdf/papers/%0Dpaper_1b.pdf
28. Caroux L, Consel C, Sauzeon H, Dupuy L. Designing an accessible and engaging email application for aging in place. In: Proceedings of the 2017 IEEE SmartWorld, Ubiquitous Intelligence & Computing, Advanced & Trusted Computed, Scalable Computing & Communications, Cloud & Big Data Computing, Internet of People and Smart City Innovation (SmartWorld/SCALCOM/UIC/ATC/CBDCom/IOP/SCI). 2017 Presented at: 2017 IEEE SmartWorld, Ubiquitous Intelligence & Computing, Advanced & Trusted Computed, Scalable Computing & Communications, Cloud & Big Data Computing,

Internet of People and Smart City Innovation (SmartWorld/SCALCOM/UIC/ATC/CBDCom/IOP/SCI); Aug 04-08, 2017; San Francisco, CA, USA. [doi: 10.1109/UIC-ATC.2017.8397527]
29. Caroux L, Consel C, Dupuy L, Sauzéon H. Verification of daily activities of older adults: a simple, non-intrusive, low-cost approach. In: Proceedings of the 16th international ACM SIGACCESS conference on Computers & accessibility. 2014 Presented at: ASSETS '14: The 16th International ACM SIGACCESS Conference on Computers and Accessibility; October 20 - 22, 2014; Rochester New York USA. [doi: 10.1145/2661334.2661360]
30. Caroux L, Consel C, Dupuy L, Sauzéon H. Towards context-aware assistive applications for aging in place via real-life-proof activity detection. J Ambient Intell Smart Environ 2018 Nov 09;10(6):445-459. [doi: 10.3233/ais-180505]
31. Consel C, Dupuy L, Sauzéon H. A unifying notification system to scale up assistive services. In: Proceedings of the 17th International ACM SIGACCESS Conference on Computers & Accessibility. 2015 Presented at: ASSETS '15: The 17th International ACM SIGACCESS Conference on Computers and Accessibility; Oct 26 - 28, 2015; Lisbon Portugal. [doi: 10.1145/2700648.2809855]
32. Consel C, Dupuy L, Sauzéon H. HomeAssist: an assisted living platform for aging in place based on an interdisciplinary approach. In: Advances in Human Factors and Ergonomics in Healthcare and Medical Devices. Cham: Springer; 2018.
33. Belloum R, Riche A, Volanschi N, Consel C. A tooled method for developing knowledge-based activity recognizers. In: Proceedings of the 2021 IEEE SmartWorld, Ubiquitous Intelligence & Computing, Advanced & Trusted Computing, Scalable Computing & Communications, Internet of People and Smart City Innovation (SmartWorld/SCALCOM/UIC/ATC/IOP/SCI). 2021 Presented at: 2021 IEEE SmartWorld, Ubiquitous Intelligence & Computing, Advanced & Trusted Computing, Scalable Computing & Communications, Internet of People and Smart City Innovation (SmartWorld/SCALCOM/UIC/ATC/IOP/SCI); Oct 18-21, 2021; Atlanta, GA, USA. [doi: 10.1109/SWC50871.2021.00013]
34. Tran A, Marsland S, Dietrich J, Guesgen H, Lyons P. Use cases for abnormal behaviour detection in smart homes. In: Aging Friendly Technology for Health and Independence. Berlin, Heidelberg: Springer; 2010.
35. ISO/TR 22411:2021 Ergonomics data for use in the application of ISO/IEC Guide 71:2014. ISO. 2021 Jan. URL: https://www.iso.org/standard/78847.html [accessed 2021-01-18]
36. Fisk A, Boot WR, Charness N, Rogers · WA. Designing for Older Adults Principles and Creative Human Factors Approaches, Third Edition. Boca Raton, Florida, United States: CRC Press; 2019.
37. Web Content Accessibility Guidelines (WCAG) 2.1. W3C Recommendations. 2018 Jun 5. URL: https://www.w3.org/TR/WCAG21/ [accessed 2019-09-18]
38. Zsiga K, Tóth A, Pilissy T, Péter O, Dénes Z, Fazekas G. Evaluation of a companion robot based on field tests with single older adults in their homes. Assist Technol 2018 Jun 19;30(5):259-266. [doi: 10.1080/10400435.2017.1322158] [Medline: 28628395]
39. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969 Sep 01;9(3 Part 1):179-186. [doi: 10.1093/geront/9.3_part_1.179]
40. Sivan A. Benton Visual Retention Test | Fifth Edition. London, United Kingdom: Pearson; 1992.
41. Fuhrer R, Rouillon F. La version française de l'échelle CES-D (Center for Epidemiologic Studies-Depression Scale). Description et traduction de l'échelle d'autoévaluation. Psychiatr psychobiol 2020 Apr 28;4(3):163-166. [doi: 10.1017/s0767399x00001590]
42. Bouisson J. Routinization preferences, anxiety, and depression in an elderly French sample. J Aging Stud 2002 Aug;16(3):295-302. [doi: 10.1016/S0890-4065(02)00051-8]
43. Bergua V, Fabrigoule C, Barberger-Gateau P, Dartigues J, Swendsen J, Bouisson J. Preferences for routines in older people: associations with cognitive and psychological vulnerability. Int J Geriatr Psychiatry 2006 Oct;21(10):990-998. [doi: 10.1002/gps.1597] [Medline: 16955425]
44. Vellas B, Guigoz Y, Garry PJ, Nourhashemi F, Bennahum D, Lauque S, et al. The mini nutritional assessment (MNA) and its use in grading the nutritional state of elderly patients. Nutrition 1999 Feb;15(2):116-122. [doi: 10.1016/s0899-9007(98)00171-3]
45. Valentini A, Federici M, Cianfarani MA, Tarantino U, Bertoli A. Frailty and nutritional status in older people: the Mini Nutritional Assessment as a screening tool for the identification of frail subjects. Clin Interv Aging 2018 Jul;Volume 13:1237-1244. [doi: 10.2147/cia.s164174]
46. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994 Mar 01;49(2):M85-M94. [doi: 10.1093/geronj/49.2.m85] [Medline: 8126356]
47. Podsiadlo D, Richardson S. J Am Geriatr Soc 1991 Feb;39(2):142-148. [doi: 10.1111/j.1532-5415.1991.tb01616.x] [Medline: 1991946]
48. Reitan RM. Ward Halstead's contributions to neuropsychology and the Halstead-Reitan neuropsychological test battery. J Clin Psychol 1994 Jan;50(1):47-70. [doi: 10.1002/1097-4679(199401)50:1<47::aid-jclp2270500106>3.0.co;2-x]
49. Derouesné C, Dealberto MJ, Boyer P, Lubin S, Sauron B, Piette F, et al. Empirical evaluation of the 'Cognitive Difficulties Scale' for assessment of memory complaints in general practice: A study of 1628 cognitively normal subjects aged 45-75 years. Int J Geriat Psychiatry 2004 Oct 13;8(7):599-607. [doi: 10.1002/gps.930080712]

50. Avila-Funes JA, Amieva H, Barberger-Gateau P, Le Goff M, Raoux N, Ritchie K, et al. Cognitive impairment improves the predictive validity of the phenotype of frailty for adverse health outcomes: the three-city study. J Am Geriatr Soc 2009 Mar;57(3):453-461. [doi: 10.1111/j.1532-5415.2008.02136.x] [Medline: 19245415]
51. Bernal-López C, Potvin O, Avila-Funes JA. Frailty is associated with anxiety in community-dwelling elderly adults. J Am Geriatr Soc 2012 Dec 11;60(12):2373-2374. [doi: 10.1111/jgs.12014] [Medline: 23231561]
52. Czaja SJ, Charness N, Fisk AD, Hertzog C, Nair SN, Rogers WA, et al. Factors predicting the use of technology: findings from the center for research and education on aging and technology enhancement (CREATE). Psychol Aging 2006 Jun;21(2):333-352 [FREE Full text] [doi: 10.1037/0882-7974.21.2.333] [Medline: 16768579]
53. Kempen GI, Steverink N, Ormel J, Deeg DJ. The assessment of ADL among frail elderly in an interview survey: self-report versus performance-based tests and determinants of discrepancies. J Gerontol B Psychol Sci Soc Sci 1996 Sep 01;51(5):P254-P260. [doi: 10.1093/geronb/51b.5.p254] [Medline: 8809001]
54. Décieux JP, Sischka PE, Schumacher A, Willems H. Psychometrical properties of a french version of the general self-efficacy short scale (ASKU). Swiss J Psychol 2020 Jan;79(1):15-25. [doi: 10.1024/1421-0185/a000233]
55. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. Medical Care 1992 Jun;30(6):473-483 [FREE Full text]
56. Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feelings of burden. Gerontologist 1980 Dec 01;20(6):649-655. [doi: 10.1093/geront/20.6.649] [Medline: 7203086]
57. Dupuy L, N'Kaoua B, Dehail P, Sauzéon H. Role of cognitive resources on everyday functioning among oldest-old physically frail. Aging Clin Exp Res 2020 Oct 24;32(10):2021-2029. [doi: 10.1007/s40520-019-01384-3] [Medline: 31650501]
58. Grober E, Buschke H, Crystal H, Bang S, Dresner R. Screening for dementia by memory testing. Neurology 1988 Jun 01;38(6):900-903. [doi: 10.1212/wnl.38.6.900] [Medline: 3368071]
59. Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol 1935 Dec;18(6):643-662. [doi: 10.1037/h0054651]
60. Wehmeyer ML, Bolding N. Self-determination across living and working environments: a matched-samples study of adults with mental retardation. Ment Retard 1999 Oct;37(5):353-363. [doi: 10.1352/0047-6765(1999)037<0353:salawe>2.0.co;2]
61. Lachman ME. Locus of control in aging research: a case for multidimensional and domain-specific assessment. Psychol Aging 1986;1(1):34-40. [doi: 10.1037/0882-7974.1.1.34]
62. Martin S, Mazzocco C, Maury P, Grosselin A, Van der Elst W, Dixon RA, et al. Compensating for memory losses throughout aging: validation and normalization of the memory compensation questionnaire (MCQ) for non-clinical French populations. Arch Gerontol Geriatr 2015 Jan;60(1):28-38 [FREE Full text] [doi: 10.1016/j.archger.2014.10.013] [Medline: 25459917]
63. Dixon R, Garrett DD, Bäckman L. Principles of compensation in cognitive neuroscience and neurorehabilitation. In: Cognitive Neurorehabilitation: Evidence and Application. Cambridge, UK: Cambridge University Press; 2008.
64. Oubaya N, Dramé M, Novella J, Quignard E, Cunin C, Jolly D, et al. Screening for frailty in community-dwelling elderly subjects: predictive validity of the modified SEGA instrument. Arch Gerontol Geriatr 2017 Nov;73:177-181. [doi: 10.1016/j.archger.2017.07.026] [Medline: 28822918]
65. Oubaya N, Mahmoudi R, Jolly D, Zulfiqar A, Quignard E, Cunin C, et al. Screening for frailty in elderly subjects living at home: validation of the Modified Short Emergency Geriatric Assessment (SEGAm) instrument. J Nutr Health Aging 2014 Nov 28;18(8):757-764. [doi: 10.1007/s12603-014-0541-1] [Medline: 25286456]
66. Piovezan R, Poyares D, Tufik S. Frailty and sleep disturbances in the elderly: possible connections and clinical implications. Sleep Sci 2013;6(4):175-179.
67. Buysse D, Reynolds CF, Monk TH, Hoch CC, Yeager AL, Kupfer DJ. Quantification of subjective sleep quality in healthy elderly men and women using the Pittsburgh Sleep Quality Index (PSQI). Sleep 1991 Aug;14(4):331-338. [Medline: 1947597]
68. Herrera-Badilla A, Navarrete-Reyes AP, Amieva H, Avila-Funes JA. Loneliness is associated with frailty in community-dwelling elderly adults. J Am Geriatr Soc 2015 Mar 20;63(3):607-609. [doi: 10.1111/jgs.13308] [Medline: 25800917]
69. Lubben JE. Assessing social networks among elderly populations. Fam Community Health 1988;11(3):42-52. [doi: 10.1097/00003727-198811000-00008]
70. Lubben J, Blozik E, Gillmann G, Iliffe S, von Renteln Kruse W, Beck JC, et al. Performance of an abbreviated version of the Lubben Social Network Scale among three European community-dwelling older adult populations. Gerontologist 2006 Aug 01;46(4):503-513. [doi: 10.1093/geront/46.4.503] [Medline: 16921004]
71. Lallemand C, Koenig V, Gronier G, Martin R. Création et validation d'une version française du questionnaire AttrakDiff pour l'évaluation de l'expérience utilisateur des systèmes interactifs. Eur Rev Appl Psychol 2015 Sep;65(5):239-252. [doi: 10.1016/j.erap.2015.08.002]
72. Demers L, Weiss-Lambrou R, Ska B. The quebec user evaluation of satisfaction with assistive technology (QUEST 2.0): an overview and recent progress. Technol Disabil 2002 Sep 29;14(3):101-105. [doi: 10.3233/tad-2002-14304]
73. Olson KE, O'Brien MA, Rogers WA, Charness N. Diffusion of technology: frequency of use for younger and older adults. Ageing Int 2011 Mar 28;36(1):123-145 [FREE Full text] [doi: 10.1007/s12126-010-9077-9] [Medline: 22685360]
74. Isaacs B, Kennie AT. The Set test as an aid to the detection of dementia in old people. Br J Psychiatry 1973 Oct 29;123(575):467-470. [doi: 10.1192/bjp.123.4.467] [Medline: 4748864]

75. Consel C, Kaye J. Aging with the internet of things. Spring Bridge Technologies Aging 2019 Mar 15;49(1) [FREE Full text]
76. Fadrique LX, Rahman D, Vaillancourt H, Boissonneault P, Donovska T, Morita PP. Overview of policies, guidelines, and standards for active assisted living data exchange: thematic analysis. JMIR Mhealth Uhealth 2020 Jun 22;8(6):e15923 [FREE Full text] [doi: 10.2196/15923] [Medline: 32568090]
77. Baig MM, Afifi S, GholamHosseini H, Mirza F. A systematic review of wearable sensors and IoT-based monitoring applications for older adults - a focus on ageing population and independent living. J Med Syst 2019 Jun 15;43(8):233. [doi: 10.1007/s10916-019-1365-7] [Medline: 31203472]
78. Queirós A, Silva A, Alvarelhão J, Rocha NP, Teixeira A. Usability, accessibility and ambient-assisted living: a systematic literature review. Univ Access Inf Soc 2013 Oct 5;14(1):57-66. [doi: 10.1007/s10209-013-0328-x]
79. Ganesan B, Gowda T, Al-Jumaily A, Fong KN, Meena SK, Tong RK. Ambient assisted living technologies for older adults with cognitive and physical impairments: a review. Eur Rev Medical Pharmacol Sci 2019;23(23):10470-10481 [FREE Full text]
80. Czaja SJ, Boot WR, Charness N, Rogers WA, Sharit J. Improving social support for older adults through technology: findings from the prism randomized controlled trial. Gerontologist 2018 May 08;58(3):467-477 [FREE Full text] [doi: 10.1093/geront/gnw249] [Medline: 28201730]
81. Rantz M, Phillips LJ, Galambos C, Lane K, Alexander GL, Despins L, et al. Randomized trial of intelligent sensor system for early illness alerts in senior housing. J Am Med Dir Assoc 2017 Oct 01;18(10):860-870 [FREE Full text] [doi: 10.1016/j.jamda.2017.05.012] [Medline: 28711423]
82. Timon CM, Heffernan E, Kilcullen SM, Lee H, Hopper L, Quinn J, et al. Development of an internet of things technology platform (the NEX system) to support older adults to live independently: protocol for a development and usability study. JMIR Res Protoc 2022 May 05;11(5):e35277 [FREE Full text] [doi: 10.2196/35277] [Medline: 35511224]
83. Pandya R, Dibner K. Learning Through Citizen Science Enhancing Opportunities by Design. Washington, DC: The National Academies Press; 2018.
84. Boot W, Charness N, Czaja SJ, Rogers WA. Designing for Older Adults Case Studies, Methods, and Tools. Boca Raton, Florida: CRC Press; 2020.
85. Nurgalieva L, Jara Laconich JJ, Baez M, Casati F, Marchese M. A systematic literature review of research-derived touchscreen design guidelines for older adults. IEEE Access 2019;7:22035-22058. [doi: 10.1109/access.2019.2898467]

Abbreviations

3C: Three-City
AAL: ambient assisted living
ADL: activities of daily life
AMI: aging multidisciplinary investigation
AT: assistive technology
FI: frail individuals
HA: HomeAssist
IADL: instrumental activities of daily life
IoT: Internet-of-Things
MMSE: Mini-Mental Scale Evaluation

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Protocol

Long-term Consequences of COVID-19 and the Pandemic: Protocol for a Web-Based, Longitudinal Observational Study (DEFEAT)

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Abstract

Background: With population-wide vaccination availability, the global COVID-19 pandemic entered a new phase. Despite vaccination status, some people who were infected with SARS-CoV-2 experience long-term symptoms.

Objective: In this study, we aim to characterize the long-term effects of SARS-CoV-2 infection and the pandemic. We also aim to build symptom clusters and determine risk factors for developing long COVID symptoms. Furthermore, we assess social participation and health-related quality of life in patients with long COVID and in the general population during a global pandemic.

Methods: With a mixed-methods, web-based approach, we aim to recruit 2000 people in Germany who are older than 18 years and can provide informed consent. In the quantitative arm of the study, we identify symptoms of and predictive factors for long COVID manifestations with cluster analysis and assess social participation during the pandemic with standardized questionnaires. The qualitative arm of the study uses individual interviews and focus group discussions to better understand the illness experience of persons who experience long COVID.

Results: Recruitment started in September 2021. Up until July 2022, we recruited approximately 4500 participants via our web-based database.

Conclusions: This study aims to build an innovative, patient-centered, web-based research platform appropriate for the pandemic by minimizing physical contact between study personnel and participants. All study activities are designed to better understand the long COVID syndrome, social participation during the pandemic, and the illness experiences of persons affected by long COVID.

Trial Registration: German Clinical Trial Registry DRKS00026007; https://tinyurl.com/yh282fkt

International Registered Report Identifier (IRRID): DERR1-10.2196/38718

(JMIR Res Protoc 2022;11(10):e38718) doi:10.2196/38718

KEYWORDS

SARS-CoV-2; COVID-19; long COVID; post–COVID-19; long haulers; pandemic; long-term effects; symptoms; long-term; risk factors; Germany; population study; quality of life; social participation; engagement

Introduction

Overview

In the beginning of the SARS-CoV-2 pandemic, lockdown and restrictions were the main measures to control further transmission of the virus. In 2021, we entered a new era of the pandemic, with several effective vaccines. Politics, society, and science developed and established effective measures for the control of the transmission of the virus. Nevertheless, more than 320 million people were infected worldwide until now, and more than 5 million people died because of the infection [1]. Approximately 10% of the infected people report symptoms 4 to 12 weeks after the COVID-19 infection, now called “Long COVID” or “Post COVID“ syndrome (hereafter: long COVID [2]). The symptoms after a SARS-CoV-2 infection are various; a study from the United Kingdom reported 55 different long-term effects [3]. In the German guideline, different symptoms of long COVID are described, such as headache, shortness of breath, cough, dysosmia or anosmia, cognitive impairment or brain fog, and fatigue [4]. Patients report a great impact on their quality of life and ability to work or even to manage their everyday life [5]. The first steps in distinguishing predictors for some long COVID symptoms were made [6]. However, it remains unclear which patients are at higher risk for a prolonged course of the disease and if there are diagnostic tools to objectify long COVID.

Even with effective and available vaccines in Germany [7], it will take effort for individuals and society to find their way back to a *normal* everyday life. An important aspect of everyday life, which was dramatically altered during phases of COVID-19 pandemic lockdown, was social participation. Studies have shown that social participation is associated with life satisfaction, self-esteem, and mental health, for example, in older persons [8] and adolescents [9]. Therefore, understanding how people directly and indirectly affected by COVID-19 resume social participation in the vaccine era is also relevant for understanding the pandemic’s effect upon community health. The assessment of social participation during the pandemic and the active involvement of those affected by long COVID in research endeavors may provide important information on how measures, communication, and care services can be optimized in the future to best suit the health needs of the community.

Primary Aim

With the joint project, DEFEAT Corona (Defense Against COVID-19 Study), we aim to improve the understanding of the long COVID syndrome and the long-term effects of the pandemic in a large cohort. We want to analyze which syndromic forms exist in patients with long COVID and how care structures should be built to ensure patient-centered support. We will assess how patients with long COVID participate socially in comparison to others who are also experiencing the pandemic.

With this study, we aim to build an innovative, web-based, and patient-centered research infrastructure to support the new challenges of the vaccine era of the COVID-19 pandemic.

Methods

Aim, Design, and Setting of the Study

The main goal of the joint project, DEFEAT Corona, is to create an innovative, web-based, and patient-centered research structure. With this platform, we want to face the challenges of the vaccine area in Lower Saxony, Germany. The 3 partners (Hannover Medical School, University Medical Center Göttingen, and Ostfalia University of Applied Sciences) plan to build a digital platform for long-term research in times of a global pandemic. There are 3 subprojects, which have the following primary and secondary objectives. Key to the project is to assess the long-term consequences of a SARS-CoV-2 infection and the pandemic in a prospective cohort study. This will be addressed in the 3 subprojects (Textbox 1).

Textbox 1. Primary and secondary aims of DEFEAT Corona (Defense Against COVID-19 Study).

Subproject 1: Back to life? Social and participation convalescence in the vaccine era

- Analysis of how social participation is experienced by patients who had COVID-19 and have long term symptoms (patients with long COVID) vs persons who were affected by pandemic regulations but not infected by the virus
- Foundation of a patient- and public-led advisory board

Subproject 2: COVID-19 special consultation Lower Saxony—vaccination response and long COVID syndrome

- Establishment of a web-based, multimodal research platform and development of a self-assessment for patients with long COVID
- Setup of an innovative and transregional special consultation service for patients with long COVID syndrome (clinical care and research)
  - Finding objective measures for the diagnosis of long COVID (eg, optical coherence tomography angiography imaging and ear, nose, and throat examination)
  - Assessment of the needs of patients with long COVID in health care

Subproject 3: machine learning for finding symptom clusters (MACLEAF SYCL)

- Data preparation for exploratory analysis and definition of criteria for cluster analysis
- Implementation of the cluster analysis to identify symptom clusters with possible adjustments or extensions

Overriding secondary objectives

- A transparent communication of new insights to a nonprofessional audience
- Sustainable transfer of knowledge
- Making research participation accessible for parts of the population living further away from university cities.

Characteristics of the Participants

Participants will be recruited via newspaper announcements, home page, posters, and flyers in local regions, general practices, or long COVID support groups in the northern German region of Lower Saxony. Furthermore, participants will be recruited in the outpatient clinics of the Hannover Medical School and University Medical Center Göttingen, through the cooperation partners, local public health authorities, primary care clinics, and ministries.

Everyone older than 18 years who can give informed consent is invited to participate in the first baseline web-based questionnaire, whether they had COVID-19 (with or without long-term effects) or not. We will also assess whether the participants live in Lower Saxony. Exclusion criteria are being younger than 18 years and refusal or inability to provide consent. Participants for subproject 2 will be recruited from the participants of the baseline questionnaire. Subproject 3 will analyze data assessed in the baseline questionnaire.

Ethics Approval and Consent to Participate

The study is registered in the German clinical trial registry (DRKS00026007) and has been approved by the institutional review board of both Hannover Medical School (9948_BO_K_2021) and University Medical Center Göttingen (29/3/21). Data security management plan has also been approved by Hannover Medical School. Informed consent will be obtained from all study participants subsequently in each study step (questionnaires, clinical assessment and specimen collection, and qualitative study). Each participant receives written information on study procedures and data management over the web-based questionnaire format.

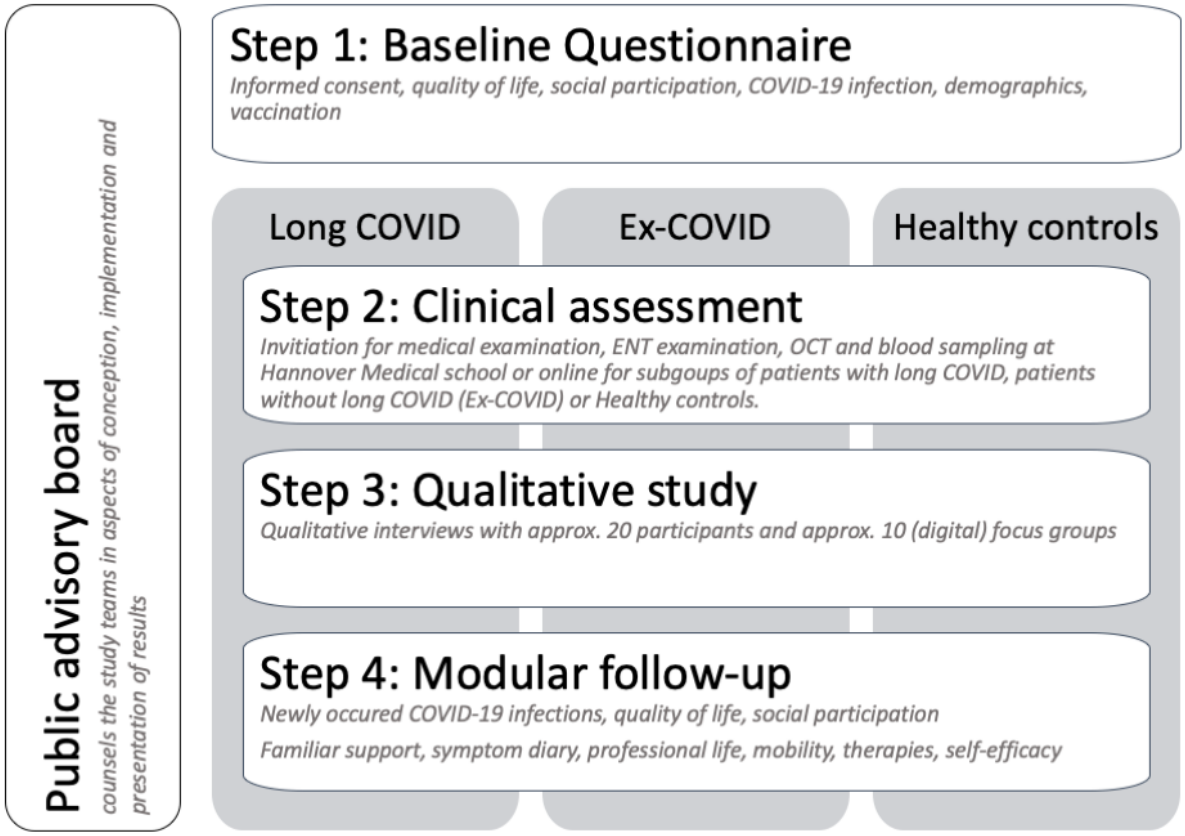
Study participation is voluntary, and participants have the right to withdraw consent at any time and without disclosure of reasons for withdrawal. A trained member of the study team is available for questions at enrollment and thereafter.

In the further steps of the study, participants will be informed about specimen and data collection, as well as the storage of samples in the Hannover Biobank for future research projects. Study participation is voluntary, and participants have the right to withdraw consent at any time and without disclosure of reasons for withdrawal. Furthermore, they will receive a written data security protocol. A trained member of the study team is available for questions at enrollment and thereafter. All collected data will be pseudonymized and stored on servers of Hanover Medical School or University Medical Center Göttingen. Publications will include anonymized data. Blood samples will be transferred to the Biobank of Hanover Medical School.

Description of All Processes, Interventions, Comparisons

The details of the study design are illustrated in Figure 1.

Figure 1. Flow chart of DEFEAT Corona (Defense Against COVID-19 Study). ENT: ears, nose, and throat; OCT: optical coherence tomography.



Step 1: Baseline Questionnaire

The baseline questionnaire will include sociodemographic questions, questions about a SARS-CoV-2 infection, the process of the disease, possible late symptoms, and vaccination status. According to the participants' answers in the basic questionnaire, they will be assigned into 3 groups: "No COVID," "Ex-COVID," and "Long COVID." Questionnaire items were adapted from the World Health Organization Case Report Form [10] and the UK Long COVID guideline [11]. We also assessed quality of life (EQ-5D [12]) and social participation (IMET [13]; Multimedia Appendix 1).

The data of the baseline questionnaire will also be used in the cluster analysis to characterize the typical symptom complexes experienced by participants with long COVID.

Step 2: Obtaining Additional Clinical Characteristics in Ex-COVID and Long COVID Groups

A portion of the "Long COVID," "Ex-COVID," and "No COVID" groups will be invited for a personal clinical assessment to the outpatient clinic of Hanover Medical School. The clinical assessment will include blood sampling of 20-30 ml (eg, full blood count, electrolytes, liver enzymes, retention parameters, and SARS-CoV-2 antibodies), an ears, nose, and throat examination, optical coherence tomography angiography imaging, and a standardized medical examination by a trained physician. Some patients with long COVID will be invited to an additional web-based consultation.

Step 3: Qualitative Study of the Long COVID Illness Experience

According to the sociodemographic data gathered in the baseline questionnaire, a diverse group of participants with long COVID will be invited to participate in the qualitative arm of the study. We aim to perform 20-30 individual interviews and 10-20 focus groups to gain a deeper understanding about how people with various long COVID symptoms experience their illness, and how they perceive the illnesses impact on social participation. This includes relationships and activities among friends and family, education, profession, everyday life, health system, and leisure activities.

Step 4: Individualized, Modular, Follow-up Questionnaires

All participants will get invitations for modular questionnaires, depending on their answer in the baseline questionnaire (eg, how their children experienced the pandemic, if the participants stated that they had children). The follow-up questionnaires will contain questions about new infections with SARS-CoV-2, changes in symptoms and recovery from symptoms, further vaccinations, quality of life (EQ-5D), and social participation (IMET) over a longer period. The project will be accompanied by a patient- and public-led advisory board.

Type of Data and Analyses Planned

Data preparation will be performed in SPSS (IBM Corp), data analysis in R (version 4.1.1; The R Foundation), and visualizations with GraphPad Prism (GraphPad Software Inc) and R. Types of data are mainly ordinal or numerical and sometimes strings of a free text, depending on the questions.

Optical coherence tomography images will be analyzed with MATLAB (MathWorks), and values will be created for vessel density and vessel distance. During the data preparation, data quality will be checked, and the handling of missing values will be addressed. Summary statistics and standard visualizations will be computed. Within the collected data, symptom clusters after an infection with SARS-CoV-2 will be found using machine learning methods. Established methods of cluster and symptom cluster analysis will be adapted and extended for the specific questionnaire. Logistic regression will be applied to identify specific risk factors for development of long COVID.

Semistructured interviews and focus groups will last about 45-75 minutes. Interview and focus group data will be recorded and transcribed according to the simplified rules of Kuckartz [14] and Dresing and Pehl [15] and subsequently analyzed using qualitative content analysis according to Mayring [16] and Kuckartz [14].

Our mixed-methods approach to exploring social participation includes data from standardized questionnaires and qualitative interviews and focus groups. These data will be combined or triangulated to gain a deeper understanding of the social participation and the illness experience of persons experiencing long COVID symptoms.

Results

The study began in July 2021 with the preparation of the first questionnaire. The first participants were recruited in September 2021 via web-based questionnaire. Until July 2022, approximately 4500 participants were recruited via a web-based questionnaire. Recruiting will continue at least until the end of 2022. The first clinical consultations of patients with long COVID took place in January 2022 and will continue throughout the duration of the study.

The qualitative study began in September 2021 with a series of preliminary exploratory discussions with members of the target population to assess important subjects and develop an interview guideline. This guideline will be used in the main qualitative study. Interviews will be conducted and analyzed, and new participants will be enrolled according to the principle of theoretical sampling. The interviews started in January 2022 and will continue until targeted sample size is achieved.

Discussion

Principal Findings

With DEFEAT Corona, we aimed to develop an innovative web-based platform for research on the sequelae of the pandemic and SARS-CoV-2 infections. The 3 subprojects focus on social participation, characteristics of long COVID, and the exploration of data-driven methods. As of July 2022, the data acquisition is projected to continue at least until December 2022.

The web-based platform is available on the DEFEAT Corona website [17]. As of July 2022, approximately 4500 people participated in our first questionnaire, so we assume that the platform has good usability. The recruitment is ongoing. We developed a questionnaire to assess social participation during a pandemic [18], which will be tested within DEFEAT Corona.

Strengths and Limitations

A limitation to the study is the method of recruiting. The first questionnaire is available on the web for the public. People who do not use web-based resources frequently (eg, older people) might not participate, which may introduce a selection bias. Nevertheless, we aimed to create a platform that is easily accessible for participants, as it is not required to travel to study centers. In addition, people who are affected by long COVID symptoms such as fatigue might be more likely to participate in the study when they can participate from the comfort of their own home instead of needing to visit a large university hospital to be enrolled in the study. Therefore, the participants of DEFEAT Corona will be a convenience sample, and we must take these factors into account, especially when relating the study findings to the population.

Future Directions

With our study design, we aim to find characteristics and determinants of the long COVID syndrome. The web-based approach can be easily adapted to another place or another disease. With the mixed-methods approach, we aim to include different aspects that might be important in our analysis. This will help us distinguish important topics regarding the long-term effects of the SARS-CoV-2 infection and the global pandemic and guide the further development of our research agenda.

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Data Availability

Data sampling is still in process. The data sets generated during this study are available from the corresponding author on reasonable request.

Authors' Contributions

GMNB, ADJ, SS, FM, and FK conceptualized the study. MM, JN, TB, SH, DS, SR, KV, and AC are involved in the recruitment of the participants as well as data collection and data analysis. MM and SS drafted the manuscript, which was revised by GMNB, FK, and SH. All authors read and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
First questionnaire of the DEFEAT Corona study (German).
[PDF File (Adobe PDF File), 216 KB - resprot_v11i10e38718_app1.pdf]

References

1. Coronavirus Research Center - COVID-19 Dashboard. Johns Hopkins University & Medecine. URL: https://coronavirus.jhu.edu/map.html [accessed 2022-01-16]
2. Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV, WHO Clinical Case Definition Working Group on Post-COVID-19 Condition. A clinical case definition of post-COVID-19 condition by a Delphi consensus. Lancet Infect Dis 2022 Apr;22(4):e102-e107 [FREE Full text] [doi: 10.1016/S1473-3099(21)00703-9] [Medline: 34951953]
3. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. Sci Rep 2021 Aug 09;11(1):16144 [FREE Full text] [doi: 10.1038/s41598-021-95565-8] [Medline: 34373540]
4. Koczulla AR, Ankermann T, Behrends U, Berlit P, Böing S, Brinkmann F, et al. [S1 Guideline Post-COVID/Long-COVID]. Pneumologie 2021 Nov 02;75(11):869-900. [doi: 10.1055/a-1551-9734] [Medline: 34474488]
5. Seeßle J, Waterboer T, Hippchen T, Simon J, Kirchner M, Lim A, et al. Persistent Symptoms in Adult Patients 1 Year After Coronavirus Disease 2019 (COVID-19): A Prospective Cohort Study. Clin Infect Dis 2022 Apr 09;74(7):1191-1198 [FREE Full text] [doi: 10.1093/cid/ciab611] [Medline: 34223884]
6. Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, et al. Attributes and predictors of long COVID. Nat Med 2021 Apr;27(4):626-631 [FREE Full text] [doi: 10.1038/s41591-021-01292-y] [Medline: 33692530]
7. Barros-Martins J, Hammerschmidt SI, Cossmann A, Odak I, Stankov MV, Morillas Ramos G, et al. Immune responses against SARS-CoV-2 variants after heterologous and homologous ChAdOx1 nCoV-19/BNT162b2 vaccination. Nat Med 2021 Sep 14;27(9):1525-1529 [FREE Full text] [doi: 10.1038/s41591-021-01449-9] [Medline: 34262158]
8. Takagi D, Kondo K, Kawachi I. Social participation and mental health: moderating effects of gender, social role and rurality. BMC Public Health 2013 Jul 31;13:701 [FREE Full text] [doi: 10.1186/1471-2458-13-701] [Medline: 23902596]
9. Santini ZI, Pisinger VSC, Nielsen L, Madsen KR, Nelausen MK, Koyanagi A, et al. Social Disconnectedness, loneliness, and mental health among adolescents in Danish high schools: a nationwide cross-sectional study. Front Behav Neurosci 2021;15:632906 [FREE Full text] [doi: 10.3389/fnbeh.2021.632906] [Medline: 33927599]
10. Global COVID-19 Clinical Platform Case Report Form (CRF) for Post COVID condition (Post COVID-19 CRF). World Health Organization. URL: https://cdn.who.int/media/docs/default-source/3rd-edl-submissions/who_crf_postcovid_feb9_2021.pdf?sfvrsn=76afd14_1&download=true [accessed 2022-09-16]
11. Shah W, Hillman T, Playford ED, Hishmeh L. Managing the long term effects of covid-19: summary of NICE, SIGN, and RCGP rapid guideline. BMJ 2021 Jan 22;372:n136. [doi: 10.1136/bmj.n136] [Medline: 33483331]
12. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001 Jul;33(5):337-343. [doi: 10.3109/07853890109002087] [Medline: 11491192]
13. Deck R, Mittag O, Hüppe A, Muche-Borowski C, Raspe H. IMET. Index zur Messung von Einschränkungen der Teilhabe. Leibniz-Zentrum für Psychologische Information und Dokumentation (ZPID). 2011. URL: https://www.psycharchives.org/en/item/7fd64c03-22df-4a6f-8197-1254771322f7 [accessed 2022-09-16]
14. Kuckartz U, Rädiker S. Qualitative Inhaltsanalyse. Methoden, Praxis, Computerunterstützung. 3. überarbeitete Auflage [Qualitative content analysis. Methods, practice, computer support. 3rd Edition]. Weinheim, Basel: Juventa; 2016.
15. Dresing T, Pehl T. Praxisbuch Interview, Transkription & Analyse:Anleitungen und Regelsysteme für qualitativ Forschende: Anleitungen und Regelsysteme für qualitativ Forschende. 6. Auflage [Interview, Transcription & Analysis Practice Book: Guidance and control systems for qualitative researchers. 6th Edition]. Marburg: Audiotranskription.de; 2015.
16. Mayring P. Qualitative Inhaltsanalyse, Grundlagen und Techniken. 12., aktualisierte und überarb. Aufl [Qualitative content analysis, basics and techniques. 12th Edition]. Weinheim, Basel: Beltz; 2015.
17. DEFEAT Corona. URL: https://www.defeat-corona.de/ [accessed 2022-09-16]
18. Schröder D, Heesen G, Heinemann S, Hummers E, Jablonka A, Steffens S, et al. Development and Validation of a Questionnaire to Assess Social Participation of High Risk-Adults in Germany During the COVID-19 Pandemic. Front Public Health 2022;10:831087 [FREE Full text] [doi: 10.3389/fpubh.2022.831087] [Medline: 35558532]

Abbreviations

DEFEAT Corona: Defense Against COVID-19 Study

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Protocol

A Novel Concentrated, Interdisciplinary Group Rehabilitation Program for Patients With Chronic Obstructive Pulmonary Disease: Protocol for a Nonrandomized Clinical Intervention Study

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Abstract

Background: Pulmonary rehabilitation has been demonstrated to be a highly effective treatment for people with chronic obstructive pulmonary disease (COPD). However, its availability is scarce worldwide, and new and innovative rehabilitation models are highly warranted. Recently, the group behind the present study published a protocol describing a novel concentrated, interdisciplinary group rehabilitation program for patients with chronic illnesses. The current paper describes an extension of this protocol to patients with COPD.

Objective: The objective of this study is to explore the acceptability of concentrated, interdisciplinary group pulmonary rehabilitation for patients with COPD. The intervention is expected to improve functional status and be highly acceptable to patients.

Methods: This study will include 50 patients aged over 40 years who fulfill the diagnostic criteria for COPD: a forced expiratory volume at the first second (FEV_1) <80% of expected and a FEV_1/forced vital capacity ratio below the lower limit of normal according to the Global Lung Function Initiative. An interdisciplinary team consisting of physicians, physiotherapists, psychologists, pharmacists, clinical nutritionists, and nurses will deliver the treatment to groups of 6 to 10 patients over 3 to 4 consecutive days with a 12-month follow-up. The intervention is divided into three distinct phases: (1) pretreatment preparation for change, (2) concentrated rehabilitation, where the patient is coached to focus on making health-promoting microchoices, and (3) integration of the changes into everyday living, aided by digital follow-up and 2 on-site clinical examinations. Statistical significance will be set at α=.05.

Results: The recruitment period will last from April 2022 until June 2023.

Conclusions: If successful, this highly novel rehabilitation format might change the way we deliver care for patients with COPD, leading to substantial societal and socioeconomic gains. The study will expand knowledge on the concentrated treatment format as a rehabilitation model for people with COPD.

Trial Registration: ClinicalTrials.gov NCT05234281; https://clinicaltrials.gov/ct2/show/NCT05234281

International Registered Report Identifier (IRRID): PRR1-10.2196/40700

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KEYWORDS

COPD; pulmonary rehabilitation; chronic illness; interdisciplinary; chronic disease; rehabilitation model; rehabilitation; treatment; group therapy; patient outcome; health intervention; pulmonary disease; intervention study

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible airflow limitation [1], with dyspnea, cough with sputum production, and fatigue as the main symptoms [1]. The disease is the third leading cause of death worldwide [2], and in 2019 3.23 million deaths were caused by COPD [2]. COPD represents a global health challenge and causes major economic and societal burdens [3,4].

Guidelines highlight that pulmonary rehabilitation is the most important treatment option in the integrated care of patients with COPD, and it ranks as one of the most cost-effective treatment strategies [1,5]. Clinically meaningful improvements in exercise tolerance, dyspnea, fatigue, anxiety and depression, lower-limb muscle strength, self-efficacy, and health-related quality of life have been demonstrated after participation in pulmonary rehabilitation, irrespective of the baseline clinical status [6]. Despite these documented effects, the treatment is underused worldwide. Data from the United States and Canada demonstrate that less than 5% of eligible patients ever participate in a pulmonary rehabilitation program [7,8], and a recently published study from Norway showed that only 5% of Norwegian municipalities had multidisciplinary pulmonary rehabilitation programs for patients with COPD [9]. The underuse of pulmonary rehabilitation calls for new rehabilitation models to increase accessibility and personalization to address individual patient goals, which is believed to improve patient outcomes [10].

Based on extensive experience with the concentrated rehabilitation format [11-15], the group behind this project recently published a protocol for concentrated, interdisciplinary group rehabilitation for chronic illnesses [16]. So far, patients with chronic low back pain, post–Covid-19 symptoms, anxiety and depression, and type 2 diabetes have been included. These disorders were chosen because they each represent a major societal challenge, and novel, effective, and cost-effective treatment approaches are highly needed. The primary symptoms of the included disorders are highly diverse, but they share health challenges that can either improve or worsen depending upon patients' own handling of their symptoms. By including patients with COPD, we may be able to further increase our knowledge of concentrated rehabilitation models for these patients. Existing rehabilitation models for patients with COPD usually have a duration of 6 weeks or more for outpatient models and 3 to 4 weeks for inpatient models [17]. A concentrated intervention period could increase access to rehabilitation and thereby increase availability.

Uncertainties related to their prognosis, health-related worries, and rumination are common in people living with COPD [18]. Most patients know the importance of being physically active, sleeping well, eating healthily, and taking their medication as prescribed, but are often unable to make use of general health advice, as their primary concern is avoiding worsening of their symptoms. However, a focus on symptom regulation with the intention of preventing worsening might actually risk increasing symptoms by conserving the health problem, particularly if the first indication of improvement is a temporary worsening of symptoms, such as dyspnea or tiredness after increased physical activity. Breaking this unhelpful pattern of symptom regulation is at the core of the concentrated rehabilitation model.

The overall structure of the concentrated rehabilitation model is identical across all disorders [16]. Aided by an interdisciplinary team, patients work in a safe setting to use current coping strategies that are described in the published protocols for chronic illnesses [16]. Our rehabilitation program can be summarized into three stages: (1) pretreatment, in which patients are prepared for change by thoroughly introducing them to the details of the rehabilitation program before it starts; (2) concentrated rehabilitation, which is delivered over 3 to 4 consecutive days in groups of 6 to 10 patients; and (3) follow-up, which includes daily digital follow-ups for the first 3 weeks after the intervention, followed by questionnaires and physical examinations at 3, 6, and 12 months. A web app will be used for the digital follow-up and for the questionnaires.

During the concentrated intervention, each patient is assisted by the interdisciplinary team, which includes physicians, physiotherapists, psychologists, pharmacists, clinical nutritionists, and nurses. This team helps patients explore new approaches in how to deal with their symptoms. Specifically, the patients are instructed to view each symptom as an opportunity to break unhelpful patterns of symptom regulation by doing things differently (ie, making "microchoices"). This approach enables the patients to systematically increase their flexibility and level of functioning when symptoms and health challenges are present. All patients focus on breaking unhelpful patterns of symptom regulation that are relevant to themselves. In addition, focusing on deliberate behavior and action instead of symptoms implies that change is within reach and possible to control [16]. Each day, the group attends a joint program for approximately 8 hours, and participants then attend individually planned training sessions in the afternoon and evening. The long sessions give each patient the opportunity to practice a broad range of potential microchoices. The training is interspersed with brief group sessions, in which each patient shares their progress in targeting and breaking unhelpful patterns of symptom regulation and receives expert feedback on how to improve their outcome by considering all microchoices. The group format offers substantial opportunities for both inspiration and support. On the last day of the intervention, every patient makes an individualized plan on how to integrate the changes they have learned into everyday living, summarized under the headings "Eat," "Move," and "Sleep," and how to systematically

make microchoices consistent with increased everyday functioning.

The aim of this study is to explore the acceptability of concentrated, interdisciplinary group rehabilitation for patients with COPD. The intervention is expected to improve functional status and to be highly acceptable to patients.

The main hypotheses are identical to the ones previously published for other disorders [16].

We hypothesize that the treatment will be acceptable, as indicated by the following: the proportion of patients who meet the inclusion criteria and accept participation will be >90%; the proportion of included patients who attend the concentrated intervention will be >90%; and the proportion of included patients who complete participation in the concentrated intervention will be >90%.

Further, we hypothesize that the patients will increase their functional exercise capacity, as measured by functional performance tests that include the Stair Climbing Test and the 60-Second Sit-to-Stand Test; improve their health status 3, 6, and 12 months after the intervention, as measured by the COPD assessment test (CAT) [19]; and be satisfied with the treatment, as defined by a mean Client Satisfaction Questionnaire 8 (CSQ-8) [20] score of 20 or more, with no single dimension below an average score ≤2. A cut-off score of 20 was chosen based on previous research that used scores ≥20 to indicate "good" satisfaction [21].

Finally, we hypothesize that there will be a significant change in the extent to which COPD affects the patients' lives, as measured with the Brief Illness Perception Questionnaire (BIPQ) [22] with the following questions: "How much does your illness affect your life?" "How much control do you feel you have over your illness?" "How concerned are you about your illness?" and "How well do you feel you understand your illness?"

Methods

Overview

The study is part of the Project Development of Smarter Health Solutions (PUSH) project, which is a collaboration between Haukeland University Hospital (Bergen, Norway) and Helse i Hardanger (HiH) (Øystese, Norway). The treatment is delivered at HiH in Øystese, which is a small municipality outside Bergen. The methods for this open, nonrandomized study are identical to already published protocols for low back pain, type 2 diabetes, post–COVID-19 fatigue, and depression or anxiety [16].

Study Design and Participants

This is a nonrandomized, 1-group pre-post study with a longitudinal 12-month follow-up period and the intention to test the acceptability and effectiveness of an interdisciplinary, concentrated group rehabilitation program for patients with COPD.

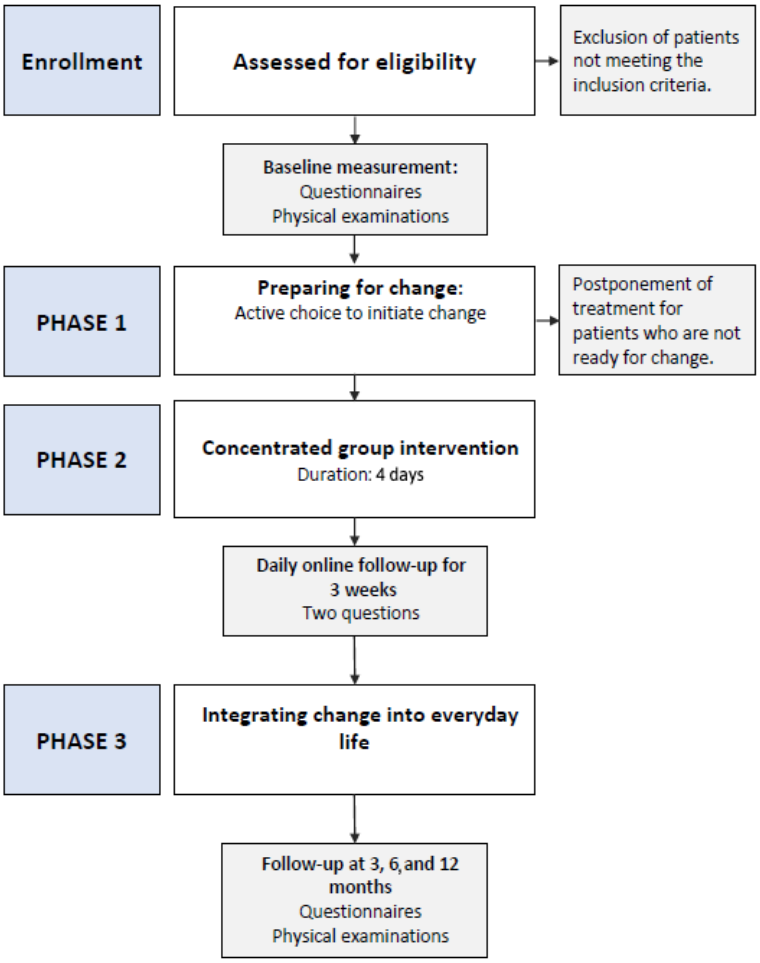
We will recruit 50 patients fulfilling the following inclusion criteria: motivation for change regarding self-management of COPD and a diagnosis of COPD based on a postbronchodilation forced expiratory volume in 1 sec (FEV_1) to forced vital capacity (FVC) ratio below the lower limit of normal according to the Global Lung Function Initiative [23]. The patients must be fluent in oral and written Norwegian, have access to a smartphone, and have sufficient digital competence to handle online questionnaires. They must be independent in activities of daily living, able to perform physical activities indoors and outdoors, and able to climb stairs. Patients will not be excluded if there are exacerbations requiring medical treatment during the last 4 weeks prior to inclusion, but their inclusion will be deferred. Patients with inflammatory disorders that affect activity level, such as rheumatoid arthritis, systemic lupus erythematosus, or other connective tissue disorders; inflammatory bowel disease; or any active cancer in the last 5 years will be excluded. Common chronic diseases with known inflammatory components, such as chronic heart disease, diabetes, and hypertension, will not be a cause for exclusion.

The treatment will be delivered in groups of 6 to 10 patients. The dates for the group sessions are predecided, and patients will be successively allocated to the groups upon availability.

Procedures and Patient Flow

Patients will be referred by their general practitioners or other physicians responsible for their treatment to the PUSH project at the Department of Thoracic Medicine at Haukeland University Hospital. To be included, the patients must be entitled to health care in the specialist health service. Patients who, based on the referral, seem to fulfill the inclusion criteria and none of the exclusion criteria will be called by one of the clinicians and will receive information about the PUSH project and the concentrated rehabilitation (Figure 1). If they are in the target group, an appointment for screening will be made. To ensure all participants receive identical information about the program, they will be asked to watch a video describing the program. The informed consent form will be signed online prior to answering the questionnaires. Each patient will then be invited to a physical examination where lung function and exercise capacity will be assessed. To ensure that the patients are prepared and ready for the intervention, they will be invited to a 1-hour group meeting 1 to 3 weeks prior to the concentrated rehabilitation, where details of the program will be described. The week before the intervention, the group leader will call each patient to ensure that they have received the necessary information and are ready for the concentrated rehabilitation program.

Figure 1. Flowchart of the study. Physical examinations at baseline and the 3-, 6-, and 12-month follow-ups include a cardiopulmonary exercise test, the Stair Climbing Test, the 60-Second Sit-to-Stand Test, and a lung function test. The cardiopulmonary exercise test will be administered only at baseline and at the 12-month follow-up. Daily online follow-up (in phase 2) includes two questions: (1) "To what extent did you allow the symptoms to decide today?" and (2) "To what extent did you make use of the principle of 'doing something else'?" (responses range from 0-10 for both).



Outcome Measures

The outcomes presented in this protocol paper address the patients' overall experiences with the concept of the concentrated treatment format. These measures will be assessed before the start of the program and 1 week, 3 months, 6 months, and 12 months after the program. Assessments of exercise capacity will be done before and at 3-month, 6-month, and 12-month postrehabilitation follow-ups. Initial results will be published based on the 3-month follow-up data and final results will be published based on the complete intervention, including the 12-month follow-up data.

Primary Outcome Measures

The acceptability of the concentrated rehabilitation program will be measured by the following variables: (1) the proportion of patients agreeing to participate in the rehabilitation among those fulfilling the inclusion criteria and offered participation; (2) the proportion of patients offered participation that start treatment; and (3) the proportion of patients that complete the treatment program (on-site). Acceptability will be measured before the start of the rehabilitation program, and during the intervention, completers and noncompleters will be registered.

The CSQ-8 [20] is an 8-item questionnaire that measures patient satisfaction with health services, where the items are rated from 1 (very low satisfaction) to 4 (very high satisfaction). The total score ranges from 8 to 32, with higher scores indicating a higher degree of satisfaction. The CSQ-8 has good psychometric properties, high internal consistency (Cronbach α=.93), and high interitem correlation [24]. The CSQ-8 will be administered 1 week after the intervention.

The BIPQ is a 9-item questionnaire designed to assess cognitive and emotional representations of illness [22]. Questions are graded from 1 to 10. The last item deals with perceived causes of illness; respondents list the perceived 3 most important causal factors in their illness. For this questionnaire, the general word "illness" can be replaced by the name of a particular illness. The word "treatment" in the treatment control item can be replaced by a particular treatment, such as "surgery" or "physiotherapy." The scale has good psychometric properties according to a recent review [25]. The BIPQ will be administered at baseline and 1 week, 3 months, 6 months, and 12 months after rehabilitation.

Secondary Outcome Measures

Pre- and posttreatment and at the follow-up assessments at 3, 6, and 12 months, the patients will be asked to rate on a scale

from 0 to 10 the extent to which they used the following strategies when trying to handle their symptoms. This questionnaire was developed in cooperation with patients with previous experience in the concentrated treatment format.

1. Wait to start an activity until I feel up to it
2. Wait to start an activity until I am certain that I will succeed
3. Ensure that the symptoms will not get worse
4. Ensure that I am prepared to handle challenges
5. Try to calm down before proceeding when I get anxious
6. Spend a lot of time on worrying and ruminating
7. Avoid socializing if I do not feel up to it
8. Ensure that I get enough rest
9. Try to not let others see how I feel
10. Try to have a positive mindset
11. Follow my gut feeling

Evaluations at Baseline and 3- and 12-Month Follow-Ups

Height and body mass will be measured to an accuracy of 0.5 cm and 0.1 kg, respectively. The patients will undergo bioelectrical impedance measurements of fat-free mass and fat mass after an overnight fast (InBody 770). BMI will be calculated by dividing weight by the square of height (kg/m^2), fat-free mass index as the fat-free mass divided by the square of height, and the fat-mass index as the fat mass divided by the square of height [26].

Spirometry will be conducted on a Vyntus Body/Aerosol Provocation System Plethysmograph (Vyaire Medical GmbH) according to the American Thoracic Society/European Respiratory Society standardization of lung function testing [27]. The highest FEV_1 and FVC ratio values from at least 3 satisfactory expiratory maneuvers will be used. Maximal voluntary ventilation will be directly measured by breathing as deeply and frequently as possible for 12 seconds in a standing position.

Cardiopulmonary exercise tests (CPETs) will be performed on a treadmill with a gradually increasing incline until exhaustion (Woodway). Prior to each CPET, complete volume and gas calibration will be done. All patients will receive initial training to become familiar with treadmill walking before the test starts. The test will start with 3 minutes of warm-up, and steady-state measurements will be conducted with a walking speed individually set between 1.8 and 3.8 kilometers per hour and initial inclination set at 0% based on the predicted fitness level of the patient. The inclination will be increased every 60 seconds by 2%, finally reaching 20%. If the participants can still continue, the speed will increase by 0.5 kilometers per hour until the patient reaches exhaustion. The test will be terminated if the test subject is unable to continue (even with encouragement), if they experience pronounced pain or dizziness, if there are ischemic electrocardiogram (ECG) changes, or if there is a decrease in systolic pressure below the resting pressure [28]. Gas exchange and ventilatory variables will be measured continuously with breath-by-breath sampling, averaged over 30-second intervals through a Hans Rudolph 2-way breathing mask (V2 Mask). The breathing mask will be connected to a Vmax SensorMedics metabolic analyzer (Jaeger CPX Vyntus) to assess ventilatory variables and the content of oxygen and carbon dioxide of expired air to calculate oxygen uptake. Percutaneous oxygen saturation (SpO_2) will be measured with an ear probe using a stationary pulse oximeter. Heart rate will be measured through a 12-lead ECG (Custo Cardio 300; Custo Med). Blood pressure will be measured with a Tango M2 (SunTech Medical). Ratings for dyspnea and leg fatigue will be recorded every second minute throughout the test using the Borg Category-Ratio 10 scale [29], with a final rating during maximal effort at the end of the test. All assessments will be measured at rest in a sitting position before the start of the test, throughout the exercise test, and for 2 minutes after termination of the test.

The Stair Climbing Test will be used to assess submaximal exercise capacity and will be performed as standardized by Tveter et al [30]. The participants walk up and down 18 steps 3 times as fast as possible. They can walk or run but not skip any steps. Time in minutes and seconds is the main outcome of the test.

The 60-Second Sit-to-Stand-Test will be used to assess lower extremity strength and will be performed as standardized by Tveter et al [30]. The participants start in a seated position in a chair with arms crossed and raised 45 cm, without any armrest, and will be instructed to complete as many full stands as possible in 60 seconds. The number of repetitions is the main outcome.

The CAT will be used to measure the impact of COPD in daily life. The questionnaire consists of 8 questions; possible scores range from 0 to 40 [19,31]. A score below 10 indicates a low impact of symptoms, a score between 10 and 20 medium impact, a score between 21 and 30 high impact, and a score over 30 very high impact [32]. A minimum clinically important change is a reduction of between 2 to 3 points [33]. The following are other measures that we will use, with their respective purposes: The Modified Medical Research Council scale is a self-administered grading system used to measure symptoms of dyspnea; the scale ranges from 0 to 4, with higher scores indicating more severe symptoms [34]. The Dyspnea-12 scale is a patient-reported scale for measuring the severity of breathlessness consisting of 12 descriptors to cover physical and psychological dimensions [35]. The General Anxiety Disorder-7 scale assesses generalized anxiety disorder [36]. The Patient Health Questionnaire-9 is a self-reported questionnaire for screening, diagnosing, monitoring, and measuring the severity of depression [37]. The Bergen Insomnia Scale measures insomnia, consisting of 6 items, with the first 3 pertaining to sleep onset and the last 3 referring to not feeling adequately rested [38]. The International Physical Activity Questionnaire–Short Form measures daily physical activity [39]. The Nordic Musculoskeletal Questionnaire quantifies musculoskeletal pain in 9 body regions [40]. The Strength, Assistance With Walking, Rising From a Chair, Climbing Stairs, and Falls questionnaire is a screening tool to identify patients with probable sarcopenia [41].

Intervention

The protocol paper reports details of the intervention [16]. In summary, the intervention consists of 3 phases (shown in Figure 1): (1) preparing for change, (2) the concentrated intervention

lasting for 3-4 days, and (3) integrating change into everyday living [16]. The focus throughout the intervention is on how to initiate and maintain change by breaking inflexible patterns of symptom regulation.

Statistical Analyses and Data Handling

The data will be analyzed with SPSS (version 28; IBM Corp) and Stata (version 17; Stata Corp). Changes in self-reported symptoms, level of everyday functioning, and exercise capacity will be examined with repeated-measure analyses. Statistical significance will be set at α=.05. The Glass delta, with pretreatment SD as the denominator, will be used to calculate within-group effect sizes. The Glass delta is the recommended effect size for intervention studies, because there are reasons to believe that the treatment will influence SD, as well as the mean [16]. Effect sizes are usually interpreted as small (0.2), moderate (0.5), or large (0.8). Considering that the current research is a nonrandomized study of a novel, interdisciplinary group treatment for patients with COPD, we expect small to moderate effect sizes.

The number of participants needed to be included in a pragmatic nonrandomized study varies in the literature. However, according to the central limit theorem, the mean of a sample of data will be closer to the overall mean for the population who are studied when the sample size increases [42]. As a rule, sample sizes around 30 to 50 are suggested to be sufficient for the central limit theorem to hold, meaning that the sample means have a normal distribution. We decided to include 50 participants to enable long-term follow-up of the patients.

Missing data regarding the primary outcome variables will be handled by multiple imputation (MI). Under the missing at random (MAR) assumption, MI is presently one of the best available methods of dealing with missing data and will provide unbiased estimates [16]. The main analyses of the primary outcomes will thus be completed under the MAR assumption. Sensitivity analyses will be performed to evaluate the robustness of the results and the potential impact that nonignorable missing data could have on the predicted results. These sensitivity analyses will be based on the pattern-mixture model [16]. In short, a pattern-mixture model involves assumptions that participants lost to follow-up can have a mean outcome that differs by an offset from participants who do not drop out. The impact on the results of various choices of clinically possible offsets can then be examined, and if the effect from the primary analysis is qualitatively maintained for the range of plausible offsets, the findings can be assumed to be robust.

Data Collection and Monitoring

The data will be collected electronically and by physical examination, and all sensitive data will be stored on an encrypted server at Western Norway Regional Health Authority Information and Communication Technology. Once the patients are included, all data entered by the participants will be monitored by an established study administrative team.

Adverse Events

If an acute condition occurs, patients will receive the necessary care and might be excluded from the study if there are concerns about safety. Such patients will be thoroughly described and accounted for in line with the illness-specific standard operating procedures. Acute exacerbations during the intervention period will be registered.

User Involvement

Helse i Hardanger has established a broad user panel with representatives recruited through Haukeland University Hospital and Helse i Hardanger. The following organizations are represented: Norwegian Asthma and Allergy Association, Norwegian Rheumatics' Association, Mental Health Norway, Breast Cancer Association, Norwegian Diabetes Association, Norwegian Association for Lung and Heart Disease, and Grannehjelpa ("neighbors' help" in Norwegian). The panel has given feedback throughout the development of the protocol and approved the final version.

Ethics Approval

The PUSH project and the web app have been approved by the Western Norway Regional Committees for Medical and Health Research Ethics (REK 2020/101638). The same organization approved this study (REK 2021/219567). The study was registered at ClinicalTrials.gov (NCT05234281). Written consent will be obtained from all participants prior to study participation, and the project will be conducted in accordance with the Helsinki Declaration.

Gender Perspectives

The inclusion criteria, as well as all interventions, are gender neutral. However, to ensure adequate external validity and proper representation, we have no absolute limits in terms of minimum inclusion rates of one gender.

Results

Recruitment started in April 2022. For the initial 3-month results, recruitment is expected to be completed by June 2023.

Discussion

Principal Findings

In this paper, we describe a protocol for the establishment and initial evaluation of a concentrated, interdisciplinary group rehabilitation program for patients with COPD. We will explore the acceptability of the intervention and hypothesize that the intervention will be positively accepted by the participants, will reduce the impact of the illness on their lives, and will improve their level of daily functioning.

This is an extension of a protocol that we recently published for a novel concentrated, transdiagnostic group intervention for patients with chronic low back pain, post-Covid-19 symptoms, anxiety or depression, or type 2 diabetes [16].

Existing rehabilitation programs often have a duration of 4 to 12 weeks, but there is no consensus about the optimal duration [17]. However, longer programs are thought to enable greater gains and allow the maintenance of benefits, with 8 weeks being considered the minimum to achieve a clinically meaningful change [16,43,44]. The future of pulmonary rehabilitation will

rely on rehabilitation models that include more choices for the patient and the possibility of increased personalization of the program [10]. If the concentrated pulmonary rehabilitation program is accepted by the patients in this study and leads to an enhanced functional status, large groups of patients might benefit from it in the future. Each patient will receive a tailored program in a group setting, which will provide the opportunity to utilize the group effect in addition to individualizing the treatment to the patient's own goals and challenges.

This is an open, nonrandomized study, with the participants as their own controls (in a pre-post comparison) and 12-month follow-up period. Although this allows summarizing the experiences and findings as described, it does not allow drawing causal conclusions on the effects of the intervention. The protocol describes a concentrated rehabilitation approach. If the intervention appears to lead to an improvement in health, it could trigger follow-up studies investigating the effects of this intervention in comparison to traditional ways of delivering pulmonary rehabilitation [6].

Limitations

Drop outs and poor adherence to the intervention might threaten the internal validity of the study. Although we aim to give clear information to the participants to limit this problem, we cannot be sure that they will participate for the whole period or that they will complete the digital and clinical examinations at the 3-, 6-, and 12-month follow-ups. A notice will be sent to the patients approximately 2 to 3 weeks before each assessment. Participants who do not answer the questionnaires online or do not show up for clinical follow-ups will be contacted by phone. The impact of missing data will be evaluated with appropriate statistical methods. Finally, although the acceptability of the concentrated treatment format has been validated for persons with diseases other than COPD [15,45], the outcomes have not been formally validated. To compensate for this, all reasons for not accepting, attending, or completing the intervention will be recorded.

Conclusion

We present a protocol for the establishment and evaluation of a concentrated pulmonary rehabilitation program for patients with COPD. The treatment focuses on how to initiate and maintain change, with a shift away from monitoring symptoms toward an active approach to daily health-promoting microchoices. This concentrated intervention has the potential to change the way we deliver pulmonary rehabilitation to patients with COPD and might increase the availability of pulmonary rehabilitation to patients who would benefit from this treatment. This rehabilitation model might be a useful addition to the treatment armamentarium of the health care system in the face of coming sociodemographic challenges, and might also increase the availability of pulmonary rehabilitation to the public.

Acknowledgments

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Data Availability

In accordance with the approvals granted for this study by the Regional Committee on Medical Research Ethics and the Norwegian Data Inspectorate, the data files will be stored securely and in accordance with the Norwegian Law of Privacy Protection. A subset of the data file with anonymized data will be made available to interested researchers upon reasonable request to author BF, providing that Norwegian privacy legislation and the General Data Protection Regulation are respected and that permission is granted by the Norwegian Data Inspectorate and the data protection officer at Haukeland University Hospital.

Conflicts of Interest

None declared.

References

1. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2022 Report. Global Initiative for Chronic Obstructive Lung Disease. URL: https://goldcopd.org/2022-gold-reports-2/ [accessed 2022-10-14]
2. Chronic obstructive pulmonary disease (COPD) 2022. World Health Organization. URL: https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd) [accessed 2022-10-14]
3. Lopez AD, Shibuya K, Rao C, Mathers CD, Hansell AL, Held LS, et al. Chronic obstructive pulmonary disease: current burden and future projections. Eur Respir J 2006 Feb;27(2):397-412 [FREE Full text] [doi: 10.1183/09031936.06.00025805] [Medline: 16452599]
4. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006 Nov;3(11):e442 [FREE Full text] [doi: 10.1371/journal.pmed.0030442] [Medline: 17132052]
5. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. National Institute for Health and Care Excellence. URL: https://www.nice.org.uk/guidance/ng115/chapter/Recommendations#managing-stable-copd2019 [accessed 2022-10-14]

6. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, ATS/ERS Task Force on Pulmonary Rehabilitation. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med 2013 Oct 15;188(8):e13-e64. [doi: 10.1164/rccm.201309-1634ST] [Medline: 24127811]
7. Camp PG, Hernandez P, Bourbeau J, Kirkham A, Debigare R, Stickland MK, et al. Pulmonary rehabilitation in Canada: A report from the Canadian Thoracic Society COPD Clinical Assembly. Can Respir J 2015;22(3):147-152 [FREE Full text] [doi: 10.1155/2015/369851] [Medline: 25848802]
8. Nishi SPE, Zhang W, Kuo Y, Sharma G. Pulmonary rehabilitation utilization in older adults with chronic obstructive pulmonary disease, 2003 to 2012. J Cardiopulm Rehabil Prev 2016;36(5):375-382 [FREE Full text] [doi: 10.1097/HCR.0000000000000194] [Medline: 27428819]
9. Frisk B, Sundør IE, Dønåsen MR, Refvem OK, Borge CR. How is the organisational settings, content and availability of comprehensive multidisciplinary pulmonary rehabilitation for people with COPD in primary healthcare in Norway: a cross-sectional study. BMJ Open 2022 Feb 17;12(2):e053503 [FREE Full text] [doi: 10.1136/bmjopen-2021-053503] [Medline: 35177448]
10. Holland AE, Cox NS, Houchen-Wolloff L, Rochester CL, Garvey C, ZuWallack R, et al. Defining modern pulmonary rehabilitation. An official American Thoracic Society workshop report. Ann Am Thorac Soc 2021 May;18(5):e12-e29 [FREE Full text] [doi: 10.1513/AnnalsATS.202102-146ST] [Medline: 33929307]
11. Hansen B, Hagen K, Öst LG, Solem S, Kvale G. The Bergen 4-Day OCD treatment delivered in a group setting: 12-month follow-up. Front Psychol 2018;9:639 [FREE Full text] [doi: 10.3389/fpsyg.2018.00639] [Medline: 29774005]
12. Stubhaug B, Lier HO, Aßmus J, Rongve A, Kvale G. A 4-Day mindfulness-based cognitive behavioral intervention program for CFS/ME. An open study, with 1-year follow-up. Front Psychiatry 2018;9:720 [FREE Full text] [doi: 10.3389/fpsyt.2018.00720] [Medline: 30618889]
13. Haukebø K, Skaret E, Ost L, Raadal M, Berg E, Sundberg H, et al. One- vs. five-session treatment of dental phobia: a randomized controlled study. J Behav Ther Exp Psychiatry 2008 Sep;39(3):381-390. [doi: 10.1016/j.jbtep.2007.09.006] [Medline: 18005932]
14. Kvale G, Hansen B, Björgvinsson T, Børtveit T, Hagen K, Haseth S, et al. Successfully treating 90 patients with obsessive compulsive disorder in eight days: the Bergen 4-day treatment. BMC Psychiatry 2018 Oct 04;18(1):323 [FREE Full text] [doi: 10.1186/s12888-018-1887-4] [Medline: 30286745]
15. Launes G, Hagen K, Sunde T, Öst LG, Klovning I, Laukvik I, et al. A randomized controlled trial of concentrated ERP, self-help and waiting list for obsessive- compulsive disorder: the Bergen 4-day treatment. Front Psychol 2019;10:2500 [FREE Full text] [doi: 10.3389/fpsyg.2019.02500] [Medline: 31803089]
16. Kvale G, Frisk B, Jürgensen M, Børtveit T, Ødegaard-Olsen ØT, Wilhelmsen-Langeland A, et al. Evaluation of novel concentrated interdisciplinary group rehabilitation for patients with chronic illnesses: protocol for a nonrandomized clinical intervention study. JMIR Res Protoc 2021 Oct 07;10(10):e32216 [FREE Full text] [doi: 10.2196/32216] [Medline: 34505838]
17. Beauchamp MK, Janaudis-Ferreira T, Goldstein RS, Brooks D. Optimal duration of pulmonary rehabilitation for individuals with chronic obstructive pulmonary disease - a systematic review. Chron Respir Dis 2011;8(2):129-140 [FREE Full text] [doi: 10.1177/1479972311404256] [Medline: 21596893]
18. Yohannes AM, Alexopoulos GS. Depression and anxiety in patients with COPD. Eur Respir Rev 2014 Sep;23(133):345-349 [FREE Full text] [doi: 10.1183/09059180.00007813] [Medline: 25176970]
19. Jones PW, Harding G, Berry P, Wiklund I, Chen W, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J 2009 Sep;34(3):648-654 [FREE Full text] [doi: 10.1183/09031936.00102509] [Medline: 19720809]
20. Larsen DL, Attkisson CC, Hargreaves WA, Nguyen TD. Assessment of client/patient satisfaction: development of a general scale. Eval Program Plann 1979;2(3):197-207. [doi: 10.1016/0149-7189(79)90094-6] [Medline: 10245370]
21. Smith D, Roche E, O'Loughlin K, Brennan D, Madigan K, Lyne J, et al. Satisfaction with services following voluntary and involuntary admission. J Ment Health 2014 Feb;23(1):38-45. [doi: 10.3109/09638237.2013.841864] [Medline: 24484191]
22. Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. J Psychosom Res 2006 Jun;60(6):631-637. [doi: 10.1016/j.jpsychores.2005.10.020] [Medline: 16731240]
23. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J 2012 Dec;40(6):1324-1343 [FREE Full text] [doi: 10.1183/09031936.00080312] [Medline: 22743675]
24. Nguyen TD, Attkisson CC, Stegner BL. Assessment of patient satisfaction: development and refinement of a service evaluation questionnaire. Eval Program Plann 1983;6(3-4):299-313. [doi: 10.1016/0149-7189(83)90010-1] [Medline: 10267258]
25. Broadbent E, Wilkes C, Koschwanez H, Weinman J, Norton S, Petrie KJ. A systematic review and meta-analysis of the Brief Illness Perception Questionnaire. Psychol Health 2015;30(11):1361-1385. [doi: 10.1080/08870446.2015.1070851] [Medline: 26181764]

26. VanItallie TB, Yang MU, Heymsfield SB, Funk RC, Boileau RA. Height-normalized indices of the body's fat-free mass and fat mass: potentially useful indicators of nutritional status. Am J Clin Nutr 1990 Dec;52(6):953-959. [doi: 10.1093/ajcn/52.6.953] [Medline: 2239792]
27. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J 2005 Aug;26(2):319-338 [FREE Full text] [doi: 10.1183/09031936.05.00034805] [Medline: 16055882]
28. Albouaini K, Egred M, Alahmar A, Wright DJ. Cardiopulmonary exercise testing and its application. Postgrad Med J 2007 Nov;83(985):675-682 [FREE Full text] [doi: 10.1136/hrt.2007.121558] [Medline: 17989266]
29. Borg G. Borg's Perceived Exertion and Pain Scales. Champaign, IL: Human Kinetics; 1998:viii, 104.
30. Tveter AT, Dagfinrud H, Moseng T, Holm I. Measuring health-related physical fitness in physiotherapy practice: reliability, validity, and feasibility of clinical field tests and a patient-reported measure. J Orthop Sports Phys Ther 2014 Mar;44(3):206-216. [doi: 10.2519/jospt.2014.5042] [Medline: 24450369]
31. Dodd JW, Hogg L, Nolan J, Jefford H, Grant A, Lord VM, et al. The COPD assessment test (CAT): response to pulmonary rehabilitation. A multicentre, prospective study. Thorax 2011 May;66(5):425-429. [doi: 10.1136/thx.2010.156372] [Medline: 21398686]
32. Jones PW, Tabberer M, Chen W. Creating scenarios of the impact of COPD and their relationship to COPD Assessment Test (CAT™) scores. BMC Pulm Med 2011 Aug 11;11:42 [FREE Full text] [doi: 10.1186/1471-2466-11-42] [Medline: 21835018]
33. Smid DE, Franssen FME, Houben-Wilke S, Vanfleteren LEGW, Janssen DJA, Wouters EFM, et al. Responsiveness and MCID estimates for CAT, CCQ, and HADS in patients with COPD undergoing pulmonary rehabilitation: a prospective analysis. J Am Med Dir Assoc 2017 Jan;18(1):53-58. [doi: 10.1016/j.jamda.2016.08.002] [Medline: 27624705]
34. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax 1999 Jul;54(7):581-586 [FREE Full text] [doi: 10.1136/thx.54.7.581] [Medline: 10377201]
35. Yorke J, Moosavi SH, Shuldham C, Jones PW. Quantification of dyspnoea using descriptors: development and initial testing of the Dyspnoea-12. Thorax 2010 Jan;65(1):21-26 [FREE Full text] [doi: 10.1136/thx.2009.118521] [Medline: 19996336]
36. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006 May 22;166(10):1092-1097. [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
37. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA 1999 Nov 10;282(18):1737-1744. [doi: 10.1001/jama.282.18.1737] [Medline: 10568646]
38. Pallesen S, Bjorvatn B, Nordhus IH, Sivertsen B, Hjørnevik M, Morin CM. A new scale for measuring insomnia: the Bergen Insomnia Scale. Percept Mot Skills 2008 Dec;107(3):691-706. [doi: 10.2466/pms.107.3.691-706] [Medline: 19235401]
39. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003 Aug;35(8):1381-1395. [doi: 10.1249/01.MSS.0000078924.61453.FB] [Medline: 12900694]
40. Dawson AP, Steele EJ, Hodges PW, Stewart S. Development and test-retest reliability of an extended version of the Nordic Musculoskeletal Questionnaire (NMQ-E): a screening instrument for musculoskeletal pain. J Pain 2009 May;10(5):517-526. [doi: 10.1016/j.jpain.2008.11.008] [Medline: 19345154]
41. Malmstrom TK, Morley JE. SARC-F: a simple questionnaire to rapidly diagnose sarcopenia. J Am Med Dir Assoc 2013 Aug;14(8):531-532. [doi: 10.1016/j.jamda.2013.05.018] [Medline: 23810110]
42. Ross SM. Introductory Statistics. Cambridge, MA: Academic Press; 2017.
43. Rossi G, Florini F, Romagnoli M, Bellantone T, Lucic S, Lugli D, et al. Length and clinical effectiveness of pulmonary rehabilitation in outpatients with chronic airway obstruction. Chest 2005 Jan;127(1):105-109. [doi: 10.1378/chest.127.1.105] [Medline: 15653969]
44. Troosters T, Casaburi R, Gosselink R, Decramer M. Pulmonary rehabilitation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2005 Jul 01;172(1):19-38. [doi: 10.1164/rccm.200408-1109SO] [Medline: 15778487]
45. Havnen A, Hansen B, Öst LG, Kvale G. Concentrated ERP delivered in a group setting: a replication study. Behav Cogn Psychother 2017 Sep;45(5):530-536. [doi: 10.1017/S1352465817000091] [Medline: 28287064]

Abbreviations

BIPQ: Brief Illness Perception Questionnaire
CAT: Chronic Obstructive Pulmonary Disease Assessment Test
COPD: chronic obstructive pulmonary disease
CPET: Cardiopulmonary Exercise Test
CSQ: Client Satisfaction Questionnaire
ECG: electrocardiogram
FEV1: forced expiratory volume at the first second
FVC: forced vital capacity

HiH: Helse i Hardanger
MAR: missing at random
MI: multiple imputation
PUSH: Project Development of Smarter Health Solutions

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Protocol

Mindfulness Training for Depressed Older Adults Using Smartphone Technology: Protocol for a Fully Remote Precision Clinical Trial

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Abstract

Background: Precision medicine, optimized interventions, and access to care are catchphrases for the future of behavioral treatments. Progress has been slow due to the dearth of clinical trials that optimize interventions' benefits, individually tailor interventions to meet individual needs and preferences, and lead to rapid implementation after effectiveness is demonstrated. Two innovations have emerged to meet these challenges: fully remote trials and precision clinical trials.

Objective: This paper provides a detailed description of Mindful MyWay, a study designed to test online mindfulness training in older adults with depression. Consistent with the concept of fully remote trials using a smartphone app, the study requires no in-person contact and can be conducted with participants anywhere in the United States. Based upon the precision medicine framework, the study assesses participants using high-frequency assessments of symptoms, cognitive performance, and patient preferences to both understand the individualized nature of treatment response and help individually tailor the intervention.

Methods: Mindful MyWay is an open-label early-phase clinical trial for individuals 65 years and older with current depression. A smartphone app was developed to help coordinate the study, deliver the intervention, and evaluate the acceptability of the intervention, as well as predictors and outcomes of it. The curriculum for the fully remote intervention parallels the mindfulness-based stress reduction curriculum, a protocolized group-based mindfulness training that is typically provided in person. After consent and screening, participants download The Healthy Mind Lab mobile health smartphone app from the Apple App Store, allowing them to complete brief smartphone-based assessments of depressive symptoms and cognitive performance 4 times each day for 4 weeks prior to and after completing the intervention. The intervention consists of an introduction video and 10 weekly mindfulness training sessions, with the expectation to practice mindfulness at home daily. The app collects participant preference data throughout the 10-week intervention period; these high-frequency assessments identify participants' individually dynamic preferences toward the goal of optimizing the intervention in future iterations.

Results: Participant recruitment and data collection began in March 2019. Final end point assessments will be collected in May 2022. The paper describes lessons learned regarding the critical role of early-phase testing prior to moving to a randomized trial.

Conclusions: The Mindful MyWay study is an exemplar of innovative clinical trial designs that use smartphone technology in behavioral and neuropsychiatric conditions. These include fully remote studies that can recruit throughout the United States, including hard-to-access areas, and collect high-frequency data, which is ideal for idiographic assessment and individualized intervention optimization. Our findings will be used to modify our methods and inform future randomized controlled trials within a precision medicine framework.

Trial Registration: ClinicalTrials.gov NCT03922217; https://clinicaltrials.gov/ct2/show/NCT03922217

International Registered Report Identifier (IRRID): DERR1-10.2196/39233

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KEYWORDS

mHealth; mindfulness; depression; aging; precision medicine; fully remote trial; technology; older; adult; smartphone; clinical trial; intervention; death; needs; preferences; online; remote; treatment; depressed; training; mind; session; medicine

Introduction

Getting to Precision Medicine in Neurobehavioral Conditions: The Role of Smartphone-Based Technology

Precision medicine, that is, individually optimized treatment, needs to be the goal for clinical trials in neurobehavioral disorders [1]. The precision medicine target is particularly critical to depression, a highly heterogeneous condition in which individual treatments usually have small effect sizes at a group level.

To successfully develop precision medicine for depression, clinical trials of behavioral interventions need to overcome many causes of treatment failure at the individual patient level. In summary, these failures are the intervention not being a good fit for that particular patient's symptom pattern (eg, proposing mindfulness training for depression when the driving force of the depressive symptoms would not respond to mindfulness), the intervention not being optimized to that individual patient (eg, does not provide content in the manner or frequency that the participant prefers or needs, leading to poor adherence or lack of benefit), and the assessment of the intervention outcomes (eg, depressive symptoms) having low reliability, leading to an apparent small treatment effect size. The precision clinical trial framework is a recently developed framework to overcome these obstacles to precision [1]. The framework explicitly develops and tests intervention optimization and personalization during a series of intervention development trials.

Another problem in clinical trials—especially those of behavior interventions—are their lack of reach and access (particularly to low-resourced individuals or those far from academic medical centers). This in turn leads to small and less generalizable study samples. Further, interventions tested only within academic medical centers tend to be implemented slowly if at all, a long-standing failure to translate science into practice [2]. Fully remote trials have been proposed as a way to overcome these problems by recruiting, screening, assessing, and treating patients where they live [3].

Smartphone-based technology can help drive the clinical trial innovations described above. In this study, we created an app designed to conduct a fully remote clinical trial of a behavior intervention—mindfulness for depression in older adults—and test it within a precision medicine framework. The study is the first phase in a line of research to both advance mindfulness as a precision medicine intervention for depression and advance clinical trial methodology.

Mindfulness for Depression in Older Adults

Nationally, 18.4% of adults 65 years and older report symptoms of depression; 12% report subjective [4] cognitive decline [5,6]. Late-life depression and cognitive decline frequently coexist and can lead to Alzheimer disease and related dementias (ADRD) [7]. Given the growing older adult population and the rising public health concerns of late-life depression and ADRD, effective and accessible interventions are needed that ameliorate both depressive symptoms and cognitive functioning.

Mindfulness-based stress reduction (MBSR) may be an effective intervention for mitigating the effects of aging on the brain [8]. MBSR combines the teaching and practice of mindfulness meditation following an 8-week structured group-based protocol. Clinical trials indicate that MBSR practice may help in improving mood symptoms and neurocognitive performance in older adults [9,10]. Wetherell and colleagues [8] found that older adults who participated in an MBSR intervention group showed greater improvement in their mood and memory performance than those in a control group. Despite these promising findings, MBSR and other forms of mindfulness have still received limited testing in older adults, with few attempts at optimization as an intervention.

Improving the Reach and Impact of Mindfulness

A traditional MBSR protocol requires frequent in-person contact, with participants attending 8 weekly mindfulness sessions that are 2 to 2.5 hours in length plus an all-day retreat. However, accessing in-person MBSR classes may be challenging for older adults given mobility concerns, physical comorbidities, transportation challenges, financial constraints, and geographic location. Mobile health (mHealth) technology provides a mechanism for reaching individuals who are unable to access or attend in-person study visits and mindfulness training [11]. Even prior to the onset of the COVID-19 pandemic, many people expressed a preference for individual

and online mindfulness training over in-person group formats [12]. Videoconferencing-based treatments have shown promise for older, rural, and minority adults [13].

Smartphone-Based Assessments for Precision Intervention Development

Although the terminology itself is somewhat imprecise, the contemporary understanding of the term *precision medicine* refers to increasingly granular aggregate data that provides mechanistic insight into either the manifestation of illness, response to a treatment intervention, or both [14]. Originally rooted in pharmacogenomics, precision medicine methods and practices were first integrated into clinical care in medical subspecialties like oncology, where biomarkers are proximally linked to illness or treatment response [15]. In the last decade, digital phenotyping, which incorporates data collected in real time from mobile devices like smartphones and wearable sensors, offers precision measures of individual behaviors, characteristics, and related contextual factors [16]. These data elements can then be examined to identify which ones significantly drive treatment engagement over time, and how they can be optimized to enhance intervention effectiveness [17]. Building upon precision medicine methods and practices, delivery of behavioral interventions such as mindfulness training for older adults would ideally use both biomarkers and digital phenotyping. Identifying needs and preferences that drive engagement would allow for more precise intervention delivery, thereby leading to improved outcomes.

However, our ability to reliably identify and detect valid markers that predict symptoms, treatment engagement, and response remains limited for neuropsychiatric disorders due, in part, to inexact outcome assessment strategies in clinical trials [1,18,19]. For example, standard outcome measures of depression symptom severity and treatment response provide a unidimensional and static view of the individual's unique characteristics, needs, and preferences that in reality are dynamic and highly dependent on contextual factors over time. However, recent advances in mobile and wearable technology make conducting *N*=1 analyses possible by generating multiple data points that enhance the detection of group- and individual-level patterns in symptoms, needs, and preferences over time, allowing for the prediction of symptom dynamics (eg, tendency to increase, sustain, or cycle), as well as user engagement (eg, how and for how long users interact with the intervention) [20,21].

Study Aims

Engagement of the target population in the app creation process is critical for developing scalable and effective mHealth interventions for this population [22]. A key factor influencing older adults' use of mHealth technology is the intervention's usability. Usability considers the extent to which the technology (eg, app) can be used by the target-specified population (eg, older adults) to achieve goal effectiveness, efficiency, and user-satisfaction benchmarks [23]. Yet older adults are rarely consulted in the design of technologies for health [24]. This may affect the adoption of the technology, adherence, optimization of treatments, and desired outcomes, thereby limiting the ability to achieve precision medicine or individually optimized treatment. Thus, it is necessary to engage the target population in testing the usability of mHealth interventions.

Here, we describe the development and early usability testing of the Mindful MyWay program and The Healthy Mind Lab mHealth app for older adults with depressive symptoms. This online internet-delivered mindfulness meditation course is comprised of prerecorded videos of mindfulness education and practice recommendations (eg, meditation) that a participant can watch on their computer or mobile device at their convenience. The study app not only serves to link participants to upcoming mindfulness classes and prompt daily home meditative practice but also deploys frequent scheduled daily assessments of depressive and cognitive symptoms. The frequent outcome assessment data will inform the development of future *N*=1 analytic models, which are critically needed for the successful development of self-adaptive algorithms for personalized digital interventions. As well, the app conducts daily needs assessments. These assessments evaluate barriers and ask questions about ways to enhance the participants' mindfulness practice. This provides user needs and preference data for future precision development of the mindfulness intervention.

Study Objectives

This study has the following objections:

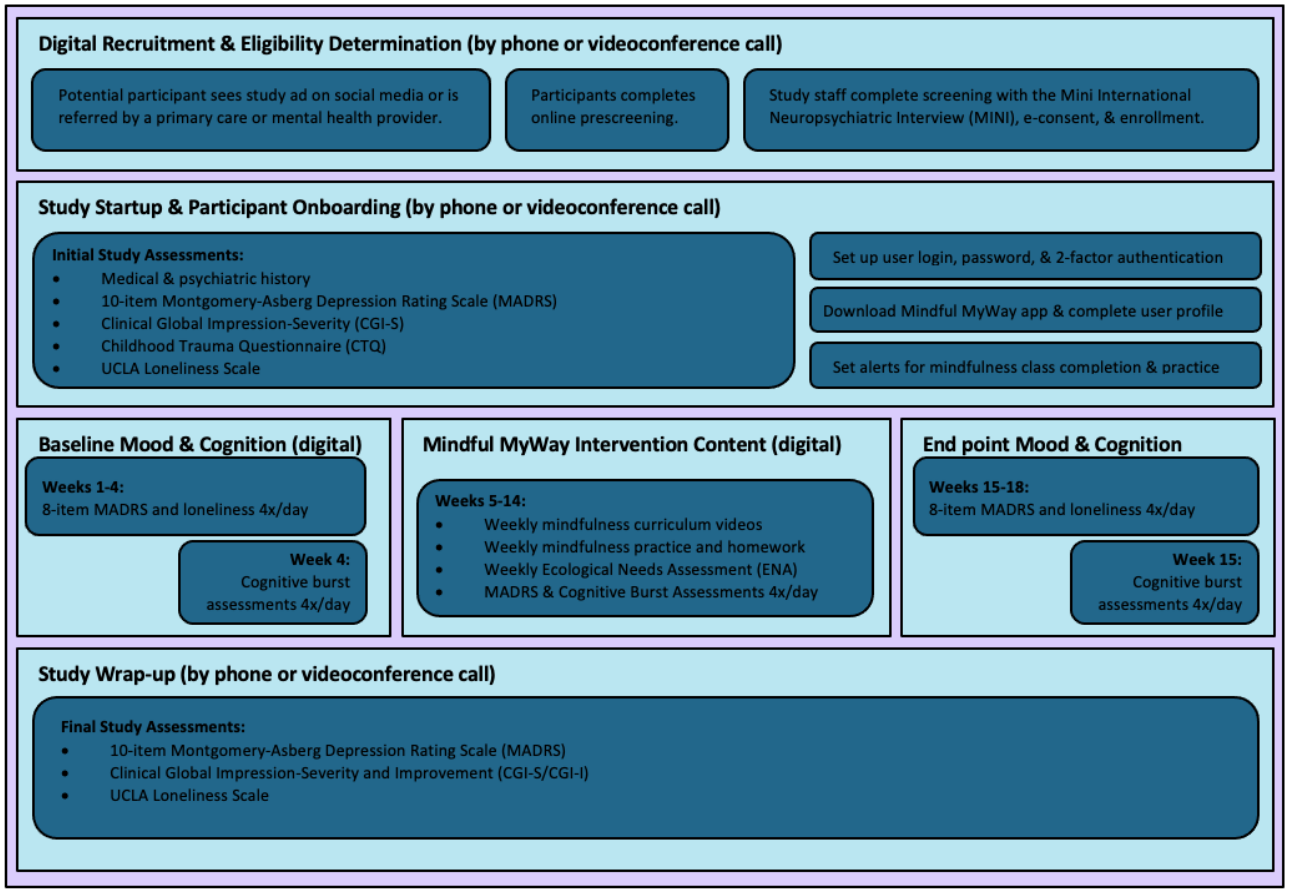
- Objective 1: To assess the usability, feasibility, and acceptability of internet-delivered mindfulness sessions and overall usability of the smartphone app
- Objective 2: To collect high-frequency ecological momentary assessment (EMA) data, such as depression symptoms and cognitive testing data from participants pre- and postintervention, and high-frequency patient preference data during the intervention
- Objective 3: To assess temporal dynamics (within-individual changes and interrelationships over time) of depressive symptoms

Methods

Study Procedures

A flowchart with the study procedures and mindfulness training intervention phases is shown in Figure 1.

Figure 1. Flowchart indicating the study procedures and mindfulness training intervention phases.



Ethics Approval

The Mindful MyWay study was determined to present no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context (45 CFR 46.117(c)(ii)/ 21 CFR 56.109(c)(1)(ii)). The study was approved and received a waiver of documentation of consent from the Washington University Institutional Review Board (IRB) on February 26, 2019 (IRB ID# 201811036).

Recruitment

Older adults aged ≥65 years with a mobile device using iOS 6 or higher who are experiencing a current depressive episode are invited to participate. Participants are excluded if they are unable to provide informed consent, have a known neurological condition that may confound the interpretation of results (eg, stroke, seizure disorder, or multiple sclerosis), are actively engaged in cognitive therapy or training, or are expressing acute suicidal or homicidal ideation. Participants are recruited from the Washington University Center for Mental Health and Wellness geriatric psychiatry clinic, a network of community outpatient primary care and psychiatry clinics used in previous clinical trials, and the institutional volunteer registry.

Screening

After completing a digital questionnaire accessed via a REDCap survey link sent in a secure email, a research team member contacts the potential participant by phone to conduct a screening interview and determine eligibility. For participants who qualify after screening, the research team member provides the instructions for downloading the Mindful MyWay smartphone app onto a mobile device using iOS version 6 or newer. Instructions for downloading and using the app are also emailed to the participant for future reference.

Electronic Informed Consent

This study was approved by the Washington University IRB as a minimal risk study and granted a waiver of written consent. Participants meeting eligibility criteria and passing prescreening procedures receive a digital consent document via email to review. Study staff schedule a time to review the consent document with the participant and answer any questions. Once all study-related procedures, risks, and benefits are explained and discussed, participants provide verbal consent to participate in the study.

Smartphone-Based Intervention and Assessments

Figure 2 shows features of the smartphone app developed for the study. This app was designed based on prior studies completed by our group using smartphone-based assessments to evaluate the effects of mindfulness interventions for older adults [25-28]. This study was inspired by qualitative work completed with participants in our previous studies indicating that digital self-guided access to mindfulness training and practice would increase the likelihood of engaging in mindfulness activities with the aim of improving mood and cognitive functioning [29]. The resulting app represents the minimum viable digital framework for promoting mindfulness practice in older adults by delivering digital mindfulness

training, which includes 10 weekly videos that are based on the MBSR curriculum developed by Kabat-Zinn [30], providing cues to engage in and track mindfulness practices. The online MBSR course videos are housed on YouTube, accessible only to participants via the study Qualtrics website, and includes 10 weekly prerecorded videos, approximately 45 minutes each.

Figure 2. Mindful MyWay app introductory screens. (A) The top row is an example of the introductory screens that allow participants to choose an individualized day and time for their class reminders. (B) The bottom row is an example of ecological momentary assessments sent to the participants 4 times each day.

Prior to beginning the Mindful MyWay study, a member of the research team guides the participant through the app download and 2-factor authentication log-in process. Participants are then asked to indicate windows of time during waking hours when they prefer to complete study assessments (Figure 2A). Participants are also mailed a workbook containing information about each session and corresponding activities, home practice suggestions that can be completed between weekly video sessions, and a glossary of terms.

During the initial app setup, participants are asked to schedule a time each week to complete the video lesson. They receive a smartphone push notification containing a URL hyperlink to an external website with a new MBSR video each week during the study. Study staff can monitor participant engagement via the Qualtrics dashboard, which tracks the completion of scheduled digital assessments and alerts study staff when assessments are missed. Study staff checks in weekly with participants via text, email, or phone to encourage continued participation and answer questions or, more frequently, to follow up on any missed assessments or critical depression scores.

Depression is assessed using a Modified Montgomery-Asberg Depression Rating Scale (MADRS) assessment, which includes eight items derived from the MADRS [25] (sadness, agitation, fatigue, concentration, motivation, anhedonia, pessimism, and thoughts of death). In June 2019, we added an EMA item measuring loneliness. The rationale for this addition was that a mindfulness intervention could reduce loneliness in older adults [31], and this study could provide critical feasibility data, such as whether EMA measurement of loneliness was feasible and whether the mindfulness intervention as designed would target loneliness or that the data (either lack of improvement or participant self-reported preferences) would indicate the need for enhancement of the intervention. The loneliness EMA item added was “I feel lonely (0, not at all, 100, very much so).” Mood assessments are conducted four times daily within 4-hour intervals during waking hours designated by the participant at study enrollment. Responses are on a visual analog scale with scores ranging from 0 (not at all) to 100 (very much so; Figure 2B).

Self-administered neuropsychological testing uses the smartphone-based Ambulatory Research in Cognition rapid burst cognitive assessments created by Dr Jason Hassenstab for the Dominantly Inherited Alzheimer’s Network (DIAN) study with the Washington University DIAN Trials Unit [32]. The goal of this high-frequency neuropsychological assessment, sometimes called “burst cognitive sampling,” is to increase the

validity and reliability of the measurement of cognitive impairment [33]. Participants provide preferred windows of time during waking hours in which to receive 4 prompts each day to complete assessments for the 7 days prior to starting the intervention and for 7 days after completing the intervention. Prior to each assessment, data about the participant's immediate environment is collected (eg, where they are, what they are doing, and who they are with). The assessment battery is comprised of three separate tests conducted in a randomized order. These include tests for spatial working memory, processing speed, and associate memory with the Grids, Symbols, and Prices tasks, respectively. Each assessment presents the individual tests in a randomized order and takes approximately 2 minutes to complete.

To identify drivers of engagement with the app, participant preferences are collected via qualitative EMAs referred to as ecological daily needs assessments (EDNAs) [26]. EDNAs are brief questions that evaluate intervention feasibility and acceptability in real time, revealing factors specific to the digital context that serve as facilitators or barriers to engagement. For the purposes of the Mindful MyWay app, engagement was defined as viewing weekly mindfulness training videos (via clicks on the website that houses the mindfulness video content) and practicing new mindfulness skills (via self-report) during the 10-week intervention period. Participants are asked each day, at random times, whether they completed the mindfulness practice and homework as prescribed (eg, "How much of the day today did you feel you were 'present' or 'mindful?'"), what type of mindfulness practice was used (eg, "If you spent time being mindful today, select which practices you used and how much time you spent."), and feedback about what would make the app more helpful (eg, "What would help you be mindful right now?"). EDNA data is collected during pilot-testing with the intent of discovering whether modifications to the timing of assessment prompts, feasibility and acceptability of active tasks, and appropriateness of intervention content are needed to optimize engagement. These data also inform the development of digital algorithms for future adaptive iterations of the intervention.

Other Assessments

These assessments are administered by study staff with participants via survey or phone at baseline and after completing the 10-week study intervention.

The Mini-International Neuropsychiatric Interview (MINI) [34] is a short-structured diagnostic interview developed for *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition; *DSM-5*) [35] psychiatric disorders and takes approximately 45 minutes to complete. In this study, the MINI is conducted by a trained member of the research team via a videoconference call during screening to confirm eligible diagnoses and to rule out any exclusionary *DSM-5* diagnoses.

The MADRS is a 10-item measure administered by a trained research staff member to assess depressive symptom severity. In this study, the 10-item MADRS is administered over the phone by a trained member of the research team via videoconference call at baseline and the end point (week 18). The UCLA Loneliness Scale is a 20-item self-report measure that assesses how often a person feels disconnected from others [36]. Participants complete this assessment online at baseline and the end point. This assessment was added at the beginning of the COVID-19 pandemic to collect data on the impact of isolation and loneliness on this older depressed population.

Plans for Data Analysis

We will analyze feasibility with respect to retention and completion rates, successful and unsuccessful recruitment methods, and successful and unsuccessful methods to prompt adherence to the intervention, including home practice of mindfulness. We will also examine participant feedback gathered via the daily needs assessments throughout the intervention period; we will examine not only group-level data but also individual data over time to ascertain whether participant needs are individually dynamic (eg, one participant has one set of needs that changes over time during the intervention period, whereas another participant has different needs that do not change in a different pattern).

With respect to predictor and outcome data, we will examine these in several ways to generate hypotheses for testing in future trials. In short, multilevel dynamic structural equation modeling (ML-DSEM) will be used because of its suitability for intensive longitudinal data [37]. In the primary model, the treatment effect will be captured as a pre-post contrast in overall response to EMA depression items, allowing the identification of individuals who show significant response versus those who do not. Those who show significant response can then be characterized via the other measures in the study. Other applications of ML-DSEM to treatment data (eg, as suggested by Hamaker and colleagues [38]) and the N=1 application of the model will be examined to yield potential insights into predictors of treatment response. The cognitive data will be averaged at baseline and postintervention to calculate a reliable assessment of cognitive status at each time point; in addition, we will assess the test-retest reliability of these cognitive data.

Results

The study was approved and received a waiver of documentation of consent from the Washington University IRB on February 26, 2019. After prescreening 151 potential participants, 31 verbally consented between March 28, 2019, and April 7, 2022, with 23 participants included in the intention-to-treat group. The mean age of participants was 71.7 (SD 4.5) years; 16 (85%) were women, and 1 (5%) was non-White. Results are expected in July 2022.

Discussion

Limitations and Directions for Future Research

One of the main challenges we faced in this study was creating a user-friendly app that reinforced participants' positive attitudes toward mHealth app use. Patient stakeholders are involved in the assessment of this app as part of the feasibility testing but were not involved in the initial development of the app. Future iterations of the study intervention and design of the app should incorporate a user-centered design with stakeholder input, particularly from patients. This is especially important as older

adults with depression may have unique technology use challenges and benefit from reinforcements to enhance adherence. Therefore, interventions should be developed in collaboration with the end user and consider factors related to usability and appropriateness of the intervention, as well as user preference, needs, and engagement. Likewise, "the scientific community will benefit from continued funding opportunities and academic research institutions adopting a digital infrastructure to support investigators in using and navigating mobile technology for clinical research and healthcare delivery" [39].

Conclusions

The Mindful MyWay study exemplifies the innovative clinical trial designs that can be conducted using smartphone technology. By using an app and internet-based video content, supplemented by phone and other distance-based contact from research staff, we are conducting a fully remote clinical trial. The entire study, from screening to outcome completion, is done at a distance; this increases reach and access of clinical trials, as well as the evidence-based interventions that ensue from them.

In this study, high-frequency data collection of outcome and participant feedback, together with advanced analytic approaches, will lead to more precise and individually relevant outcome assessment, as well as personalized intervention optimization. Our findings will be used to modify our methods and inform future randomized controlled trials within a precision medicine framework.

This study is being conducted in depressed older adults with a mindfulness intervention. However, the broad methods being used are widely applicable to behavioral intervention research, especially for neurobehavioral conditions such as depression in which a precision medicine approach is needed to advance the science of interventions. As the COVID-19 era has shown us that fully remote interventions and trials are indeed feasible, we expect more such research in the future.

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Data Availability

All data requests should be directed to the corresponding author.

Conflicts of Interest

TRG and JK receive consulting fees from Pritikin ICR. EJL receives grant support (nonfederal) from COVID Early Treatment Fund, Mercatus Center Emergent Ventures, the Skoll Foundation, the Patient-Centered Outcomes Research Institute, and Janssen; consulting fees from IngenioRx, Boehringer-Ingelheim, Merck, Prodeo, and Pritikin ICR; and has applied for a patent for the use of fluvoxamine in the treatment of COVID-19. GEN reported receiving grants from Alkermes, the Center for Brain Research in Mood Disorders, the Center for Diabetes Translational Research, the Institute for Public Health, the McDonnell Center for Neuroscience, and the Barnes Jewish Hospital Foundation, and reported serving as a consultant to Sunovion, Alkermes, and Elira. No other disclosures were reported.

References

1. Lenze EJ, Nicol GE, Barbour DL, Kannampallil T, Wong AW, Piccirillo J, et al. Precision clinical trials: a framework for getting to precision medicine for neurobehavioural disorders. J Psychiatry Neurosci 2021 Jan 04;46(1):E97-E110 [FREE Full text] [doi: 10.1503/jpn.200042] [Medline: 33206039]
2. Morris ZS, Wooding S, Grant J. The answer is 17 years, what is the question: understanding time lags in translational research. J R Soc Med 2011 Dec;104(12):510-520 [FREE Full text] [doi: 10.1258/jrsm.2011.110180] [Medline: 22179294]
3. Nickels S, Edwards MD, Poole SF, Winter D, Gronsbell J, Rozenkrants B, et al. Toward a mobile platform for real-world digital measurement of depression: user-centered design, data quality, and behavioral and clinical modeling. JMIR Ment Health 2021 Aug 10;8(8):e27589 [FREE Full text] [doi: 10.2196/27589] [Medline: 34383685]
4. Vos SJ, Xiong C, Visser PJ, Jasielec MS, Hassenstab J, Grant EA, et al. Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study. Lancet Neurology 2013 Oct;12(10):957-965. [doi: 10.1016/s1474-4422(13)70194-7]
5. Mental health and aging in America. Centers for Disease Control and Prevention. 2008. URL: https://www.cdc.gov/aging/publications/mental-health.html [accessed 2022-10-16]
6. Villarroel MA, Terlizzi EP. Symptoms of depression among adults: United States, 2019. NCHS Data Brief 2020 Sep(379):1-8. [Medline: 33054920]

7. Lenze EJ, Voineskos AN, Butters MA, Karp JF, OPTIMUM and OPTIMUM-Neuro collaborative team. Stopping cognitive decline in patients with late-life depression: a new front in the fight against dementia. Am J Geriatr Psychiatry 2018 Aug;26(8):828-834 [FREE Full text] [doi: 10.1016/j.jagp.2018.05.014] [Medline: 30049598]
8. Wetherell JL, Hershey T, Hickman S, Tate SR, Dixon D, Bower ES, et al. Mindfulness-based stress reduction for older adults with stress disorders and neurocognitive difficulties: a randomized controlled trial. J Clin Psychiatry 2017 Jul;78(7):e734-e743 [FREE Full text] [doi: 10.4088/JCP.16m10947] [Medline: 28686822]
9. Hashizume S, Nakano M, Kubota K, Sato S, Himuro N, Kobayashi E, et al. Mindfulness intervention improves cognitive function in older adults by enhancing the level of miRNA-29c in neuron-derived extracellular vesicles. Sci Rep 2021 Nov 08;11(1):21848. [doi: 10.1038/s41598-021-01318-y] [Medline: 34750393]
10. Lenze EJ, Hickman S, Hershey T, Wendleton L, Ly K, Dixon D, et al. Mindfulness-based stress reduction for older adults with worry symptoms and co-occurring cognitive dysfunction. Int J Geriatr Psychiatry 2014 Oct;29(10):991-1000 [FREE Full text] [doi: 10.1002/gps.4086] [Medline: 24677282]
11. Spijkerman MPJ, Pots WTM, Bohlmeijer ET. Effectiveness of online mindfulness-based interventions in improving mental health: a review and meta-analysis of randomised controlled trials. Clin Psychol Rev 2016 Apr;45:102-114 [FREE Full text] [doi: 10.1016/j.cpr.2016.03.009] [Medline: 27111302]
12. Wahbeh H, Svalina MN, Oken BS. Group, one-on-one, or internet? preferences for mindfulness meditation delivery format and their predictors. Open Med J 2014;1:66-74 [FREE Full text] [doi: 10.2174/1874220301401010066] [Medline: 27057260]
13. Batsis JA, DiMilia PR, Seo LM, Fortuna KL, Kennedy MA, Blunt HB, et al. Effectiveness of ambulatory telemedicine care in older adults: a systematic review. J Am Geriatr Soc 2019 Aug;67(8):1737-1749 [FREE Full text] [doi: 10.1111/jgs.15959] [Medline: 31066916]
14. What is the Precision Medicine Initiative? MedlinePlus. 2022 May 17. URL: https://medlineplus.gov/genetics/understanding/precisionmedicine/initiative/ [accessed 2022-08-15]
15. Primorac D, Bach-Rojecky L, Vađunec D, Juginović A, Žunić K, Matišić V, et al. Pharmacogenomics at the center of precision medicine: challenges and perspective in an era of Big Data. Pharmacogenomics 2020 Jan;21(2):141-156 [FREE Full text] [doi: 10.2217/pgs-2019-0134] [Medline: 31950879]
16. Huckvale K, Venkatesh S, Christensen H. Toward clinical digital phenotyping: a timely opportunity to consider purpose, quality, and safety. NPJ Digit Med 2019;2:88. [doi: 10.1038/s41746-019-0166-1] [Medline: 31508498]
17. Baumgartner R. Precision medicine and digital phenotyping: digital medicine's way from more data to better health. Big Data Soc 2021 Dec 22;8(2):205395172110664. [doi: 10.1177/20539517211066452]
18. Lenze EJ, Rodebaugh TL, Nicol GE. A framework for advancing precision medicine in clinical trials for mental disorders. JAMA Psychiatry 2020 Jul 01;77(7):663-664. [doi: 10.1001/jamapsychiatry.2020.0114] [Medline: 32211837]
19. Mofsen AM, Rodebaugh TL, Nicol GE, Depp CA, Miller JP, Lenze EJ. When all else fails, listen to the patient: a viewpoint on the use of ecological momentary assessment in clinical trials. JMIR Ment Health 2019 Apr 21;6(5):e11845 [FREE Full text] [doi: 10.2196/11845] [Medline: 31066701]
20. Beltz AM, Wright AGC, Sprague BN, Molenaar PCM. Bridging the nomothetic and idiographic approaches to the analysis of clinical data. Assessment 2016 Aug;23(4):447-458 [FREE Full text] [doi: 10.1177/1073191116648209] [Medline: 27165092]
21. McNeish D, Hamaker EL. A primer on two-level dynamic structural equation models for intensive longitudinal data in Mplus. Psychol Methods 2020 Oct;25(5):610-635. [doi: 10.1037/met0000250] [Medline: 31855015]
22. Wilson J, Heinsch M, Betts D, Booth D, Kay-Lambkin F. Barriers and facilitators to the use of e-health by older adults: a scoping review. BMC Public Health 2021 Aug 17;21(1):1556 [FREE Full text] [doi: 10.1186/s12889-021-11623-w] [Medline: 34399716]
23. Bevan N, Carter J, Harker S. ISO 9241-11 revised: what have we learnt about usability since 1998? In: Human-Computer Interaction: Design and Evaluation 17th International Conference, HCI International 2015, Los Angeles, CA, USA, August 2–7, 2015. Proceedings, Part I. Cham: Springer; 2015:143-151.
24. Nimmanterdwong Z, Boonviriya S, Tangkijvanich P. Human-centered design of mobile health apps for older adults: systematic review and narrative synthesis. JMIR Mhealth Uhealth 2022 Jan 14;10(1):e29512 [FREE Full text] [doi: 10.2196/29512] [Medline: 35029535]
25. Kharasch ED, Neiner A, Kraus K, Blood J, Stevens A, Schweiger J, et al. Bioequivalence and therapeutic equivalence of generic and brand bupropion in adults with major depression: a randomized clinical trial. Clin Pharmacol Ther 2019 May;105(5):1164-1174 [FREE Full text] [doi: 10.1002/cpt.1309] [Medline: 30460996]
26. Nicol GE, Ricchio AR, Metts CL, Yingling MD, Ramsey AT, Schweiger JA, et al. A smartphone-based technique to detect dynamic user preferences for tailoring behavioral interventions: observational utility study of ecological daily needs assessment. JMIR Mhealth Uhealth 2020 Nov 13;8(11):e18609 [FREE Full text] [doi: 10.2196/18609] [Medline: 33055063]
27. Ramsey AT, Wetherell JL, Depp C, Dixon D, Lenze E. Feasibility and acceptability of smartphone assessment in older adults with cognitive and emotional difficulties. J Technol Hum Serv 2016;34(2):209-223 [FREE Full text] [doi: 10.1080/15228835.2016.1170649] [Medline: 27683018]

28. Wilks H, Aschenbrenner AJ, Gordon BA, Balota DA, Fagan AM, Musiek E, et al. Sharper in the morning: cognitive time of day effects revealed with high-frequency smartphone testing. J Clin Exp Neuropsychol 2021 Oct;43(8):825-837. [doi: 10.1080/13803395.2021.2009447] [Medline: 35037593]
29. Parra D, Wetherell J, Van Zandt A, Brownson R, Abhishek J, Lenze E. A qualitative study of older adults' perspectives on initiating exercise and mindfulness practice. BMC Geriatr 2019 Dec 23;19(1):354 [FREE Full text] [doi: 10.1186/s12877-019-1375-9] [Medline: 31865906]
30. Kabat-Zinn J. Full Catastrophe Living: Using the Wisdom of Your Body and Mind to Face Stress, Pain, and Illness. New York City, NY: Dell Publishing; 1990.
31. Creswell JD, Irwin MR, Burklund LJ, Lieberman MD, Arevalo JMG, Ma J, et al. Mindfulness-Based Stress Reduction training reduces loneliness and pro-inflammatory gene expression in older adults: a small randomized controlled trial. Brain Behav Immun 2012 Oct;26(7):1095-1101 [FREE Full text] [doi: 10.1016/j.bbi.2012.07.006] [Medline: 22820409]
32. Öhman F, Hassenstab J, Berron D, Schöll M, Papp KV. Current advances in digital cognitive assessment for preclinical Alzheimer's disease. Alzheimers Dement (Amst) 2021;13(1):e12217 [FREE Full text] [doi: 10.1002/dad2.12217] [Medline: 34295959]
33. Thompson LI, Harrington KD, Roque N, Strenger J, Correia S, Jones RN, et al. A highly feasible, reliable, and fully remote protocol for mobile app-based cognitive assessment in cognitively healthy older adults. Alzheimers Dement (Amst) 2022;14(1):e12283 [FREE Full text] [doi: 10.1002/dad2.12283] [Medline: 35415201]
34. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59 Suppl 20:22-33;quiz 34. [Medline: 9881538]
35. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA: American Psychiatric Association; 2013.
36. Russell DW. UCLA Loneliness Scale (Version 3): reliability, validity, and factor structure. J Pers Assess 1996 Feb;66(1):20-40. [doi: 10.1207/s15327752jpa6601_2] [Medline: 8576833]
37. Asparouhov T, Hamaker EL, Muthén B. Dynamic Structural Equation Models. Structural Equation Modeling Multidisciplinary J 2017 Dec 27;25(3):359-388. [doi: 10.1080/10705511.2017.1406803]
38. Hamaker EL, Asparouhov T, Muthén B. Dynamic structural equation modeling as a combination of time series modeling, multilevel modeling, and structural equation modeling. In: Hoyle RH, editor. The Handbook of Structural Equation Modeling (2nd edition). New York City, NY: Guilford Press; 2021.
39. Keenoy KE, Lenze EJ, Nicol GE. Going remote: implementing digital research methods at an academic medical center during COVID-19. J Clin Transl Sci 2021;5(1):e189 [FREE Full text] [doi: 10.1017/cts.2021.865] [Medline: 34812289]

Abbreviations

ADRD: Alzheimer disease and related dementias
DIAN: Dominantly Inherited Alzheimer's Network
DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
EDNA: ecological daily needs assessment
EMA: ecological momentary assessment
IRB: Institutional Review Board
MADRS: Modified Montgomery-Asberg Depression Rating Scale
MBSR: mindfulness-based stress reduction
mHealth: mobile health
MINI: Mini-International Neuropsychiatric Interview
ML-DSEM: multilevel dynamic structural equation modeling

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Protocol

Developing a Parenting App to Support Young Children's Socioemotional and Cognitive Development in Culturally Diverse Low- and Middle-Income Countries: Protocol for a Co-design Study

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Abstract

Background: Digital technologies are widely recognized for their equalizing effect, improving access to affordable health care regardless of gender, ethnicity, socioeconomic status, or geographic region. The Thrive by Five app is designed to promote positive interactions between children and their parents, extended family, and trusted members of the community to support socioemotional and cognitive development in the first 5 years of life and to strengthen connections to culture and community.

Objective: This paper aims to describe the iterative co-design process that underpins the development and refinement of Thrive by Five's features, functions, and content. Minderoo Foundation commissioned this work as a quality improvement activity to support an engaging user experience and inform the development of culturally appropriate and relevant content for parents and caregivers in each country where the app is implemented.

Methods: The app content, referred to as Collective Actions, comprises "The Why," that presents scientific principles that underpin socioemotional and cognitive development in early childhood. The scientific information is coupled with childrearing activities for parents, extended family, and members of the community to engage in with the children to support their healthy development and to promote positive connections between parents, families, and communities and these young children. Importantly, the initial content is designed and iteratively refined in collaboration with a subject matter expert group from each country (ie, alpha testing). This content is then configured into the app (either a beta version or localized version) for testing (ie, beta testing) by local parents and caregivers as well as experts who are invited to provide their feedback and suggestions for improvements in app content, features, and functions via a brief web-based survey and a series of co-design workshops. The quantitative survey data will be analyzed using descriptive statistics, whereas the analysis of qualitative data from the workshops will follow established thematic techniques.

Results: To date, the co-design protocol has been completed with subject matter experts, parents, and caregivers from 9 countries, with the first results expected to be published by early 2023. The protocol will be implemented serially in the remaining 21 countries.

Conclusions: Mobile technologies are the primary means of internet connection in many countries worldwide, which underscores the potential for mobile health programs to improve access to valuable, evidence-based, and previously unavailable parenting information. However, for maximum impact, it is critically important to ensure that mobile health programs are designed in collaboration with the target audience to support the alignment of content with parents' cultural values and traditions and its relevance to their needs and circumstances.

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KEYWORDS

child development; digital technology; global health; co-design; participatory research; stakeholder participation; mobile app

Introduction

Digital Health Solutions

In 2015, the United Nations General Assembly unanimously adopted the 2030 Agenda for Sustainable Development, which specifically highlighted the opportunity to capitalize on the spread of information and communications technology (ICT) to accelerate human progress worldwide [1]. Before and since that time, digital technology has acted as a revolutionizing force across diverse industries, and increasingly so in relation to health. Digital tools can directly influence some of the cultural and societal barriers to optimal health and development, such as accessibility and affordability. The Review Committee on the Functioning of the International Health Regulations (2005) during the COVID-19 response highlighted that strengthening IT systems and digitizing health systems are important ways of responding to and solving significant health challenges, even in developing countries [2]. Digitization of activities for parents and caregivers to promote childhood development is one such innovation [3]. For example, app-based digital technologies can also be used to provide information, maintain child development records (eg, vaccination records), and enhance access points to local and more distant health services.

Technology Use in Low- and Middle-Income Countries

In recent years, there has been considerable growth in telecommunications infrastructure in low- and middle-income countries (LMICs). Table 1 highlights examples of large-scale initiatives in a range of LMICs that have driven ICT infrastructure growth to increase access to "smart" technologies to improve the standard of living. Despite such projects, it is estimated that 53% of people do not have access to the internet in developing countries, which stands in stark contrast to the 13% without access in developed countries [4]. Mobile technologies are the primary point of access to the internet in LMICs, with mobile broadband connections comprising 87% of total broadband connections [5]. However, gender remains a critical factor impacting access to mobile devices and, in turn, the internet. In LMICs, more than 300 million fewer women have access to the internet via a mobile device relative to men, with the widest gap in access evident in South Asia [6]. This reflects the way that technology use is mediated not only by access but by cultural practices and community norms [7]. Despite the marked digital divide, both men and women from LMICs report that ownership of a mobile phone coupled with internet access improves safety and facilitates access to previously unavailable information to improve daily life [6].

Table 1. Examples of technology infrastructure projects in low- and middle-income countries.

Country	Project
Afghanistan	A recent project funded by a US $50 million International Development Association Grant (Emergency Recovery Loan) resulted in a significant expansion in connectivity, increasing internet users from 15,000 in 2011 to 3.5 million in 2017 [8].
Indonesia	The Palapa Ring Project was recently completed in Indonesia, improving 4G internet access in all Indonesian cities as well as the regencies [9].
Kenya	Kenya's "Vision 2030" includes plans to significantly upgrade the ICT[a] infrastructure, including the expansion of fiber optic networks to public service institutions and providing 4G networks to ensure faster internet and improved bandwidth capacity [10].
Kyrgyzstan	In 2019, the Kyrgyzstan government adopted the "Digital Kyrgyzstan 2019-2023" strategy, which aims to improve digital infrastructure and access to the internet nationally, increase the digital literacy of its citizens through education, and develop e-government services [11].
Namibia	Namibia's "Harambee Prosperity Plan II 2021-2025" includes the expansion of ICT infrastructure as one of its primary goals, with one aim being the provision of universal broadband access by 2025 [12].
Uzbekistan	In 2019, the Uzbekistan government approved the "Smart Cities" plan that aims to implement over 400 IT systems and infrastructure in the field of transportation, health, housing, education, and municipal services [13].

[a]ICT: information and communications technology.

In 2019, more than 204 billion apps were downloaded globally, reflecting an increase of approximately 5% compared with 2018 [14]. Social media apps, such as TikTok (ByteDance) and WhatsApp and Facebook (Meta), are consistently the most downloaded apps globally [15]. However, apps are being increasingly developed to address health-related problems in developing countries. For example, SASAdoctor, an app available via Android devices to all Kenyans, aims to improve the accessibility of affordable health consultations, particularly for the uninsured [16]. Furthermore, there is evidence of growing interest in and funding for mobile health (mHealth) programs to educate and empower women [17,18]. With the growth in the ICT sector generally and mobile phone subscriptions specifically, there is now a tremendous opportunity to implement mHealth initiatives globally and particularly in LMICs.

Taking Account of Cultural Context

Mobile phones have become a powerful medium for disseminating important health messages. However, when considering mHealth initiatives, it is critical to understand the context, culture, attitudes, behaviors, and expectations of those for whom the digital solution is being designed [7]. With regard to child development, local culture significantly influences child care and parenting behaviors [19]. Furthermore, although parenting programs have generally been shown to be effective in improving children's behavior [20], the same benefits are typically not evident in LMICs [21]. It has been suggested that cultural and linguistic differences and variability in accessibility and method of delivery may limit the usability and acceptability of such programs [22]. Failing to adequately account for context in population health interventions has been shown to result in ineffectiveness and has the potential to cause harm, widening health disparities by excluding access by some groups (eg, on the basis of ethnicity, language, or socioeconomic status) [23]. Although some mHealth interventions claim to be "universal," a critical review highlights that their content is often underpinned by Western or individualist conceptualizations of the self, failing to incorporate non-Western or Indigenous perspectives on health and well-being [24]. Indeed, a meta-analysis showed that culturally adapted interventions were more effective than unadapted versions of the same intervention [25]. In addition, effective multicultural parenting programs have been shown to include culturally relevant content and provide information and skills training to bolster the confidence of parents [26]. Taken together, these findings underscore the critical importance of understanding the cultural values and traditions that drive parenting behaviors and parent-child and family-child interactions, including variations based on demographics, religion, and region. Accounting for cultural context will inform the iterative development and refinement of a parenting app, enabling it to be more appropriate and effective for the target audiences.

The Importance of Co-design Methodologies

The World Health Organization's Global Strategy on Digital Health (2020-2025) prioritizes the development and adoption of appropriate, acceptable, and scalable digital health solutions to promote health and well-being on a global scale [27]. Using strategies to enhance community and consumer engagement with digital health solutions is a priority in the health, medical, and research sectors internationally [28,29]. To that end, the Principles of Digital Development, which were created in consultation with a variety of international organizations including the Bill and Melinda Gates Foundation, the Swedish International Development Agency, the United Nations International Children's Emergency Fund, the United Nations Development Program, the World Bank, the US Agency for International Development, and the World Health Organization, highlight the importance of designing products in collaboration with the end user [30]. Co-design methodologies are essential for successful digital health projects, as they are an effective way to understand the context, culture, attitudes, behaviors, and expectations of those for whom the digital solution is being designed. In turn, this enables the solution to be adapted and iteratively refined to align with the local cultural context. Research has consistently shown that the active participation of all stakeholders (ie, consumers, researchers, product designers, etc) throughout the design of technical systems and services helps support the development of an end product that meets the needs of its intended user base, improves usability, and increases the engagement of all individuals [31,32]. Through the co-design process, end users become active partners in the development process, including idea generation, prototyping, and iterative feedback. In this way, co-design with end users promotes collaboration among research, industry, and local communities to address real-world problems [33,34].

Thrive by Five

Minderoo Foundation is an Australian philanthropic organization whose vision for the Thrive by Five International Program is to inspire an increased understanding of and focus on the importance of early childhood development [35]. To facilitate this mission, the international Thrive by Five app, which will be free to use, is being developed for use by parents and caregivers in at least 30 countries around the globe, including countries in Africa (eg, Kenya, Namibia, and Ethiopia), Central Asia (eg, Kyrgyzstan and Uzbekistan), Southeast Asia (eg, Indonesia and Malaysia), South Asia (eg, Afghanistan), Middle East (eg, Jordan), North America (eg, the United States), and South America (eg, Brazil and Peru). In addition to increasing awareness of early childhood as a critical developmental period, the objectives of the Thrive by Five app are to (1) empower parents with the knowledge they need to support the healthy development of their child; (2) ensure universal access to this valuable parenting information regardless of region, socioeconomic status, literacy, gender, or other barriers; and (3) develop strong partnerships with in-country organizations to validate the cultural appropriateness and relevance of the app content as well as its features and functionality. Despite notable gains with regard to infrastructure development, limitations in access to devices, the internet, and electricity in many of the countries involved in this project may prevent some parents and caregivers from accessing the Thrive by Five app. Acknowledging that the app is the flagship of the broader Thrive by Five International Program, alternate means of disseminating content (eg, medical centers and hospitals, print media, radio, television, and WhatsApp) will be explored. The focus of this quality improvement research protocol is on the co-design,

development, and refinement of the features, functions, and content of the app; however, the content developed through this process will be available for dissemination through a broader multichannel approach if necessary.

Minderoo Foundation contracted BBE, an Australian software development company, to design and develop the app's features and functionalities. To complement this work, researchers from the University of Sydney partnered with Minderoo Foundation to support the development of the Thrive by Five content. Importantly, the content is underpinned by a scientific framework that highlights key neurobiological systems that support a child's socioemotional and cognitive development (eg, reward, stress-response) and emphasizes a collectivist approach to parenting. The key elements of the content, referred to as "Collective Actions," are "The Why" that present scientific information about early childhood development in approachable, lay language and childrearing activities that parents, extended family, and the broader community can engage in with the child to support their development at different ages in the first 5 years of life.

This project will see the app implemented in 30 countries. Importantly, the content of the app will be adapted to the cultural context of each country to support its appropriateness and relevance. The aim is to celebrate the valued traditions of each country's cultures while providing content to guide parents to best support their child's development, given the challenges faced in each country. Critically, before embarking on work in any country, Minderoo Foundation identifies an in-country partner to provide support, guidance, and expertise throughout the duration of the project. This includes providing information about the local context; resourcing beta testers to test and review the app features, functions, and content; and assisting with app implementation and promotion. Over the course of the project, the partners are expected to be a mix of governmental and nongovernmental organizations with aims aligned with the Thrive by Five International Program, including the promotion of opportunities for healthy early childhood development and education.

Objectives

By capitalizing on the current momentum in ICT infrastructure development and growing familiarity with and support for mHealth globally, we have the opportunity in this ambitious project to demonstrate the power of community engagement as a means to (1) develop and iteratively refine a novel mHealth app for parents; (2) facilitate the successful implementation and adoption of Thrive by Five to promote and optimize socioemotional and cognitive development of children from birth to age 5 years; and (3) strengthen relationships among parents, families, and communities with children in the early years and foster connections to community and culture. The objective of this paper is to outline the protocol for the co-design work that will be conducted as part of this project to support the development of an app that is usable, acceptable, and engaging and content that is culturally appropriate and relevant to the end users in each country. This work has been commissioned by Minderoo Foundation as a quality improvement activity to inform the iterative refinement of the Thrive by Five app.

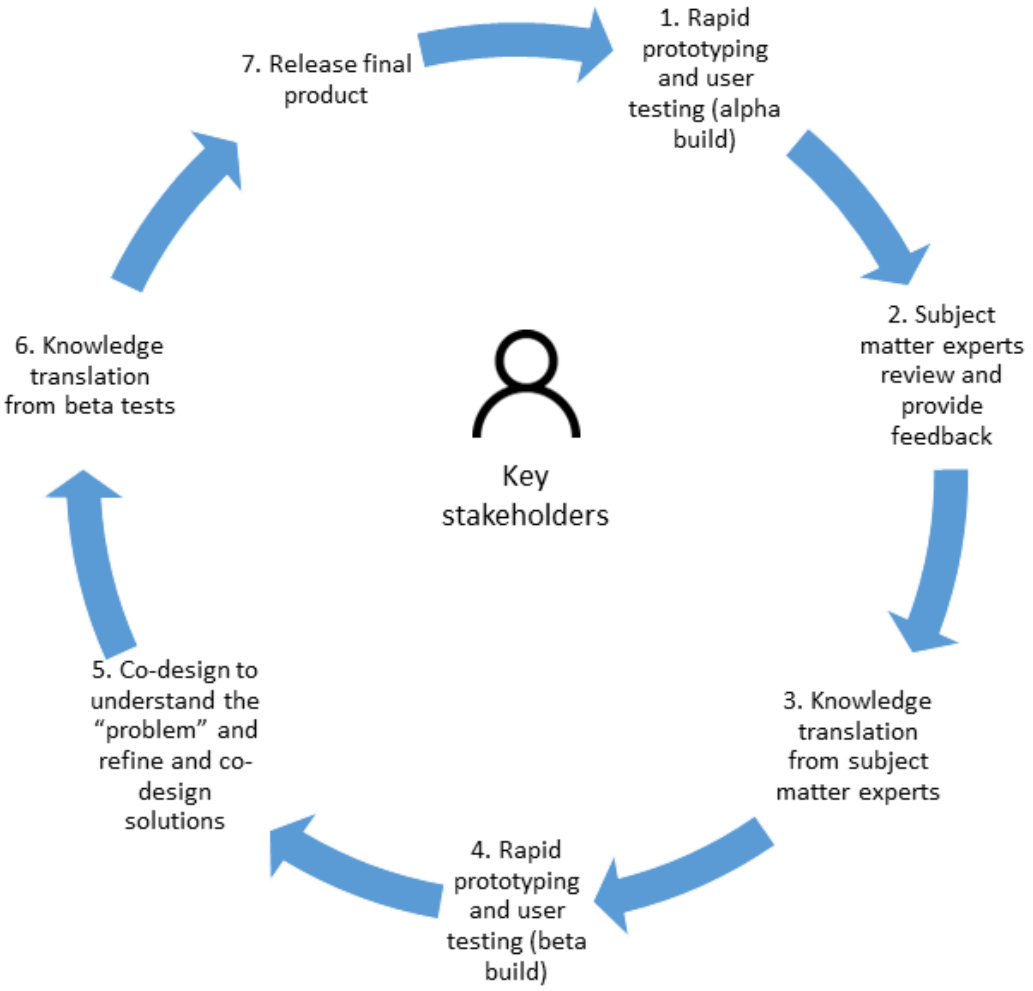
Methods

Research and Development Cycle

Overview

The Medical Research Council's Framework for Complex Interventions emphasizes an iterative approach to the development, feasibility testing, evaluation, and implementation of interventions [36]. The initial development phase focuses on stakeholder engagement and co-design to determine what outcomes might be expected from the development and implementation of the intervention in a real-world setting. In alignment with this approach, our research team's established research and development (R&D) cycle, as illustrated in Figure 1, highlights the importance of co-design methodologies to explicitly position end users as empowered participants in all stages from design and development to implementation and evaluation [37-40]. This R&D cycle has been adapted to suit the needs of this large-scale international project, as explained in greater detail below. For ease of understanding, the alpha build refers to the first iteration of an app, whereas the beta build is a complete app that is used for testing to improve quality, usability, and user experience.

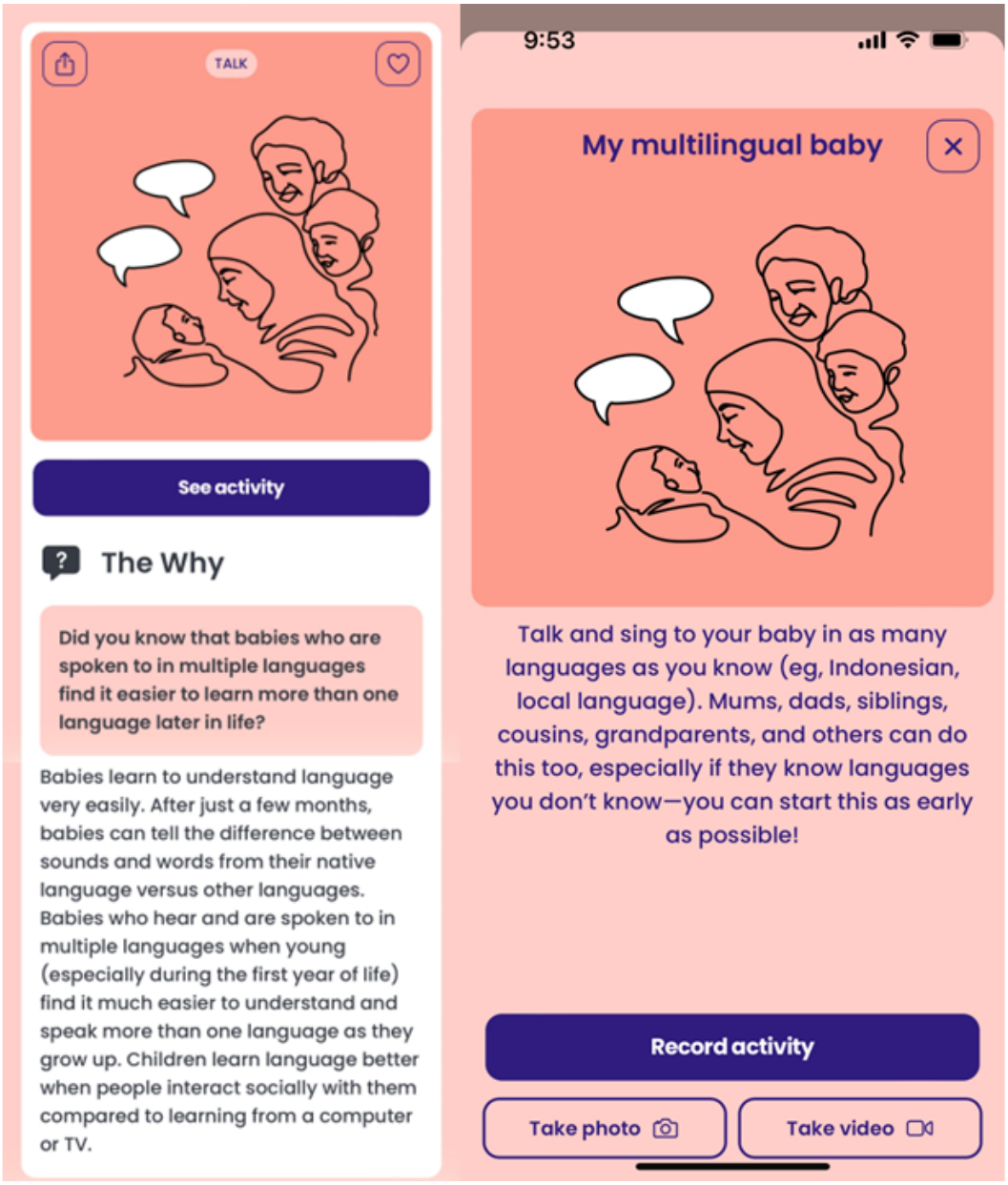
Figure 1. Research and development cycle.



Alpha Testing

The core features and functionality of the Thrive by Five app were established by BBE in partnership with Minderoo Foundation. Following a comprehensive literature review about the cultures, traditions, and values of the people and the history and social context of the target country, researchers from the University of Sydney develops preliminary content to populate the app, comprising 20-50 "The Why" and corresponding childrearing activities. As highlighted in Figure 2, the "The Why" reflects scientific information related to child development presented in lay language. This information is coupled with childrearing activities for parents, extended family, and trusted members of the community to engage in with the child to support their socioemotional and cognitive development. A subject matter expert (SME) group, convened by the in-country partner, is invited to provide feedback regarding the relevance and appropriateness of this initial content for the local context. The SME group may include, but is not limited to, specialists in early childhood development and education, psychology, medicine, and anthropology as well as representatives from relevant government ministries. The input of this group is critical to support the researchers in developing and tailoring content to the cultural context, supporting its relevance and applicability to the potential users. Having tested both the app functionality and content internally (ie, alpha testing), either a beta or a local version of the app is created for each country for testing by real-world users (ie, beta testing).

Figure 2. Example of a "Collective Action".



Beta Testing

Overview

A representative sample of parents and family members as well as key local stakeholders (eg, preprimary schoolteacher and child psychologist) will be invited to test Thrive by Five naturalistically (ie, in a manner of their own choosing) for a minimum of 1 week. Any participant incentives, such as transport, catering, and vouchers, will be determined by the in-country partner. In the first 2 countries (ie, Indonesia and Afghanistan) where the proof of concept for the Thrive by Five app was tested, more than 50 users were invited to test the app. For all future implementations, at least 25 beta testers will be invited to test the app. The identification of beta testers will be facilitated by the in-country partner. Testers will use the app at their own discretion during this period; no specifications will be set as to the frequency of use or number of activities completed. To ensure that a diversity of voices contribute to the testing process, whenever feasible, participants will be recruited from metropolitan, regional, and rural communities, including men and women from varied demographic backgrounds (eg, education, socioeconomic status, literacy, and religion). Although it will not always be feasible to include individuals from remote locations in the workshop activities, various strategies will be used to facilitate their engagement, including conducting workshops in regional areas, transporting participants from regional areas to workshop locations, using videoconferencing technologies, and allowing participants to provide written feedback and suggestions for content.

Quantitative Data

All testers will be asked to complete a brief questionnaire about their experience of using Thrive by Five and its impact on their feelings of connectedness to their child. The questions that will be asked to the beta testers are presented in Multimedia Appendix 1, with the corresponding response options.

In addition to direct quantitative user feedback, data analytics embedded in the Thrive by Five app or website will be available to examine user behavior (eg, frequency of use, average time of each use, and features with longest and shortest average periods of engagement) to determine which features are preferred relative to those that may require refinement or removal.

Qualitative Data

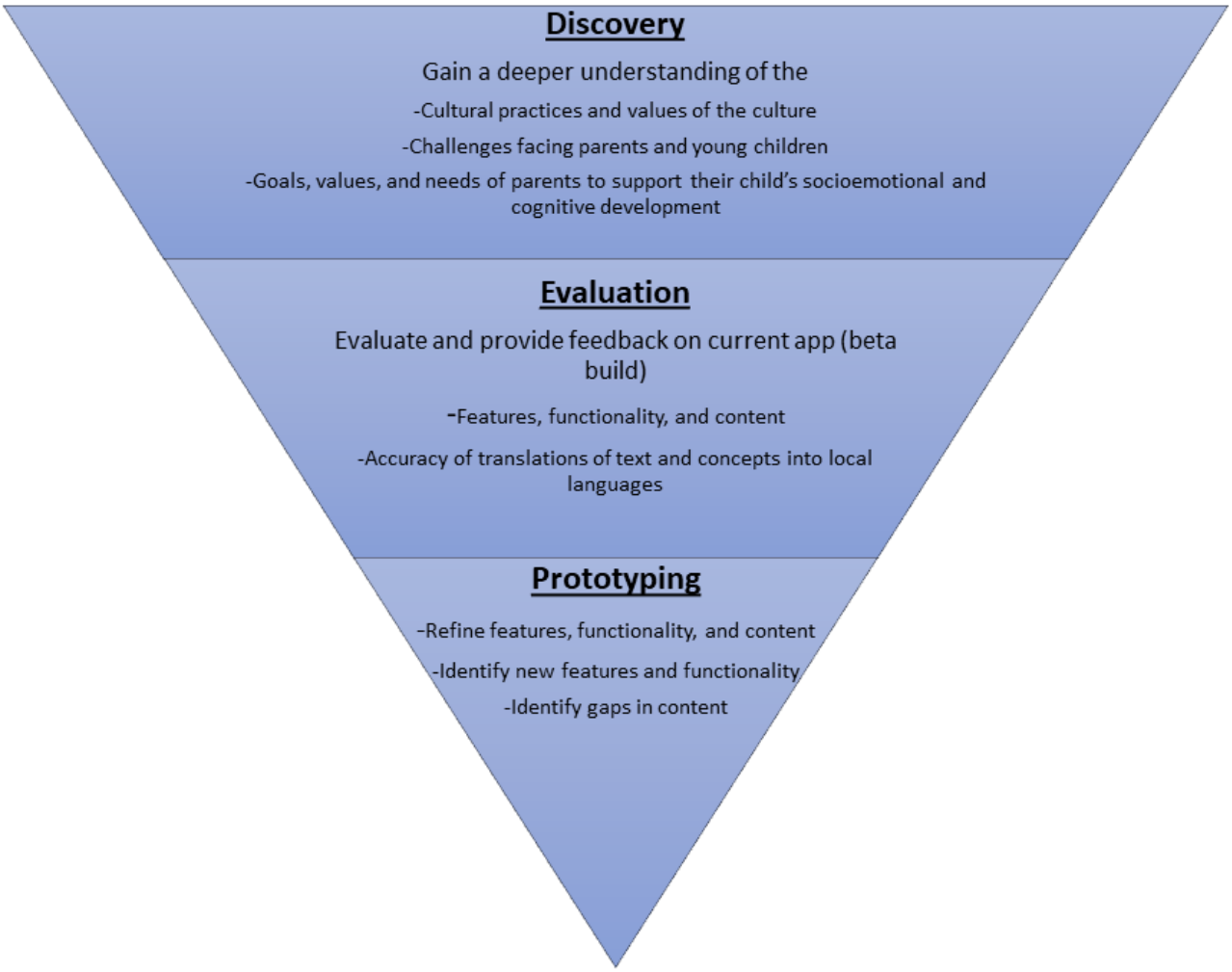
Central to the R&D cycle are co-design workshops. Direct engagement with potential end users through workshops is essential for testing and evaluating the user experience, functionality, and features. Furthermore, workshop participants will be asked to provide feedback on the relevance and cultural appropriateness of the content of the Thrive by Five app. All data from the workshops will be used to iteratively develop and refine the digital tool. Given the disparities in demographics (eg, age, education, and marital status), literacy, socioeconomic status, and cultural traditions and beliefs, workshop participants may be grouped based on commonalities in demographics and culture, in accordance with guidance from the in-country partner. This distribution of workshop participants is intended to enable all participants to feel comfortable in sharing their honest opinions, experiences, and beliefs.

Up to six 1.5- to 3-hour co-design workshops (depending on the need for translation), each with 4 to 6 participants, will be conducted via Zoom (or alternate video conferencing technology) over a 4-week period using an agenda consisting of 3 stages: “discovery,” “evaluation,” and “prototyping” (Figure 3). The workshop time will be halved, with the first part being used to explore expert, parent, and caregiver feedback on the app user experience, features, and functions, and the second part being dedicated to exploring how the content can be developed for and tailored to the needs of the parents and caregivers in each country. The workshops will be cofacilitated by representatives from the University of Sydney, Minderoo Foundation, and BBE in collaboration with a “local champion” identified by the in-country partner. With regard to the latter, the local champion does not need to have specialist credentials but rather a connection to the community and an eagerness to support the objectives of the Thrive by Five International Program. Research has shown that such champions can increase the awareness of and interest in participating in research among potential participants as well as other stakeholders involved in the research process (eg, health professionals) [41]. They will help ensure that all workshop participants feel comfortable sharing their open and honest feedback. Whenever possible, one or more facilitators will conduct the workshops in person, with other facilitators participating via video conferencing. Detailed notes will be taken by 2 scribes from the University of Sydney. In addition, the workshops will be recorded to ensure the accuracy of the notes. Depending on the language used to conduct the workshops, the in-country partner may be required to provide a translator to ensure that all participants are able to communicate in their preferred language. No formal certification is required to serve as a translator for this project, and in-country partners are responsible for identifying individuals with an appropriate level of fluency in the required languages. Simultaneous translation will be used whenever possible. If consecutive translation is required, facilitators and workshop participants will pause after every 1-3 sentences to enable accurate translations. Any questions arising from the translation will be checked with the in-country partner to ensure clarity.

A variety of methods will be used during the workshops to promote engagement from participants, including primarily prompted discussions and the development of user personas and specific use cases as appropriate. Importantly, BBE and Minderoo Foundation are responsible for leading the discussion regarding user experience, including the features and functionality. The researchers are responsible for leading the discussion about the cultural context into which the app and content are being implemented with the aim of developing content to promote and optimize socioemotional and cognitive development of children from birth to age 5 years. A sample agenda for a series of workshops for a country is available in Multimedia Appendix 2. Topics for discussion will be sent to participants at least 1 week before the workshop to allow time for preparation for those who choose to do so. The agenda questions are designed to identify challenges faced by parents and caregivers of children aged <5 years that may be able to be addressed through the Thrive by Five content. In addition, the questions explore traditional customs and beliefs that can be used to help contextualize app content.

The workshops support the exploration of a number of critical areas, such as the (1) look and feel of the app, including the design, language, tone of voice, colors, and illustrations; (2) usability, acceptability, and engagement of the Collective Actions; (3) relevance and appropriateness of the Collective Actions; (4) desired attributes, skills, and values for children; (5) information about children’s socioemotional and cognitive development that would be of benefit; (6) essential people (kin or other caregivers) in a child’s life who may benefit from shared use of the app to support childrearing; (5) barriers to and facilitators of the uptake and adoption of the app and the Collective Actions; (6) preferred features, functionality, and content; and (7) gaps in the test version, including features, functionality, and content. These research questions are critical to support the development of content for the final product that is appropriate for the cultural context. In addition, the co-design work will facilitate the discovery of areas for future development.

Figure 3. Structure of each co-design workshop.



Refinement and Future Content Development

Learnings from the beta testing process will then be examined internally by the research team to identify content that requires revision and gaps in the content to be developed for the end product. Importantly, a full library (ie, at least 100) of "Collective Actions" will be developed before implementation, all of which will be validated by the SME group. The research team will also identify key themes (eg, health advice, information about childhood nutrition, and early childhood learning activities) to guide future content development, including the potential to create alternate forms of content, such as longer-form articles. Furthermore, the developers from BBE, in collaboration with the researchers and Minderoo Foundation, will review the experiences reported by beta testers in relation to the app features and functionality. This process enables the technology team to consider ways to refine the app, either before implementation or for future iterations. Over the course of this project, it is anticipated that new features, functions, and content will be developed, tested, and implemented as part of the Thrive by Five app based on cumulative learnings, thus benefiting future countries embarking on the co-design process as well as countries that have already implemented the app.

Knowledge Translation and Qualitative Analysis

Knowledge translation refers to the synthesis, exchange, and application of knowledge by stakeholders to enhance the benefits of innovation in strengthening health systems and improving health outcomes [42]. The aim is to promote the translation of research findings into technology development and real-world implementation, bridging what has been coined "the know-do gap" [42]. In this instance, the knowledge translation process will inform the iterative refinement of the app to enhance its usability, acceptability, relevance, and cultural appropriateness for each of the 30 target countries.

Descriptive statistics will be used to characterize the sample of beta testers and to analyze the findings from the web-based surveys. Interpretation of the qualitative data from the workshops will follow established thematic techniques (ie, inductive reasoning) [43]. All raw data will be reviewed and checked across all participants by a senior researcher to develop a coding framework tailored to each country's context, outlining all the key concepts. Subsequently, the data will be coded in NVivo 12 software (QSR International) using this framework by 2 researchers. The coding will follow an established iterative process of reading, coding, and exploring the pattern and content of coded data, followed by reflection and discussion to reach consensus.

Ethics Approval

This study has been approved by the University of Sydney Human Research Ethics Committee (protocol 2021/956).

Results

The co-design process has been completed in Indonesia, Afghanistan, Namibia, Kenya, Kyrgyzstan, Uzbekistan, the Democratic Republic of the Congo, Cameroon, and Ethiopia, with the results expected to be published in early 2023. This includes participation of a total of 174 parents and caregivers and 58 in-country SMEs in 55 workshops in the 9 countries between January 2021 and August 2022. The remaining 21 countries will commence work on a rolling basis. A report summarizing the qualitative and quantitative findings from each country will be provided to Minderoo Foundation to inform their quality improvement processes.

Discussion

The Value of Co-design in the Development of Digital Health Solutions

Co-design is recognized as a critical component in the development of digital health solutions, ensuring that the products meet the needs of end users. However, a well-designed product in isolation is not sufficient to drive improved outcomes. In this project, we place considerable emphasis on the cultural appropriateness of the content for local settings to inform the iterative development of the Thrive by Five app and content to support its acceptability and relevance in a range of countries globally. Importantly, a qualitative study conducted with 162 ethnically diverse North American parents (63% non-Hispanic White, 14% African American, 10% Hispanic, 9% Asian or Pacific Islander, and 4% other) found a preference for self-administered parenting programs, such as via television, web-based programs, or written materials, as opposed to those requiring home visits, therapists, and weekly groups [44]. To that end, apps are cost-effective and well placed to fit into parents' daily routines. However, research has shown that standardized, evidence-based apps designed specifically to support research objectives, with no opportunity for iterative refinement, are far less popular than commercial apps among users [45].

Given the previously mentioned findings, to facilitate successful engagement and adoption, it is essential to capitalize on the adaptability of apps, including the potential to fix bugs and glitches and improve functionality to enhance user experience. However, and perhaps more importantly, co-design methodologies enable the iterative refinement of apps and will be used in this project to improve the cultural relevance and appropriateness of the Thrive by Five app by actively integrating local cultural practices into the Collective Actions to strengthen family and community relationships and foster connections to cultural traditions and values from a young age. Notably, a systematic review of 72 studies presenting evidence from studies of Indigenous communities globally found consistently positive associations between cultural connections and health and well-being outcomes [46]. Greater participation in culture has been shown to have positive effects on social and emotional well-being; physical health, including blood pressure, BMI, and cholesterol levels; and health-related lifestyle factors, such as smoking, alcohol consumption, nutrition, and physical activity levels [46]. These findings highlight the holistic nature of health and well-being and the importance taking into account cultural traditions and values when designing, developing, and implementing health-related digital health solutions. This is particularly important when engaging with communities and cultural groups not typically involved in more traditional research methods, such as clinical trials [47].

Conclusions

Several programs have been developed to support early childhood education and reduce the loss of developmental potential for disadvantaged children in LMICs. A review of 63 studies of such programs highlighted three factors critical to improving outcomes for children: (1) guidance about activities to support the socioemotional, cognitive, and behavioral development of the child; (2) skills training for parents and other caregivers to enhance the cognitive stimulation of the child and to foster a supportive environment; and (3) emphasis on parental health, well-being, and self-efficacy. Importantly, these key elements are already being developed and incorporated into the beta versions of the Thrive by Five app. However, the vital co-design process will emphasize the validation of the cultural appropriateness and relevance of all content as well as provide an opportunity to identify areas for improvement, adaptation, and refinement for the unique context present in each country.

Acknowledgments

The authors would like to thank all in-country partners, subject matter experts, and beta testers who contributed their valuable time and knowledge to support this project. In addition, the authors would like to thank the technology team at BBE for their ongoing efforts to develop, build, and refine the Thrive by Five app. This research is being conducted by the University of Sydney's Brain and Mind Centre pursuant to a 3-year agreement between the University of Sydney and Minderoo Foundation Limited (Minderoo). Minderoo Foundation's Thrive by Five International Project targets parents and caregivers of children aged 0-5 years to support the cognitive and socioemotional development and well-being of young children across diverse cultures. Minderoo Foundation identified 9 potential providers for the Thrive by Five International Project to undertake the content, research, and evaluation components of the project. Of these potential providers, 3 universities were shortlisted. An internal panel of 6 members was convened to assess the shortlisted candidates against 4 main criteria that were weighted equally: cost, credibility (ie, demonstrated company knowledge, expertise, experience, and track record), reliability (ie, experience, abilities, and accessibility

of the nominated personnel), and approach and methodology. The panel made a unanimous decision to award the University of Sydney's Brain and Centre as the content, research, and evaluation partner for the Thrive by Five International Program.

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Authors' Contributions

IBH and YJCS were integral in securing funding to support the study. The quality improvement activity was designed by HML, YJCS, MA, ME, VL, MP, NF, and MT, with subsequent contributions from JC and JT. MA, ME, VL, AY, GC, CW, MSN, and MP contributed to data collection. Scientific oversight and guidance were provided by IBH and JT to ensure that all activities were conducted responsibly and in a culturally appropriate manner. All authors contributed to and approved the final manuscript.

Conflicts of Interest

IBH is the Co-Director, Health and Policy at the Brain and Mind Centre at the University of Sydney. The Brain and Mind Centre operates an early intervention youth service at Camperdown under contract with headspace. He is the Chief Scientific Advisor to, and a 3.2% equity shareholder in, InnoWell Pty Ltd. InnoWell was formed by the University of Sydney (45% equity) and PwC (Australia; 45% equity) to deliver the Aus $30 million (US $21.63 million) Australian Government–funded Project Synergy (2017-2020; a 3-year program for the transformation of mental health services) and to lead the transformation of mental health services internationally through the use of innovative technologies. Importantly, InnoWell has no role in the development, production, or distribution of the Thrive by Five app. VL is a board member for Matana Foundation, a philanthropic organization that provides funding to programs for disadvantaged young people in Australia. She does not receive any financial benefit for this role. NF and MT are employed by Minderoo Foundation.

Multimedia Appendix 1
Survey questions and responses to collect feedback on the beta version of Thrive by Five.
[DOCX File , 14 KB - resprot_v11i10e39225_app1.docx]

Multimedia Appendix 2
Co-design workshop agenda.
[DOCX File , 18 KB - resprot_v11i10e39225_app2.docx]

References

1. Transforming our world: the 2030 agenda for sustainable development. United Nations General Assembly. 2015. URL: https://www.unfpa.org/sites/default/files/resource-pdf/Resolution_A_RES_70_1_EN.pdf [accessed 2021-07-06]
2. Strengthening preparedness for health emergencies: implementation of the international health regulations (2005). World Health Organization. 2021 Jan 12. URL: https://www.who.int/teams/ihr/ihr-review-committees/covid-19 [accessed 2021-06-18]
3. Stewart E, Milton A, Yee HF, Song MJ, Roberts A, Davenport T, et al. eHealth tools that assess and track health and well-being in children and young people: systematic review. J Med Internet Res 2022 May 12;24(5):e26015 [FREE Full text] [doi: 10.2196/26015] [Medline: 35550285]
4. Bamford R, Hutchinson G, Macon-Cooney B. The progressive case for universal internet access: how to close the digital divide by 2030. Institute.Global. 2021 Mar 2. URL: https://institute.global/sites/default/files/articles/The-Progressive-Case-for-Universal-Internet-Access-How-to-Close-the-Digital-Divide-by-2030.pdf [accessed 2021-09-16]
5. Measuring digital development Facts and figures 2020. International Telecommunication Union. 2020. URL: https://www.itu.int/en/ITU-D/Statistics/Documents/facts/FactsFigures2020.pdf [accessed 2021-09-27]
6. Rowntree O, Shanahan M. Connected women: the mobile gender gap report 2020. GSMA Connected Women. 2020. URL: https://www.gsma.com/mobilefordevelopment/wp-content/uploads/2020/05/GSMA-The-Mobile-Gender-Gap-Report-2020.pdf [accessed 2021-09-16]
7. Lupton D. Digital Health: Critical and Cross-Disciplinary Perspectives (Critical Approaches to Health). New York: Routledge; 2018.
8. Expanding connectivity to pave the way for digital transformation in Afghanistan. The World Bank. 2021 Feb 11. URL: https://www.worldbank.org/en/results/2021/02/11/expanding-connectivity-pave-way-digital-transformation-afghanistan [accessed 2021-06-18]
9. Medina A. Indonesia's Palapa Ring: bringing connectivity to the Archipelago. ASEAN Briefing. 2020 Jan 28. URL: https://www.aseanbriefing.com/news/indonesias-palapa-ring-bringing-connectivity-archipelago/ [accessed 2021-09-17]
10. Third Medium Term Plan 2018-2022. Government of the Republic of Kenya. 2018. URL: http://vision2030.go.ke/wp-content/uploads/2019/01/THIRD-MEDIUM-TERM-PLAN-2018-2022.pdf [accessed 2021-09-17]
11. The concept of digital transformation 'Digital Kyrgyzstan' – 2019-2023. Ministry of Digital Development of The Kyrgyz Republic. URL: http://ict.gov.kg/index.php?r=site%2Fsanarip&cid=27 [accessed 2021-09-17]

12. Harambee Prosperity Plan II 2021-2025. Republic of Namibia. URL: http://hppii.gov.na/wp-content/uploads/2021/03/HPP2.pdf [accessed 2021-09-17]
13. Measures to implement the concept of introducing technology "Smart City" in the Republic of Uzbekistan. Ministry of Innovative Development of the Government of Uzbekistan. URL: https://mininnovation.uz/en/activities/measures-to-implement-the-concept-of-introducing-technology-smart-city-in-the-republic-of-uzbekistan [accessed 2021-09-26]
14. The State of Mobile in 2020: the key stats you need to know. App Annie. URL: https://www.appannie.com/en/ [accessed 2020-07-15]
15. Blacker A. apptopia. 2021 Jan 7. URL: https://blog.apptopia.com/worldwide-us-download-leaders-2020 [accessed 2021-09-26]
16. Lin C. 10 health care apps in developing countries. The Borgen Project. 2020 Aug 14. URL: https://borgenproject.org/health-care-apps/ [accessed 2021-09-16]
17. Skills to last a lifetime: how girls in Uzbekistan are learning tech and helping others. United Nations Sustainable Development Group. 2021 Feb 8. URL: https://unsdg.un.org/latest/stories/skills-last-lifetime-how-girls-uzbekistan-are-learning-tech-and-helping-others [accessed 2021-09-15]
18. Vigliar V. Afghanistan: using technology to empower women. Aljazeera. 2016 Jul 22. URL: https://www.aljazeera.com/features/2016/7/22/afghanistan-using-technology-to-empower-women [accessed 2021-06-18]
19. Harkness S, Super CM. Culture and parenting. In: Bornstein MH, editor. Handbook of Parenting (Vol 2. Biology and Ecology of Parenting). New York: Routledge; 2002.
20. Mingebach T, Kamp-Becker I, Christiansen H, Weber L. Meta-meta-analysis on the effectiveness of parent-based interventions for the treatment of child externalizing behavior problems. PLoS One 2018 Sep 26;13(9):e0202855 [FREE Full text] [doi: 10.1371/journal.pone.0202855] [Medline: 30256794]
21. Morelli G, Quinn N, Chaudhary N, Vicedo M, Rosabal-Coto M, Keller H, et al. Ethical challenges of parenting interventions in low- to middle-income countries. J Cross Cultural Psychol 2017 Dec 19;49(1):5-24 [FREE Full text] [doi: 10.1177/0022022117746241]
22. Lachman J, Sherr L, Cluver L, Ward C, Hutchings J, Gardner F. Integrating evidence and context to develop a parenting program for low-income families in South Africa. J Child Fam Stud 2016 Feb 22;25(7):2337-2352 [FREE Full text] [doi: 10.1007/s10826-016-0389-6]
23. Craig P, Di Ruggiero E, Frohlich K, Mykhalovskiy E, White M on behalf of the Canadian Institutes of Health Research (CIHR)–National Institute for Health Research (NIHR) Context Guidance Authors Group. Taking account of context in population health intervention research: guidance for producers, users and funders of research. NIHR Evaluation, Trials and Studies Coordinating Centre. 2018. URL: https://www.journalslibrary.nihr.ac.uk/downloads/FullReport-CIHR-NIHR-01.pdf [accessed 2022-03-25]
24. Lindsay N, Baker T, Calder-Dawe O. Mental coaching through crisis: digital technologies and psychological governance during COVID-19. Critical Public Health 2021 Aug 30;32(1):104-115. [doi: 10.1080/09581596.2021.1965543]
25. Hall GC, Ibaraki AY, Huang ER, Marti CN, Stice E. A meta-analysis of cultural adaptations of psychological interventions. Behav Ther 2016 Nov;47(6):993-1014. [doi: 10.1016/j.beth.2016.09.005] [Medline: 27993346]
26. Masiran R, Ibrahim N, Awang H, Lim PY. Improving multicultural parenting program for children with emotional and behavioral problems: an integrated review. Asian J Psychiatr 2020 Jun;51:101851. [doi: 10.1016/j.ajp.2019.101851] [Medline: 31711780]
27. World Health Organization. Global Strategy on Digital Health 2020-2025. Geneva: World Health Organization; 2021.
28. Australia's National Digital Health Strategy. Australian Government Australian Digital Health Agency. URL: https://www.digitalhealth.gov.au/sites/default/files/2020-11/Australia%27s%20National%20Digital%20Health%20Strategy%20-%20Safe%2C%20seamless%20and%20secure.pdf [accessed 2021-07-06]
29. Five year forward view. NHS England. 2014 Oct. URL: https://www.england.nhs.uk/wp-content/uploads/2014/10/5yfv-web.pdf [accessed 2021-07-06]
30. Principles of digital development homepage. Principles of Digital Development. URL: https://digitalprinciples.org/ [accessed 2021-07-06]
31. Bjerkan J, Hedlund M, Hellesø R. Patients' contribution to the development of a web-based plan for integrated care - a participatory design study. Inform Health Soc Care 2015 Mar;40(2):167-184. [doi: 10.3109/17538157.2014.907803] [Medline: 24786524]
32. Clemensen J, Larsen SB, Kyng M, Kirkevold M. Participatory design in health sciences: using cooperative experimental methods in developing health services and computer technology. Qual Health Res 2007 Jan;17(1):122-130. [doi: 10.1177/1049732306293664] [Medline: 17170250]
33. van Niekerk L, Chater R, Naydenova E, Lim J, Chamas L, Manderson L, et al. Social Innovation in Health: Case Studies and Lessons Learned From Low- and Middle-income Countries. Geneva: World Health Organization; 2017.
34. When the shopkeeper measures blood pressure: Novartis Foundation and partners prove effectiveness of community-based approach to tackling hypertension. Novartis Foundation. 2018 Nov 27. URL: https://www.novartisfoundation.org/news/media-release/when-shopkeeper-measures-blood-pressure-novartis-foundation-and-partners-prove-effectiveness-community-based-approach-tackling-hypertension [accessed 2021-07-06]

35. Ensuring every child has a bright future. Minderoo Foundation. URL: https://www.minderoo.org/thrive-by-five/#overview [accessed 2021-09-27]
36. Skivington K, Matthews L, Simpson SA, Craig P, Baird J, Blazeby JM, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. BMJ 2021 Sep 30;374:n2061 [FREE Full text] [doi: 10.1136/bmj.n2061] [Medline: 34593508]
37. Davenport T, Milton A, Ospina-Pinillos L, Whittle L, Ricci C, Burns J. Project Synergy research and development cycle: iterative processes of participatory design, user testing, implementation and feasibility testing. Med J Aust 2019 Oct 7;211(7):S8-11.
38. LaMonica HM, Davenport TA, Burns J, Cross S, Hodson S, Veitch J, et al. Technology-enabled mental health service reform for open arms - veterans and families counselling: participatory design study. JMIR Form Res 2019 Sep 19;3(3):e13662 [FREE Full text] [doi: 10.2196/13662] [Medline: 31538937]
39. LaMonica HM, Davenport TA, Roberts AE, Hickie IB. Understanding technology preferences and requirements for health information technologies designed to improve and maintain the mental health and well-being of older adults: participatory design study. JMIR Aging 2021 Jan 06;4(1):e21461 [FREE Full text] [doi: 10.2196/21461] [Medline: 33404509]
40. Ospina-Pinillos L, Davenport TA, Ricci CS, Milton AC, Scott EM, Hickie IB. Developing a mental health eClinic to improve access to and quality of mental health care for young people: using participatory design as research methodologies. J Med Internet Res 2018 May 28;20(5):e188 [FREE Full text] [doi: 10.2196/jmir.9716] [Medline: 29807878]
41. Oduola S, Wykes T, Robotham D, Craig TK. What is the impact of research champions on integrating research in mental health clinical practice? A quasiexperimental study in South London, UK. BMJ Open 2017 Sep 11;7(9):e016107 [FREE Full text] [doi: 10.1136/bmjopen-2017-016107] [Medline: 28899890]
42. Pablos-Mendez A, Shademani R. Knowledge translation in global health. J Contin Educ Health Prof 2006;26(1):81-86. [doi: 10.1002/chp.54] [Medline: 16557508]
43. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006 Jan;3(2):77-101. [doi: 10.1191/1478088706qp063oa]
44. Metzler CW, Sanders MR, Rusby JC, Crowley RN. Using consumer preference information to increase the reach and impact of media-based parenting interventions in a public health approach to parenting support. Behav Ther 2012 Jun;43(2):257-270 [FREE Full text] [doi: 10.1016/j.beth.2011.05.004] [Medline: 22440064]
45. Pagoto S, Schneider K, Jojic M, DeBiasse M, Mann D. Evidence-based strategies in weight-loss mobile apps. Am J Prev Med 2013 Nov;45(5):576-582. [doi: 10.1016/j.amepre.2013.04.025] [Medline: 24139770]
46. Bourke S, Wright A, Guthrie J, Russell L, Dunbar T, Lovett R. Evidence review of indigenous culture for health and wellbeing. Int J Health Wellness Soc 2018;8(4):11-27. [doi: 10.18848/2156-8960/cgp/v08i04/11-27]
47. Hingle M, Patrick H. There are thousands of apps for that: navigating mobile technology for nutrition education and behavior. J Nutr Educ Behav 2016 Mar;48(3):213-8.e1. [doi: 10.1016/j.jneb.2015.12.009] [Medline: 26965099]

Abbreviations

ICT: information and communications technology
LMIC: low- and middle-income country
mHealth: mobile health
R&D: research and development
SME: subject matter expert

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Protocol

Telepresence Robot Intervention to Reduce Loneliness and Social Isolation in Older Adults Living at Home (Project DOMIROB): Protocol for a Clinical Nonrandomized Study

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Abstract

Background: There is a growing prevalence of loneliness and social isolation among older adults (OAs). These problems are often associated with depressive states, cognitive decline, sleep disorders, addictions, and increased mortality. To limit loneliness and social isolation in OAs, some authors recommend the use of new communication technologies to maintain a social link with family members as well as with health and social care professionals. Among these communication tools, telepresence robots (TRs) seem to be a promising solution. These robots offer users the possibility of making video calls with their relatives, social workers, and health care professionals, to maintain social contact and access to support services while living at home. Nevertheless, TRs have been relatively unstudied in real-life environments.

Objective: The main objective of this study is to measure the impact of a 12-week intervention using a TR on the feeling of loneliness and on social isolation of OAs living at home. Its secondary objective is to establish recommendations for the implementation of TRs in the studied context.

Methods: A nonrandomized study will be conducted among 60 OAs living at home who will participate in the study for 24 weeks. During this period, they will host a TR for 12 weeks to use it in their home. After the end of the intervention a 12-week follow-up ensues. In total, 4 evaluations will be performed over the entire experimental phase for each participant at weeks 0, 6, 12, and 24. A multidimensional assessment of the impact of the robot will be performed using a multimethod approach including standardized scales and a semistructured interview. This assessment will also help to identify the ergonomic aspects that influence the robot's usability and acceptability among OAs.

Results: Data collection started in September 2020 and is expected to be completed in early 2023. In August 2022, 56 participants were recruited for the study. Data analysis will take place between August 2022 and is expected to be completed in early 2023.

Conclusions: The DOMIROB study will provide new knowledge on the impact of social TRs in OAs living at home. The results will make it possible to suggest technological, ethical, and organizational recommendations for the use and implementation of TRs for OAs in real-life settings.

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KEYWORDS

older adults; telepresence robot; feeling of loneliness; social isolation; home; acceptability; usability

Introduction

The Risk of Loneliness and Social Isolation Among Older Adults

Throughout the world, social isolation and loneliness among older adults (OAs) living at home has reached very high levels. In Europe, in 2018, it was estimated that around 10% of individuals aged over 75 years were socially isolated [1]. In France, in 2017, nearly 300,000 individuals over the age of 60 years experienced social withdrawal [2]. In the United States, one-quarter (25%) of the population over 65 years were socially isolated in 2020 [3]. In Canada, in 2009, 12% of the population over the age of 65 years also encountered this problem [4]. In 2019, it was estimated that about 6 million (7.62%) elderly people lived alone in Japan [5]. However, being socially isolated and experiencing a feeling of loneliness are not the same thing. A person can objectively live in a socially isolated way (ie, having a reduced social network, a lack of social contact or support) and not feel lonely, and conversely, they could not live in a context of social isolation and experience a feeling of loneliness [6]. Loneliness seems to be even more widespread than social isolation among OAs. Several studies estimate that about one-third of OAs experience a feeling of loneliness [7-9], especially after the age of 80 years, with approximately 50% of OAs reporting frequent loneliness [10].

Loneliness and social isolation have particularly harmful consequences for OAs' psychological and physical health (depression, addictions, cognitive decline, sleep disorders, and excess mortality) [11-15]. Retirement, loss of professional contacts, widowhood, death of relatives and friends, and chronic diseases (which can limit travel) favor withdrawal and social isolation in OAs [16,17].

New Technologies: A Socialization Solution for OAs?

Several authors have advocated interventions using technologies, such as computers, tablets, the internet, SMS text messaging and social media apps, videoconferencing, or robots, to alleviate loneliness and improve quality of life in OAs [18,19]. Digital technologies (eg, tablets, social networks, video games, and robots) can be useful to mitigate the consequences of social isolation and loneliness in OAs [19-23]. Digital tools allow users to get information through the internet, to maintain social contact with their relatives, and to improve social participation via different communication tools (eg, instant messaging and social networks). Nevertheless, the digital divide persists, notably because these technologies are not tailored to OAs' needs and preferences. It is important that the technology is ergonomic, easy to use, and useful for this population. For example, it is recommended to use simplified interfaces and contents that meet OAs' capacities and preferences in addition to introducing tools (eg, stands, tablet holders, stylus) that can increase the comfort and ease of use of the equipment for the individual [24]. Today, different actors from the field of innovation and digital technologies work on the development of adapted solutions to meet OAs' needs that could minimize the digital divide. Telepresence robots (TRs) are an example. TRs are tools that help create a connection between 2 distinct environments through cameras, microphones, speakers, and a screen. TRs offer a videoconferencing functionality integrated on a navigation base with wheels that allow the robot to move around in an environment. TRs can be used to promote social contact with relatives and friends and access to a wide range of distant assistance services. Although TRs seem to have promising functionalities for the management of isolation in OAs, they remain poorly studied and deployed in home environments.

TRs: A Solution That Has Not Been Thoroughly Studied for Seniors Living at Home

Since the beginning of the COVID-19 health crisis, different stakeholders have shown an increasing interest in innovative remote communication solutions and TRs [25-38]. However, thus far, there is limited available evidence concerning the implementation and usefulness of TRs in a home-dwelling OA population. TRs have so far been studied mainly in controlled settings [39-49], although some studies involving OAs have been conducted in institutional settings (hospital services or senior residences) [50-58] and a few of them at home [59-63]. In particular, studies conducted with OAs at home have highlighted the benefits and issues associated with the use of TRs.

With regard to the benefits of using TRs at home, cognitively healthy users have had a positive experience [60-63]. Participants in the experiments reported good acceptance, usability, perceived usefulness [59], and reliability of the TRs [63]. In the study by Cesta et al [43] the users mentioned good social and functional acceptability of the robot without any loss of interest in its use over time. They considered the mobility, entertainment, and obstacle detection features of the robot to be satisfactory [61]. They mentioned that TRs could be beneficial for physical health, psychological well-being, social contact, and independent living [60]. In the trial carried out by Bakas et al [62], OAs showed an improvement in quality of life and sleep, as well as a decrease in depression following a TR intervention.

Elderly participants of TR studies have also mentioned some issues when experimenting with these tools at home. In the study by Gonzalez-Jimenez et al [59], some participants feared that video calls with TRs might replace real human contact with relatives and friends. They also noted that the robot was too big and too noisy and that its battery required too much energy. In another study [60], the obstacles identified to the implementation of TRs were the unsuitability of the robot's wheels for different types of floors and a slight confusion for some users when using the handheld remote control. Concerns about operating the robot from a distance were also reported by some secondary users (eg, family members or friends). One participant with mild cognitive impairment requested the withdrawal of the robot due to the significant difficulties encountered while using it. Therefore, the authors concluded that TRs were not suitable for OAs with mild cognitive impairment. Participants also emphasized the need for good speech recognition, navigation, and self-location of TRs [61] in addition to a good internet connection to optimize their use [59,63].

Although these studies reported interesting results regarding the implementation and acceptability of TRs in OAs homes,

some methodological limitations were identified, such as small sample sizes included in the studies (between 2 and 20 participants), and the fact that in some protocols the TR was tested using different implementation periods for different users within the same sample, which does not allow to have the same frequency of use of the TR and may affect its impact. Besides, the psychosocial effects of the TR intervention (eg, including outcomes such as depressive symptoms or quality of life) was measured in only 1 study [61].

To overcome the aforesaid limitations identified in the literature, the DOMIROB project aims to implement a TR and assess its impact in 60 OAs living at home for a period of 12 weeks, with the same length of implementation for all participants. The main objective of this study is to measure the impact of a TR intervention on the feeling of loneliness and social isolation of OAs living at home who may benefit from the robot for a 12-week period. We hypothesize that the use of a TR at home would reduce the feeling of loneliness and social isolation in OAs.

The experimental protocol of the DOMIROB project, inspired by the MARTA (Multidimensional Assessment of Telepresence Robot for Older Adults) model [59], allows the psychosocial and ergonomic dimensions of TRs to be examined using a multimethod longitudinal design. To avoid the risk of complex and cumbersome evaluation for the users, we have reduced the number of evaluation scales in the MARTA model and have only kept the measures for loneliness, perceived social support, depression, acceptability, usability, self-perceived health, and the effect of a device on independent living. Concerning the qualitative evaluation of the experimentation, we propose a complementary and original assessment performed using a semidirective interview inspired by the Core Model of the European Network for Health Technology Assessment (EUnetHTA) [64], which is described later.

Methods

Study Design

The DOMIROB protocol is a nonrandomized, quasi-experimental field trial using a multimethod and multidimensional assessment. The experimental phase of the study took place between September 2020 and February 2023. Volunteer OAs were recruited between September 2020 and August 2022 in Paris, France. This study included 60 OAs who agreed to host and use a TR in their home for a period of 12 weeks.

Determination of Sample Size

The sample size and power calculation for this study were performed based on 1 of the main outcome measures for this study: the feeling of loneliness, as assessed with the Perceived Loneliness Scale (UCLA; version 3) [65]. From a statistical point of view, we consider that the average score for the UCLA scale, observed for people aged 65 years and over, is 31.51/80 [65]. The higher the score, the greater the perceived loneliness is evaluated. Therefore, our hypothesis aims at a decrease in the average score in the UCLA scale of 3-5 points. If we want to show a decrease of 15% in the average score on the UCLA, between the assessment done at week 0 and week 24 with a power of 0.8 and a risk α of .05, then 60 individuals should be included. A decrease in the UCLA loneliness score of 15% after a 12-week implementation of the TR is clinically relevant.

Objectives

Main Objective and Primary Outcome Measures

The main objective of this study is to measure the impact of a 12-week intervention using a TR in the home of OAs on their feeling of loneliness and social isolation. To measure the impact of TRs on the feeling of loneliness, we will use the UCLA (version 3) [65]. We will assess social isolation using the Multidimensional Scale of Perceived Social Support (MSPSS), which is a tool for measuring the perception of social support that a person has [66]. We will compare the results obtained in the assessments performed at weeks 0, 6, 12, and 24 to identify the possible decreases in the scores of the different scales at different times of the implementation of the TR at home.

Secondary Objectives and Secondary Outcome Measures

The secondary objective of this study is to establish recommendations for the implementation of TRs in the homes of the OAs. The goal is therefore to study the use of TRs over 12 weeks using ergonomic and health-related and psychosocial criteria. The ergonomic parameters include an evaluation of the perceived usability of the robot software (System Usability Scale [SUS]) [67] and the acceptance of the robot (ALMERE model) [68]. The psychosocial parameters include an evaluation of depressive states (Geriatric Depression Scale [GDS]) [69] and the psychosocial impact of the robot (Psychosocial Impact of Assistive Devices Scale [PIADS]) [70]. These secondary outcome measures are assessed at weeks 6 and 12 (Table 3).

These assessments will help us determine whether TRs are useful tools to reinforce social contact for OAs living at home. We will identify the most suitable target population (eg, autonomous OAs, dependent OAs) as well as the most suitable framework and environment of use (eg, home, senior residence) for the deployment of TRs. We will also suggest organizational, ethical, and practical recommendations for the implementation and use of TRs by community-dwelling OAs.

Participants

The recruitment of volunteer participants is carried out through the outpatient clinic of the Parisian geriatric hospital (Broca Hospital, Assistance Publique–Hôpitaux de Paris) and its network of professionals, “seniors” associations, and town halls in the Paris region. The inclusion and exclusion criteria for participation in the study are described in Textbox 1.

Information leaflets are given to professionals working in the outpatient hospital of Broca Hospital to distribute them to potential volunteers during consultations. Senior citizens’ associations also distribute the information leaflet to their members and the local city halls disseminate a communication about the study to their users. When OAs wish to volunteer to take part in the trial, they contact the researcher in charge of the study to discuss the modalities in more detail, either by email or by telephone, using the information given on the information leaflet. During this first contact, a detailed explanation of the

study is given. After having obtained answers to all their questions, volunteers receive an email with an information note describing the whole study at least 24 hours before inclusion, to give them time to withdraw from participation if wished. Participants are divided into 6 groups of 10 people; 10 robots were available simultaneously. A group of 10 participants was formed every 12 weeks. Each participant who agrees to participate is invited to sign the study's no-opposition form. The recruitment procedure is described in Figure 1.

Textbox 1. Inclusion and exclusion criteria for the DOMIROB study.

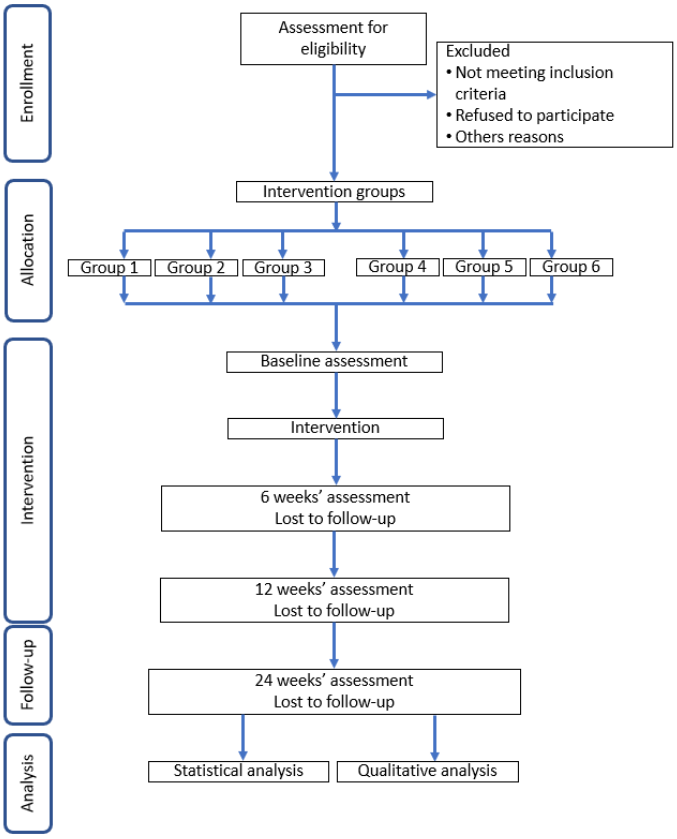
Inclusion criteria

- Being 65 years of age and over;
- living in the Paris region (Île-de-France);
- express nonopposition to participating in the study;
- agree to host a telepresence robot in the home for 12 weeks; and
- having an internet connection at home.

Exclusion criteria

- Being under 65 years of age;
- expressed opposition to participating in the study;
- having moderate or major neurocognitive disorders (Mini-Mental State Examination score <20; [71]);
- being under guardianship or curatorship; and
- living in housing unsuitable for the telepresence robot (surface area and configuration of the home not suitable for robot circulation).

Figure 1. Flow chart of the recruitment process.



Ethics Approval and Consent

The research protocol was submitted to, and approved by, a French national institutional review board for research involving human participants (Comité de Protection des Personnes, France) on April 27, 2020 (national number: 2020-A00381-38. Trial registration: ClinicalTrials.gov, trial registration number NCT04767100).

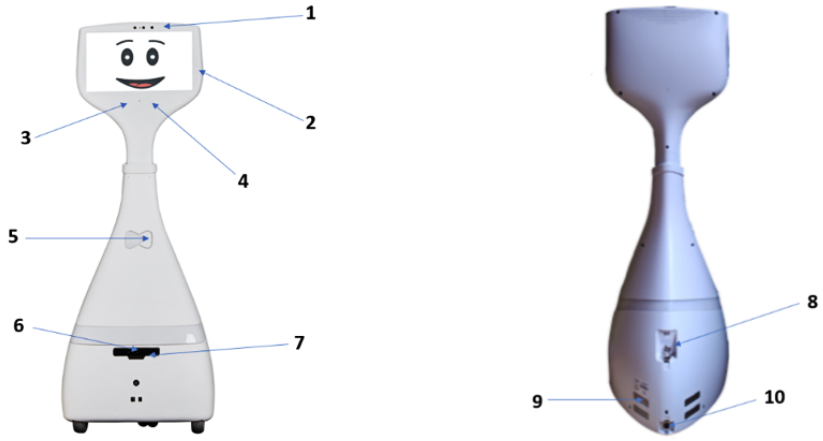
Materials

The TR used in this study is the Cutii, a robotic platform for remote communication. This TR is equipped with a touch screen,

microphones, loudspeakers, cameras, an obstacle detector, and a mobile system allowing navigation in the environment (Figure 2). Cutii allows users to maintain a connection with their environment. Its interface has different functionalities allowing, for example, to make video calls and to participate in intellectual (eg, virtual museum tour) and physical (eg, yoga) stimulation activities. Cutii's services include the following:

- An agenda with a calendar to schedule the activities.
- A contact directory for video calls.
- An "activities" tab allowing users to participate in collective live sessions of intellectual and physical activities/workshops (eg, gymnastics, yoga, art therapy, virtual museum tours) led by professionals through the video call feature.
- A "leisure" tab allowing users to play digital games (eg, memory games, sudoku, quiz).
- A "video" tab to watch documentaries (eg, cooking, traveling, animals' life).
- A "teleconsultation" tab that allows users to consult a health professional remotely through the video calling system.

Figure 2. Front and back view of the telepresence robot Cutii. Note: 1: video call camera; 2: touch screen; 3: speaker; 4: microphone; 5: battery indicator light; 6: navigation camera; 7: obstacle detector; 8: power switch; 9: port for dock charging; 10: port for charging by charger.



Measures

We will use a multimethod approach assessment protocol partly inspired by the MARTA model [43], which has been developed to assess TR interventions involving OAs and complemented by the EUnetHTA model. The assessment uses standardized scales and a semistructured interview format (Multimedia Appendix 1). Sociodemographic data of the participants are also collected (age, sociocultural level, lives alone or accompanied, has children/grandchildren or not) as well as their Mini-Mental State Examination (MMSE) [72] score, which measures the global cognitive functioning, and the 12-Item Short-Form Health Survey (SF-12) [73] score, which measures the perception of one's health status.

Standardized Scales

The MMSE [72] measures the global cognitive functioning of OAs. MMSE scores range from 0 to 30, with scores of 26 or higher being considered normal (ie, absence of cognitive impairment). Moderate or major neurocognitive disorders are considered to be present when the score is below 20 [66].

The UCLA (version 3) [65] measures the feeling of loneliness in participants with 20 questions. Participants answer the questions using a Likert scale consisting of 4 response choices: "1=never," "2=rarely,", "3=sometimes," and "4=always." The scoring of this scale is based on the sum of the scores obtained for each item. The score correlates directly with loneliness, that is, the higher the score, the more lonely the participant feels.

The MSPSS [66] measures the social support perceived by a person. This 12-item scale is divided into 3 subscales: "family," "friends," and "others." Participants respond to each statement using a Likert scale ranging from "1=totally disagree" to "7=totally agree." The global score allows the researcher to identify 3 levels of perceived social support: high (61-84), moderate (36-60), and low (0-35).

The 30-item GDS [69] measures depressive states in a geriatric population. It is composed of 30 items to which participants answer "yes" or "no." The total score is calculated by assigning a "0" or a "1" to each item according to the participant's response. The highest score is therefore 30. A score ranging from 0 to 9 represents a normal state. A score from 10 to 19 or from 20 to 30 represents, respectively, a moderate or severe depression.

The SF-12 [73] is a questionnaire developed from the SF-36 questionnaire. The SF-12 provides a self-reported measure of the impact of physical and mental health in the everyday life of individuals. The average score is 50 and all scores above this threshold are considered normal.

The SUS [67] defines the level of usability of a system, tool, software, or digital technology with regard to its effectiveness, efficiency, and overall ease of use. After having experienced the use of the device, the person responds to 10 items using a Likert scale consisting of 5 responses ranging from "1=strongly disagree" to "5=strongly agree." The total score ranging from 0 to 100 represents a gradually increasing usability. A product is considered as having a good usability if the score is above 70.

The ALMERE model [68] measures OAs' acceptance toward socially assistive robots. It can be used to predict and understand the use of a system by observing the influences on the intention

to use it. The ALMERE model questionnaire is composed of 39 items divided into 13 dimensions: "Anxiety," "Attitude Towards Technology," "Facilitating Conditions," "Intention to Use," "Perceived Adaptiveness," "Perceived Enjoyment," "Perceived Ease of Use," "Perceived Sociability," "Perceived Usefulness," "Social Influence," "Social Presence," "Trust," and "Use." These dimensions predict the actual intention to use the system. To answer the items, the participants respond using a 5-point Likert scale ranging from "1=strongly disagree" to "5=strongly agree." Scores of 1 and 2 represent poor satisfaction, 3 denotes fair satisfaction, 4 means good satisfaction, and 5 promotes excellent satisfaction.

The PIADS [70] is a self-report questionnaire designed to assess the effects of an assistive device on functional independence, well-being, and quality of life. Participants respond to 26 items on a 7-point Likert scale ranging from "–3" to "+3." The final score of –3 represents the strongest negative impact, 0 indicates no perceived impact, and 3 denotes the strongest positive impact.

Measurements performed during the experimental phase of the DOMIROB study are listed in Table 1. The calendar of the assessments is specified in Table 2.

Table 1. DOMIROB project protocol measures.

Measurement tools	Dimensions assessed
Mini-Mental State Examination (MMSE) [72]	Global cognitive efficiency
Perceived Loneliness Scale (UCLA) [65]	Subjective feelings of loneliness
Multidimensional Scale of Perceived Social Support (MSPSS) [66]	Perceived social support (social isolation)
Depression: Geriatric Depression Scale (GDS) [69]	Depressive states
Perceived health status: 12-item Short Form Health Survey (SF-12) [73]	Self-assessment of health
System Usability Scale (SUS) [67]	Telepresence robot usability
Acceptance model (ALMERE) [68]	Telepresence robot acceptance
Psychological Impact of the Assisted Device (PIADS) [70]	Psychosocial impact of a device
Sociodemographic data	Age, socioeducational level, and family status
Semistructured interview	Eight dimensions of the European Network for Health Technology Assessment Core Model: "Health Problem and Current Use of the Technology," "Description and Technical Characteristics of the Technology," "Safety," "Clinical Effectiveness," "Costs and Economic Evaluation," "Ethical Analysis," "Organizational Aspects," "Patients and Social Aspects" [65]

Table 2. Semistructured interview based on the European Network for Health Technology Assessment Model.

Item	Health Technology Assessment dimension
What impact did the robot have on your health/well-being?	Current Use of the Technology (CUR)
How did you find the robot's features and services? Did you find them useful? Why do you think so?	Description and Technical Characteristics of the Technology (TEC)
What do you think are the potential risks and side effects caused by the use of the robot? What can be done to prevent them?	Safety (SAF)
Do you think this robot can have an impact on the loneliness/isolation of the users? Why?	Clinical Effectiveness (EFF)
How much would you be willing to invest to benefit from the robot in your home? Would you prefer to purchase or to rent the robot? In the case of a rent, would it be for a short or long term?	Costs and Economic Evaluation (ECO)
In your opinion, what are the ethical issues to be identified and defined before the deployment of these robots in the homes of future users?	Ethical Analysis (ETH)
In your opinion, what skills and knowledge are necessary for a good deployment of these robots in users' homes?	Organizational Aspects (ORG)
What factors would restrain you from using this type of robot?	Patients and Social Aspects (SOC)
Nonapplicable	Legal Aspects (LEG)

Semistructured Interview

We designed a semistructured interview based on the EUnetHTA Core Model version 3.0 [65]. This model allows a systematic assessment of the characteristics, effects, or impacts of health care technologies. The main objective of the HTA model is to facilitate decision making in the field of health care to improve the uptake of new health technologies.

The 9 dimensions of the EUnetHTA Core Model allow the identification of issues that are necessary for the deployment and use of new technological tools in the field of health. These dimensions include "Health and Current Use of the Technology," "Description and Technical Characteristics of the Technology," "Safety," "Clinical Effectiveness," "Costs and Economic Evaluation," "Ethical Analysis," "Organizational Aspects," "Patients and Social Aspects," and "Legal Aspects." The interview guide used in the DOMIROB protocol was designed using the first 8 dimensions of the EUnetHTA Core Model (Table 2). The "Legal" dimension was excluded because its assessment did not directly concern the TR end users and was therefore entrusted to a specialized consulting firm. The semistructured interviews were integrated to our protocol with the aim of examining different dimensions that may inform the choice of TRs to provide social and care services to OAs and to establish recommendations for the use of TRs for future users.

Procedure and Time Schedule

All stages of the experimental phase are illustrated in Figure 3, which describes the different actors involved in each step of the experimental phase, its length, the eventual assessment carried out at that moment, and the respective assessment tools.

During their participation in the protocol, the participants complete 4 assessments (including scales and interviews) as shown in Table 3.

The first evaluation is performed at the time of inclusion at week 0 (ie, approximately 1 week before the implementation of the TR in the volunteers' homes; Figure 4). A second evaluation (intermediate evaluation) is conducted 6 weeks after the beginning of the experiment at home. A third evaluation (final evaluation) is carried out at the end of the implementation phase (week 12). To conclude the participation in the protocol, the volunteers are invited to take part in a final assessment (follow-up evaluation) at week 24, approximately 12 weeks after the robot has been removed from the participants' homes. Assessments of participants are conducted face-to-face for the inclusion, and then via the video call functionality of the Cutii robot or by telephone at weeks 6, 12, and 24. Semistructured interviews at week 12 are conducted by a psychologist and recorded using a voice recorder to be transcribed and analyzed.

Figure 3. Steps of the experimental phase. GDS: Geriatric Depression Scale; MMSE: Mini-Mental State Examination; MSPSS: Multidimensional Scale of Perceived Social Support; PIADS: Psychosocial Impact of Assistive Devices Scale; SF-12: 12-Item Short-Form Health Survey; SUS: System Usability Scale; UCLA: Perceived Loneliness Scale.

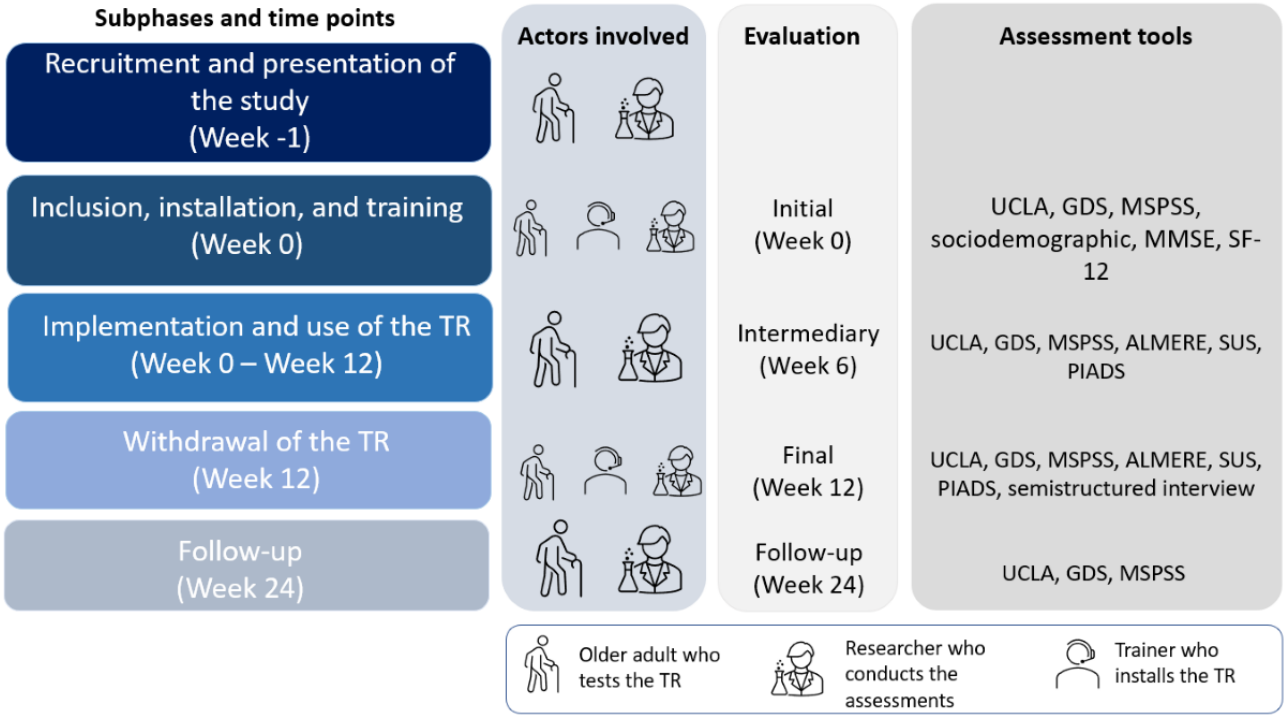
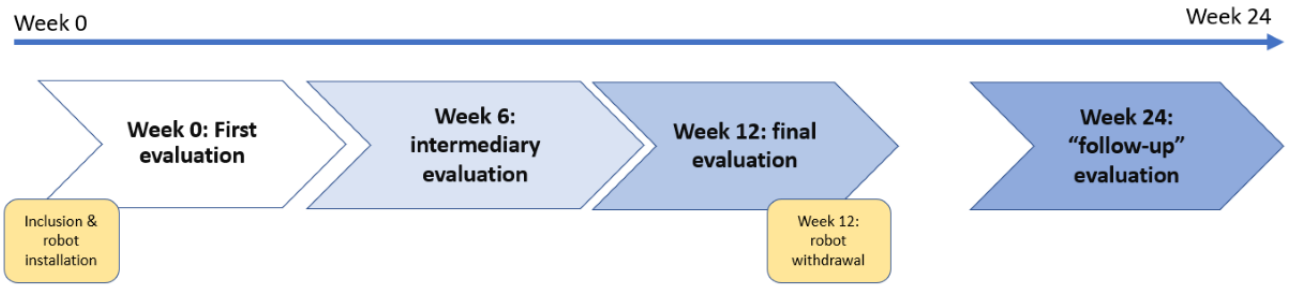


Table 3. Calendar of the assessment carried out in the DOMIROB protocol.

Measures	Evaluations			
	Inclusion (week 0)	Week 6	Week 12	Week 24
Mini-Mental State Examination (MMSE)	✓			
Perceived Loneliness Scale (UCLA)	✓	✓	✓	✓
Multidimensional Scale of Perceived Social Support (MSPSS)	✓	✓	✓	✓
Geriatric Depression Scale (GDS)	✓	✓	✓	✓
12-Item Short-Form Health Survey (SF-12)	✓			
System Usability Scale (SUS)		✓	✓	
The ALMERE model		✓	✓	
Psychosocial Impact of Assistive Devices Scale (PIADS)		✓	✓	
Sociodemographic data	✓			
Semistructured interview (Health Technology Assessment model)			✓	

Figure 4. Experimental and evaluation phases in the DOMIROB protocol.



Installation and Training

For the implementation phase of the robot, a team of 2 professionals, experts of the Cutii robot, install the robot in the participant's home. The team and the participant choose the location of the dock of the robot, which is close to an outlet to facilitate its recharging. During the intervention, the team connects the robot to the participant's Wi-Fi network and ensures it works properly. After the installation, the team provides the participants with a 60-minute training session to familiarize them with its functionalities and operation. The training session includes information about how to use the robot, its maintenance, and the procedure to follow in case of malfunction. In case of malfunction, participants can contact the project support team at any time during the study. Participants are informed that their environment can be visualized during the video call service and the group workshops so that they can make the arrangements when necessary to preserve their privacy.

Period of Use of the Robot

During the experimental phase, participants are invited to discover the different functionalities of the robot. Participants are free to use the TR as needed and wished. Volunteers can discover the "video call" functionality by making videoconferences with their relatives or taking part in the live sessions (workshops, activities). Every week the workshop facilitators offer live cultural and physical workshops (eg, yoga, soft gym, guided tours of museums) through the robot's "video call" feature. The robot also offers users games, reading, and music applications.

Data Analysis

Quantitative Analysis (Standardized Scales)

The descriptive data for all the questionnaires will be presented in the form of both average scores and SDs. Inferential statistical analyses of the results obtained during the different evaluation weeks will then be performed. All collected data will be analyzed using the open-source statistics program Jeffreys's Amazing Statistics Program (version 0.14.1; JASP Team). For the scores of questionnaires on social isolation (GDS, MSPSS, and UCLA), a 1-way ANOVA or its nonparametric alternative (the Friedman test) will be applied according to the result of Shapiro-Wilk normality test. Then the Mauchly test of sphericity will be performed to see if any postcorrection of the degrees of freedom has to be made so that the valid F-ratio can be obtained. For the questionnaires concerning the use of TRs (SUS, PIADS, and ALMERE), the Shapiro-Wilk test will be used to verify the assumption of normal distribution of data to determine whether the paired (2-tailed) sample t test or Wilcoxon signed-rank test will be used. It should be noted that for a better interpretation of the results of the ALMERE, the Cronbach α index will be used to ensure a proper internal consistency of the questionnaire. Similarly, the multiple linear regression will be used to determine the predictive links between different aspects presented in the ALMERE model.

Qualitative Analysis (Semistructured Interviews)

For the analysis of semistructured interviews, we used a framework analysis approach [74], a thematic analysis that allows one to identify a qualitative data set of deductively derived themes (based on the dimensions directly addressed in the interview guide, in our case the EUnetHTA Core Model dimensions) and inductively derived themes (newly emergent data). The combination of deductively and inductively derived themes constitutes the framework. This approach has the advantage of allowing the identification, description, and analysis of qualitative data in an efficient way with certain flexibility. To conduct this framework analysis, the interview recordings are listened to and transcribed to have a comprehensive and global understanding of the participants' answers. We then identify the themes related to the dimensions of the EUnetHTA Core Model [64] (eg, "Health Problem and Current Use of Technology," "Description of the Technology and Technological Characteristics," "Safety"), which are linked to the questions administered to participants during the interview. The identification of more abstract concepts follows, with the aim of creating the framework for the analysis. In this study, this refers to the regrouping or ranking of the aspects or arguments that can facilitate or hinder the implementation or the adoption of an intervention with TRs in the OAs' home. Then, in the indexing stage, where the transcripts are classified according to the framework, verbatims are labeled with codes and grouped under the corresponding categories of the framework. Finally, all the themes are listed in a Microsoft Excel table with different subcategories as well as their corresponding verbatim and labels. Finally, by discovering the patterns in the data and identifying the similarities, the results are interpreted.

Results

Recruitment will end in August 2022. A total of 56 participants have been recruited into the study. Analysis of the results started in August 2022 and its completion is expected at the beginning of 2023.

Discussion

Expected Findings

The main objective of the DOMIROB project is to measure the impact of TRs on social isolation and loneliness in OAs living at home. As far as the benefits of the trial are concerned, we expect that the TR intervention improves the feeling of loneliness and social isolation of OAs as suggested by Troen [75]. Cesta et al [43] showed that TRs can bring a better sense of well-being with a boost in self-esteem and a decrease in social isolation in an aging population. For our study, we begin with the premise that the implementation of a TR could provide participants with new social contacts, a feeling of social belonging, and a strengthening of already existing social ties. These actions should translate into a decrease in the feeling of loneliness and social isolation as well as anxiety-depressive states measured by standardized scales.

So far, there are little data on the impact of TR implementation in community-dwelling persons. Available results in the literature mainly concern exploratory studies that included a limited number of participants, used short intervention periods, and experimental protocols that evaluated only 1 or 2 impact dimensions. The DOMIROB protocol, designed and adapted from the MARTA model [43], proposes a multidimensional assessment to study the psychosocial and ergonomic outcomes of the TR intervention using a multimethod approach. This study will evaluate the impact of TRs in a sample of OAs in an ecological situation over a similar length of use of the TR for all participants.

The use of the MARTA model was chosen because the study conducted by Cesta et al [43] has many similarities with the DOMIROB project. Both studies aimed to evaluate the usability and acceptability of TRs in an ecological setting with an elderly population. The adaptability of the MARTA model allows us to define a protocol that meets our objectives. As our main aim is to measure the impact of TRs on social isolation in OAs living at home, we chose to keep the psychosocial scales of the MARTA model, although not all of them were used in the study by Cesta et al [43]. Further, 2 participants included in this study lived together. Two scales, namely, the Temple Presence Inventory (TPI) [76] and the Positive and Negative Affect Schedule (PANAS) [77], were excluded from the DOMIROB project to reduce the number of assessment tools and to limit fatigue and cognitive overload in OAs during the evaluations. Indeed, the Cesta et al [43] study was carried out over a period of 12 months with only a couple of OAs, whereas the DOMIROB project aims to recruit 60 participants, with each volunteer participating in the study for 6 months during a total experimental period of 18 months.

The DOMIROB project is a truly comprehensive study on the implementation of TRs for OAs living in home, particularly regarding the psychosocial impact of TRs on OAs in home. It is also the first study to include a multidimensional assessment of both psychosocial and ergonomic aspects. This trial will allow the identification of OAs' profiles for whom the implementation of TRs seems the most relevant. We expect that TR implementation for OAs at home could contribute to limit their social withdrawal. However, it is also conceivable that TRs fail to meet the main aim of the intervention, that they are unsuitable for the users' homes, or that their use and maintenance require significant help, thus limiting their interest for OAs who cannot regularly benefit from the assistance of a third person.

The results of this study will contribute to not only the development of recommendations for the use and development of educational tools, but also for health professionals to integrate these tools into their practice, to identify facilitating factors and the organizational and ethical constraints related to the implementation of TRs in OAs' homes. Results from the qualitative analysis (semistructured interview), based on the EUnetHTA Core Model, will help to identify the different impacts of TRs on the health and daily life of users and to identify some socioeconomic issues related to the implementation of these new tools. At the end of the

experimental phase, usage, ethical, and organizational recommendations will be established to design a users' guide.

Study Limitations

This study has several limitations. First, we did not consider having a confirmed feeling of loneliness or being socially isolated an inclusion criterion for the recruitment of participants, which could limit the impact of the intervention. However, we would like to emphasize that as shown in the literature [7-10], loneliness and social isolation are frequently observed in this age group. Second, the persons recruited for this study were required to have an internet connection at home. This inclusion criteria may induce a bias because OAs who are already internet users may have a more positive view of digital technologies, such as TRs, and be more familiar with them, than people who do not have internet at home. Third, all the volunteers are recruited in Ile-de-France (ie, Paris and its suburbs). Thus, one cannot exclude the possibility that OAs living in other environments (eg, in rural areas) might show an acceptance of robots different from that of OAs living in more urban areas. Fourth, the experimental group was not compared with a control group because of logistical constraints. Fifth, participants in this protocol tested the robot at home in different contexts and periods of the year (eg, lockdown period linked to COVID-19, summer or winter periods, holiday or working periods). Therefore, one cannot exclude the fact that the use of TRs might be different according to the context when it is tested by OAs. Finally, one could discuss the test-retest reliability of the scales (eg, UCLA, MSPSS, and GDS), considering that the authors administer them once every 6 weeks. For example, the UCLA has a test-retest reliability of 1 year. Therefore, using this tool once every 6 weeks could be a potential limitation of this study.

Conclusions

The DOMIROB project aims to measure the impact of TRs on the feeling of loneliness and social isolation in OAs living at home and to establish practical, ethical, and organizational recommendations for the use of these new tools.

Acknowledgments

This article is part of a PhD thesis that aims to highlight the advantages of using social TR with regard to the social isolation of an elderly population living at home. We express our gratitude to the partners who supported this project: the Île-de-France region, Gérond'if, and the Fondation du Domicile.

Data Availability

The data sets generated during or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions

BI, A-SR, and MP were responsible for study conceptualization and methodology. BI, A-SR, MP, and WL performed formal analysis and investigation. BI and WL performed writing—original draft preparation. BI, MP, A-SR, and WL performed review and editing. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Assessment and interview tools used during the experimental phase.
[DOCX File , 16 KB - resprot_v11i10e40528_app1.docx]

References

1. European Commission. Mental Health. European Commission. 2018. URL: https://ec.europa.eu/health/non_communicable_diseases/mental_health_fr [accessed 2020-07-07]
2. Loneliness and isolation when over 60 in France in 2017. Les petits frères des pauvres. 2017 Sep 27. URL: https://www.petitsfreresdespauvres.fr/informer/nos-actualites/solitude-et-isolement-quand-on-a-plus-de-60-ans-en-france-en-2017 [accessed 2019-12-09]
3. National Academies of Sciences, Engineering, and Medicine. Social Isolation and Loneliness in Older Adults: Opportunities for the Health Care System. Washington, DC: The National Academies Press; 2020:1-316.
4. Gilmour H, Ramage-Morin P. Isolement social et mortalité chez les personnes âgées au Canada. Statistics Canada 2020 Jun 17;31(3):29-41 [FREE Full text] [doi: 10.25318/82-003-X202000300003-FRA]
5. Tsuji T, Saito M, Ikeda T, Aida J, Cable N, Koyama S, et al. Change in the prevalence of social isolation among the older population from 2010 to 2016: A repeated cross-sectional comparative study of Japan and England. Arch Gerontol Geriatr 2020 Aug 22;91:104237 [FREE Full text] [doi: 10.1016/j.archger.2020.104237] [Medline: 32861955]

6. Van As BAL, Imbimbo E, Franceschi A, Menesini E, Nocentini A. The longitudinal association between loneliness and depressive symptoms in the elderly: a systematic review. Int Psychogeriatr 2022 Jul;34(7):657-669. [doi: 10.1017/S1041610221000399] [Medline: 33849675]
7. Holmén K, Ericsson K, Winblad B. Social and emotional loneliness among non-demented and demented elderly people. Archives of Gerontology and Geriatrics 2000 Dec;31(3):177-192. [doi: 10.1016/s0167-4943(00)00070-4]
8. Savikko N, Routasalo P, Tilvis R, Strandberg T, Pitkälä KH. Predictors and subjective causes of loneliness in an aged population. Arch Gerontol Geriatr 2005 Nov;41(3):223-233. [doi: 10.1016/j.archger.2005.03.002] [Medline: 15908025]
9. Victor CR, Scambler SJ, Bowling A, Bond J. The prevalence of, and risk factors for, loneliness in later life: a survey of older people in Great Britain. Ageing and Society 2005 Apr 22;25(6):357-375. [doi: 10.1017/s0144686x04003332]
10. Pinquart M, Sörensen S. Risk Factors for Loneliness in Adulthood and Old Age--A Meta-Analysis. Hauppauge, NY: Nova Science Publishers; 2003.
11. Peretti-Watel P. Lien social et santé en situation de précarité : état de santé, recours aux soins, abus d'alcool et réseau relationnel parmi les usagers des services d'aide. estat 2006;391(1):115-130. [doi: 10.3406/estat.2006.7156]
12. Holwerda TJ, Deeg DJH, Beekman ATF, van Tilburg TG, Stek ML, Jonker C, et al. Feelings of loneliness, but not social isolation, predict dementia onset: results from the Amsterdam Study of the Elderly (AMSTEL). J Neurol Neurosurg Psychiatry 2014 Feb;85(2):135-142. [doi: 10.1136/jnnp-2012-302755] [Medline: 23232034]
13. Hoertel N, Crochard A, Rouillon F, Limosin F. [Patterns of alcohol consumption in France and their medical and social consequences as seen through the family circle and friends and general practitioners]. Encephale 2014 Apr;40 Suppl 1:S11-S31. [doi: 10.1016/j.encep.2014.02.008] [Medline: 24661582]
14. Luo Y, Hawkley LC, Waite LJ, Cacioppo JT. Loneliness, health, and mortality in old age: a national longitudinal study. Soc Sci Med 2012 Mar;74(6):907-914 [FREE Full text] [doi: 10.1016/j.socscimed.2011.11.028] [Medline: 22326307]
15. Patterson AC, Veenstra G. Loneliness and risk of mortality: a longitudinal investigation in Alameda County, California. Soc Sci Med 2010 Jul;71(1):181-186. [doi: 10.1016/j.socscimed.2010.03.024] [Medline: 20417589]
16. Blanpain N, Shon JLPK. A chaque étape de sa vie, ses relations. HAL. 2021 Mar 1. URL: https://hal.archives-ouvertes.fr/hal-02149538/document [accessed 2022-10-13]
17. Soulières M, Charpentier M. Are older people living alone socially isolated? A qualitative study of their experiences. J Gerontol Soc Work 2022 Jan 05;65(6):664-677. [doi: 10.1080/01634372.2021.2019163] [Medline: 34986739]
18. Cacioppo S, Grippo AJ, London S, Goossens L, Cacioppo JT. Loneliness: clinical import and interventions. Perspect Psychol Sci 2015 Mar;10(2):238-249 [FREE Full text] [doi: 10.1177/1745691615570616] [Medline: 25866548]
19. Khosravi P, Rezvani A, Wiewiora A. The impact of technology on older adults' social isolation. Computers in Human Behavior 2016 Oct;63:594-603. [doi: 10.1016/j.chb.2016.05.092]
20. Woodward AT, Freddolino PP, Blaschke-Thompson CM, Wishart DJ, Bakk L, Kobayashi R, et al. Technology and aging project: training outcomes and efficacy from a randomized field trial. Ageing Int 2010 Sep 28;36(1):46-65. [doi: 10.1007/s12126-010-9074-z]
21. Ring L, Shi L, Totzke K, Bickmore T. Social support agents for older adults: longitudinal affective computing in the home. J Multimodal User Interfaces 2014 Jun 18;9(1):79-88. [doi: 10.1007/s12193-014-0157-0]
22. Kahlbaugh PE, Sperandio AJ, Carlson AL, Hauselt J. Effects of playing Wii on well-being in the elderly: physical activity, loneliness, and mood. Activities, Adaptation & Aging 2011 Oct;35(4):331-344. [doi: 10.1080/01924788.2011.625218]
23. Willems CG, Spreeuwenberg MD, van der Heide LA, De Witte L. Implementing technology in home-care: Lessons learned from examples in the Netherlands. Assistive Technology Research Series 2012 Jan;30:161-178 [FREE Full text] [doi: 10.3233/978-1-60750-994-3-161]
24. Boot W, Charness N, Czaja SJ. Designing for Older Adults: Case Studies, Methods, and Tools. Boca Raton, FL: CRC Press; 2020:143.
25. Smith C, Gregorio M, Hung L. Facilitators and barriers to using telepresence robots in aged care settings: a scoping review protocol. BMJ Open 2021 Sep 17;11(9):e051769 [FREE Full text] [doi: 10.1136/bmjopen-2021-051769] [Medline: 34535485]
26. Naudé B, Rigaud A, Pino M. Video calls for older adults: A narrative review of experiments involving older adults in elderly care institutions. Front Public Health 2021 Jan 14;9:751150 [FREE Full text] [doi: 10.3389/fpubh.2021.751150] [Medline: 35096731]
27. Laban G, Kappas A, Morrison V, Cross E. Protocol for a mediated long-term experiment with a social robot. Science Gate Preprint posted online on 2021. [doi: 10.31234/osf.io/4z3aw]
28. Getson C, Nejat G. Socially assistive robots helping older adults through the pandemic and life after COVID-19. Robotics 2021 Sep 13;10(3):106. [doi: 10.3390/robotics10030106]
29. Javaid M, Haleem A, Pratap Singh R, Suman R, Rab S. Significance of machine learning in healthcare: Features, pillars and applications. International Journal of Intelligent Networks 2022;3:58-73. [doi: 10.1016/j.ijin.2022.05.002]
30. Manley NA, Boron JB, Shade MY, Jain I, Kim J, Chirackal RS, et al. A robotic device to enhance nursing home provider telepresence during and after the COVID-19 pandemic. J Am Med Dir Assoc 2022 Feb;23(2):311-314.e2 [FREE Full text] [doi: 10.1016/j.jamda.2021.11.013] [Medline: 34896058]

31. Conroy I, Murray A, Kirrane F, Cullen L, Anglim P, O'Keeffe D. Key requirements of a video-call system in a critical care department as discovered during the rapid development of a solution to address COVID-19 visitor restrictions. JAMIA Open 2021 Oct 01;4(4):ooab091 [FREE Full text] [doi: 10.1093/jamiaopen/ooab091] [Medline: 34805775]
32. Tjostheim I, Waterworth J. The Psychosocial Reality of Digital Travel: Being in Virtual Places. Berlin, Germany: Springer; 2022.
33. Kim J, Kim S, Kim S, Lee E, Heo Y, Hwang C, et al. Companion robots for older adults: Rodgers' evolutionary concept analysis approach. Intell Serv Robot 2021 Nov 16;14(5):729-739 [FREE Full text] [doi: 10.1007/s11370-021-00394-3] [Medline: 34804242]
34. Camacho EC, Ospina NI, Calderón JM. COVID-Bot: UV-C based autonomous sanitizing robotic platform for COVID-19. IFAC-PapersOnLine 2021;54(13):317-322. [doi: 10.1016/j.ifacol.2021.10.466]
35. Latikka R, Rubio-Hernández R, Lohan ES, Rantala J, Nieto Fernández F, Laitinen A, et al. Older adults' loneliness, social isolation, and physical information and communication technology in the era of ambient assisted living: a systematic literature review. J Med Internet Res 2021 Dec 30;23(12):e28022 [FREE Full text] [doi: 10.2196/28022] [Medline: 34967760]
36. Raje S, Reddy N, Jerbi H, Randhawa P, Tsaramirsis G, Shrivas NV, et al. Applications of healthcare robots in combating the COVID-19 Pandemic. Appl Bionics Biomech 2021 Nov 23;2021:7099510-7099519 [FREE Full text] [doi: 10.1155/2021/7099510] [Medline: 34840604]
37. Lin C, Rhim J, Moon A. Mobile Robotic Telepresence: A New Social Hierarchy? TSAR. 2021. URL: https://tsar2021.ai.vub.ac.be/uploads/papers/TSAR_2021_paper_2.pdf [accessed 2022-10-13]
38. Gonsher I, Han Y, Gokaslan A, Desingh K. Prototyping Mixed Reality Large Screen Mobile Telepresence Robots. Open Review. 2022. URL: https://openreview.net/pdf?id=H9Ul0sApqy9 [accessed 2022-10-13]
39. Baisch S, Kolling T, Schall A, Rühl S, Selic S, Kim Z, et al. Acceptance of social robots by elder people: Does psychosocial functioning matter? Int J of Soc Robotics 2017 Jan 18;9(2):293-307. [doi: 10.1007/s12369-016-0392-5]
40. Beer J, Takayama L. Mobile Remote Presence Systems for Older Adults: Acceptance, Benefits, and Concerns. In: HRI '11: Proceedings of the 6th international conference on Human-robot interaction. New York, NY: ACM Press; 2011 Mar Presented at: HRI'11: International Conference on Human-Robot Interaction; March 6-9, 2011; Lausanne, Switzerland p. 19-26 URL: http://www.leilatakayama.org/downloads/Takayama.OlderAdultsTexai_HRI2011_prepress.pdf [doi: 10.1145/1957656.1957665]
41. Caleb-Solly P, Dogramadzi S, Huijnen CA, Heuvel HVD. Exploiting ability for human adaptation to facilitate improved human-robot interaction and acceptance. The Information Society 2018 Apr 26;34(3):153-165. [doi: 10.1080/01972243.2018.1444255]
42. Cavallo F, Esposito R, Limosani R, Manzi A, Bevilacqua R, Felici E, et al. Robotic services acceptance in smart environments with older adults: user satisfaction and acceptability study. J Med Internet Res 2018 Sep 21;20(9):e264 [FREE Full text] [doi: 10.2196/jmir.9460] [Medline: 30249588]
43. Cesta A, Cortellessa G, Orlandini A, Tiberio L. Long-term evaluation of a telepresence robot for the elderly: Methodology and ecological case study. Int J of Soc Robotics 2016 Jan 20;8(3):421-441. [doi: 10.1007/s12369-016-0337-z]
44. Granata C, Pino M, Legouverneur G, Vidal J, Bidaud P, Rigaud A. Robot services for elderly with cognitive impairment: Testing usability of graphical user interfaces. THC 2013 Jun 01;21(3):217-231. [doi: 10.3233/thc-130718]
45. Hiyama A, Kosugi A, Fukuda K, Kobayashi M, Hirose M. Facilitating Remote Communication Between Senior Communities with Telepresence Robots. In: Zhou J, Salvendy G, editors. Human Aspects of IT for the Aged Population. Applications, Services and Contexts. Vol 10298. Berlin, Germany: Springer; 2017:501-515.
46. Kristoffersson A, Coradeschi S, Loutfi A, Severinson-Eklundh K. Assessment of interaction quality in mobile robotic telepresence. IS 2014 Aug 20;15(2):343-357. [doi: 10.1075/is.15.2.16kri]
47. Schroeter C, Mueller S, Volkhardt M. Realization and user evaluation of a companion robot for people with mild cognitive impairments. New York, NY: IEEE; 2013 Presented at: ICRA 2013 - IEEE International Conference on Robotics and Automation; May 6-10, 2013; Karlsruhe, Germany p. 1153-1159. [doi: 10.1109/icra.2013.6630717]
48. Tiberio L, Cesta A, Cortellessa G, Padua L, Pellegrino A. Assessing affective response of older users to a telepresence robot using a combination of psychophysiological measures. New York, NY: IEEE; 2012 Presented at: The 21st IEEE International Symposium on Robot and Human Interactive Communication; September 9-13, 2012; Paris, France p. 2012. [doi: 10.1109/roman.2012.6343855]
49. Wu Y, Wrobel J, Cornuet M, Kerhervé H, Damnée S, Rigaud A. Acceptance of an assistive robot in older adults: a mixed-method study of human-robot interaction over a 1-month period in the Living Lab setting. Clin Interv Aging 2014 May;9:801-811 [FREE Full text] [doi: 10.2147/CIA.S56435] [Medline: 24855349]
50. Boman I, Bartfai A. The first step in using a robot in brain injury rehabilitation: patients' and health-care professionals' perspective. Disabil Rehabil Assist Technol 2015 Apr 28;10(5):365-370. [doi: 10.3109/17483107.2014.913712] [Medline: 24766268]
51. Broadbent E, Kerse N, Peri K, Robinson H, Jayawardena C, Kuo T, et al. Benefits and problems of health-care robots in aged care settings: A comparison trial. Australas J Ageing 2016 Mar 13;35(1):23-29. [doi: 10.1111/ajag.12190] [Medline: 26364706]

52. Gerłowska J, Skrobas U, Grabowska-Aleksandrowicz K, Korchut A, Szklener S, Szczęśniak-Stańczyk D, et al. Assessment of perceived attractiveness, usability, and societal impact of a multimodal robotic assistant for aging patients with memory impairments. Front Neurol 2018 Jun 1;9:392 [FREE Full text] [doi: 10.3389/fneur.2018.00392] [Medline: 29910769]
53. Koceski S, Koceska N. Evaluation of an assistive telepresence robot for elderly healthcare. J Med Syst 2016 May;40(5):121. [doi: 10.1007/s10916-016-0481-x] [Medline: 27037685]
54. Moyle W, Jones C, Cooke M, O'Dwyer S, Sung B, Drummond S. Connecting the person with dementia and family: a feasibility study of a telepresence robot. BMC Geriatr 2014 Jan 24;14(1):7 [FREE Full text] [doi: 10.1186/1471-2318-14-7] [Medline: 24456417]
55. Niemelä M, van AL, Tammela A, Aaltonen I. A Telepresence Robot in Residential Care: Family Increasingly Present, Personnel Worried About Privacy. In: Kheddar A, Yoshida E, Ge SS, editors. Social Robotics. Vol 10652. Berlin, Germany: Springer; 2017:85-94.
56. Pineau J, Montemerlo M, Pollack M, Roy N, Thrun S. Towards robotic assistants in nursing homes: Challenges and results. Robotics and Autonomous Systems 2003 Mar;42(3-4):271-281. [doi: 10.1016/s0921-8890(02)00381-0]
57. Stafford RQ, MacDonald BA, Jayawardena C, Wegner DM, Broadbent E. Does the robot have a mind? Mind perception and attitudes towards robots predict use of an eldercare robot. Int J of Soc Robotics 2013 Apr 23;6(1):17-32. [doi: 10.1007/s12369-013-0186-y]
58. Niemelä M, van Aerschot L, Tammela A, Aaltonen I, Lammi H. Towards ethical guidelines of using telepresence robots in residential care. Int J of Soc Robotics 2019 Feb 22;13(3):431-439. [doi: 10.1007/s12369-019-00529-8]
59. Gonzalez-Jimenez J, Galindo C, Gutierrez-Castaneda C. Evaluation of a Telepresence Robot for the Elderly: A Spanish Experience. In: Ferrández Vicente JM, Álvarez Sánchez JR, de la Paz López F, Toledo Moreo Fco J, editors. Natural and Artificial Models in Computation and Biology. Vol 7930. Berlin, Germany: Springer; 2013:141-150.
60. Seelye AM, Wild KV, Larimer N, Maxwell S, Kearns P, Kaye JA. Reactions to a remote-controlled video-communication robot in seniors' homes: a pilot study of feasibility and acceptance. Telemed J E Health 2012 Dec;18(10):755-759 [FREE Full text] [doi: 10.1089/tmj.2012.0026] [Medline: 23082794]
61. Zsiga K, Tóth A, Pilissy T, Péter O, Dénes Z, Fazekas G. Evaluation of a companion robot based on field tests with single older adults in their homes. Assist Technol 2018 Jun 19;30(5):259-266. [doi: 10.1080/10400435.2017.1322158] [Medline: 28628395]
62. Bakas T, Sampsel D, Israel J, Chamnikar A, Bodnarik B, Clark JG, et al. Using telehealth to optimize healthy independent living for older adults: A feasibility study. Geriatr Nurs 2018 Sep;39(5):566-573 [FREE Full text] [doi: 10.1016/j.gerinurse.2018.04.002] [Medline: 29804689]
63. Fiorini L, Sorrentino A, Pistolesi M, Becchimanzi C, Tosi F, Cavallo F. Living with a telepresence robot: results from a field-trial. IEEE Robot. Autom. Lett 2022 Apr;7(2):5405-5412. [doi: 10.1109/lra.2022.3155237]
64. EUnetHTA. HTA Core Model ® version 3. HTA Core Model. URL: https://www.htacoremodel.info/BrowseModel.aspx [accessed 2021-01-26]
65. Russell DW. UCLA Loneliness Scale (Version 3): reliability, validity, and factor structure. J Pers Assess 1996 Feb;66(1):20-40. [doi: 10.1207/s15327752jpa6601_2] [Medline: 8576833]
66. Zimet GD, Dahlem NW, Zimet SG, Farley GK. The Multidimensional Scale of Perceived Social Support. Journal of Personality Assessment 1988 Mar;52(1):30-41. [doi: 10.1207/s15327752jpa5201_2]
67. Brooke J. SUS - A Quick and Dirty Usability Scale. Berlin, Germany: Springer; Aug 09, 2011:1-8.
68. Heerink M, Kröse B, Evers V, Wielinga B. Assessing acceptance of assistive social agent technology by older adults: the Almere model. Int J of Soc Robotics 2010 Sep 4;2(4):361-375. [doi: 10.1007/s12369-010-0068-5]
69. Yesavage JA, Brink T, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: A preliminary report. Journal of Psychiatric Research 1982 Jan;17(1):37-49. [doi: 10.1016/0022-3956(82)90033-4]
70. Jutai J, Day H. Psychosocial Impact of Assistive Devices Scale (PIADS). TAD 2002 Sep 29;14(3):107-111. [doi: 10.3233/tad-2002-14305]
71. Vellas B, Gauthier S, Allain H, Andrieu S, Aquino J, Berrut G, et al. Consensus sur la démence de type Alzheimer au stade sévère. Revue Neurologique 2005 Sep;161(8-9):868-877. [doi: 10.1016/S0035-3787(05)85152-5]
72. Kalafat M, Hugonot-Diener L, Poitrenaud J. Standardisation et étalonnage français du "Mini Mental State" (MMS) version GRÉCO [French standardization and range for the GRECO version of the "Mini Mental State" (MMS)]. Revue de neuropsychologie 2003;13(2):209-236 [FREE Full text]
73. Ware J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996 Mar;34(3):220-233. [doi: 10.1097/00005650-199603000-00003] [Medline: 8628042]
74. Goldsmith L. Using framework analysis in applied qualitative research. TQR 2021 Jun 20:e1. [doi: 10.46743/2160-3715/2021.5011]
75. Troen SB. In Brief: Using Videophones as an Antidote to Isolation of the Elderly and a Learning Tool for the Young (Vol 18). Amsterdam, The Netherlands: IOS Press; 2006:141.
76. Lombard M, Ditton T, Weinstein L. Measuring presence: the temple presence inventory. Cleveland State University. 2009. URL: https://academic.csuohio.edu/kneuendorf/frames/LombardDittonWeinstein09.pdf [accessed 2022-10-13]

77. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: The PANAS scales. Journal of Personality and Social Psychology 1988;54(6):1063-1070. [doi: 10.1037/0022-3514.54.6.1063]

Abbreviations

EUnetHTA: European Network for Health Technology Assessment
GDS: Geriatric Depression Scale
MARTA: Multidimensional Assessment of Telepresence Robot for Older Adults
MMSE: Mini-Mental State Examination
MSPSS: Multidimensional Scale of Perceived Social Support
OA: older adult
PANAS: Positive and Negative Affect Schedule
PIADS: Psychosocial Impact of Assistive Devices Scale
SF-12: 12-Item Short-Form Health Survey
SUS: System Usability Scale
TPI: Temple Presence Inventory
TR: telepresence robot
UCLA: Perceived Loneliness Scale

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Protocol

Older Adults Living in Disadvantaged Areas: Protocol for a Mixed Methods Baseline Study on Homes, Quality of Life, and Participation in Transitioning Neighborhoods

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Abstract

Background: Swedish policy states that older adults should be able to age safely with continued independence and lead active lives. However, this plays out differently in different Swedish municipalities depending upon degree of demographic change, globalization, and urbanization. Internationally, older adults living in disadvantaged areas have worse physical and mental health, activity restrictions, and reduced life expectancy. In Sweden, research on how disadvantaged areas impact older adults' quality of life is virtually nonexistent. We argue that disadvantaged areas exist in both urban and rural contexts.

Objective: We aimed to investigate how older adults' homes and neighborhoods influence their community participation, quality of life, identity, and belonging in urban and rural disadvantaged areas in Sweden, and how these person–context dynamics are experienced by older adults in transitioning neighborhoods.

Methods: The study has a mixed methods design and includes 3 phases. Adults 65 years and older living in certain urban and rural disadvantaged areas in the south of Sweden will be included. Phase 1 is an interview study in which qualitative data are collected on neighborhood attachment, identity, and belonging through semistructured interviews and photo-elicitation interviews with 40 subjects. A variety of qualitative data analysis procedures are used. In phase 2, a survey study will be conducted to explore associations between observable and self-rated aspects of housing and neighborhood (physical, social, and emotional), participation, and quality of life; 400 subjects will be recruited and added to the 40 phase-1 subjects for a total of 440. The survey will include standardized measures and study-specific questions. Survey data will be analyzed with mainstream statistical analyses and structural equation modeling to understand the interactions between quality of life, home and neighborhood factors, and sociodemographic factors. In phase 3, the integration study, survey data from the 40 participants who participated in both data collections will be analyzed together with qualitative data with a mixed methods analysis approach.

Results: As of the submission of this protocol (August 2022), recruitment for the interview study is complete (N=39), and 267 participants have been recruited and have completed data collection in the survey study. We expect recruitment and data collection to be finalized by December 2022.

Conclusions: With an increasing proportion of older adults, an increasing number of disadvantaged areas, and an increasing dependency ratio in more than 50% of Swedish municipalities, these municipalities are transforming and becoming increasingly segregated. This study will add unique knowledge on what it is like to be older in a disadvantaged area and deepen knowledge on housing and health dynamics in later life. Further, the design of the current study will allow future follow-up studies to facilitate longitudinal analysis (if funding is granted) on aging in a transforming societal context.

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KEYWORDS

aging; housing; neighborhood; quality of life; participation; rural areas; disadvantaged areas; aging-in-place; relocation; socioeconomic status; older adults; elderly; mental health; physical health; social participation; health dynamics

Introduction

Background

Inclusive and accessible living environments are fundamental to well-being, and Swedish aging policy states that older adults should be able to age safely, maintain their independence, and continue to lead active lives. However, with demographic change, globalization, and urbanization, health inequality is a growing societal challenge. The chances of older adults being able to lead a good life vary depending upon which of Sweden's 290 self-governed municipalities they live in. There is a lack of knowledge on what it is like to age in areas where the societal challenges are most evident. International studies show that the quality of life of older adults living in disadvantaged areas is affected in many ways. They have worse physical and mental health, activity, and participation restrictions—and shorter life expectancy. In Sweden, research on how living in a disadvantaged area affects older adults' quality of life is virtually nonexistent. We argue that disadvantaged areas exist in both urban and rural contexts, but conditions, experiences, and perceptions may be quite different. This study addresses how the home and neighborhood influence quality of life for older adults who live in urban and rural disadvantaged areas and how these person–context dynamics are experienced. In the proposed study, we will investigate urban disadvantaged areas with a high proportion of crime, social unrest, fast population turnover, and a high percentage of unemployment [1]. We will also investigate rural disadvantaged areas with a consistently decreasing population and a shrinking tax base for health and social care services [2]. We will study areas that are changing in many ways. Older adults tend not to move as often as younger adults, thus experiencing the consequences of disadvantaged areas in transition. By focusing on older adults, the results will aid in understanding how societies can ensure healthy lives, promote quality of life at all ages, and have sustainable cities and communities that provide opportunities for all.

Disadvantaged Areas in Sweden

In 2016, the Swedish National Police published their first-ever report on what they called "socially disadvantaged areas"; the most recent report, from 2017, listed 61 areas in Sweden. According to the Swedish National Police, a socially disadvantaged area is a geographically defined urban area with low socioeconomic status, high levels of crime, fast population turnover, and a high proportion of immigrants. Residents are at risk of being excluded, feeling alienated, losing faith in the future, and having health problems. Over time, criminal networks have become increasingly present [1]. Typically, the neighborhoods are large residential areas with little traffic. Landlords are typically public housing companies, and the dwellings are rented apartments in multi-dwelling blocks. The areas have been criticized for not being well kept, needing maintenance and repairs, and being overcrowded. Lately, retail store owners have been reluctant to establish businesses in these neighborhoods, which reduces amenities. Approximately 81% of the population is of non–Swedish origin, and the proportion of older adults is smaller than the national average: approximately 12.5%, compared to 19% nationally. Of the Swedish-born population, the majority are likely older and have lived in the area for many years. For older adults, safety and security risks and not having access to local services are important concerns, as are feelings of alienation from the neighborhood. Contrastingly, other surveys show that many residents like their neighborhood and that crime rates are slowly decreasing [3]. Turning to rural areas, depopulated areas make up another supposedly disadvantaged area. Depopulated areas are municipalities or parts of municipalities that have been characterized by significant population decline for the last 20 years due to urbanization, high unemployment rates, and weak housing markets [2]. These areas also have a larger proportion of older adults than the national average: 25%, compared to 19% nationally, and due to a reduced tax base (ie, a high social dependency rate) public health and social care services are expensive to provide and facilities are sometimes closed. It is also difficult to provide small, suitable dwellings for older adults who want to downsize [2]. In these areas one finds that older adults mostly live in single-family houses, are homeowners, and were born in Sweden. Car dependency is high. Retail store owners have had a hard time keeping shops and businesses running, which reduces amenities in the area. It is likely that urban and rural disadvantaged areas are influencing older adults' quality of life in ways that are unique to each, but also in other ways that are similar in both. An understanding of how the context influences older adults in both urban and rural disadvantaged areas is needed to reveal the heterogeneity of living conditions of older adults in Sweden.

Sweden could be described as a social democratic welfare state in transition. The Swedish population, and older adults in particular, are known to show high levels of trust toward government officials, media, and fellow citizens in general. The health care and social care systems have universal coverage, but local differences in service provision are a growing challenge to equality [4]. The wave of immigrants that entered Sweden in 2014 to 2015 has affected municipalities in rural areas (where many were placed upon arrival) and urban areas (where many settled by choice). With increasing societal challenges in Sweden and with new generations of non–Swedish born older adults living in disadvantaged areas, research on aging in Swedish disadvantaged areas can contribute to international knowledge on quality of life in later life in disadvantaged areas.

Overview of the Research Field

In general, older adults tend to move less often than younger adults, and the home becomes an essential arena for social life with increasing age. Health and quality of life are likely more influenced by the home and neighborhood in older adults than in younger people [5]. Accessible homes support older adults in managing activities of daily living independently for longer [6]. High housing satisfaction is related to higher life

satisfaction, and higher neighborhood social cohesion supports participation in activities and in society. However, we do not know whether previous findings from Swedish and European home-health-dynamics studies of older adults, which had participants who were fairly healthy and socioeconomically well-off (eg, the ENABLE AGE Project [7]), apply to older adults in disadvantaged areas. We do not know if previous findings on the importance of weak ties among neighbors apply within areas that are transitioning and have fast population turnover, as in disadvantaged areas in Sweden [8].

International reviews of older adults living in neighborhoods with low socioeconomic status (SES) show that a variety of neighborhood factors negatively impact depression, cognitive skills, and overall health [9-11]. Further, disadvantaged areas can restrict outdoor mobility possibilities for participation, and ultimately increase the risk of mortality [12-15].

Several authors conclude that there is a need for more nuanced measures of neighborhood quality, both objective and self-rated. It is also necessary to investigate contradictory results (eg, ethnic enclaves in the United States seem to have a positive effect on health for Latino populations but not for African American populations [11]) and to identify modifiable aspects of the living environment to develop interventions supporting quality of life. A meta-analysis of neighborhood effects on mortality included 11 studies from Sweden; however, none focused on older adults [15]. The authors found reduced life expectancy among residents from areas with low neighborhood SES, and they concluded that in order to better understand how social and physical neighborhood factors contribute to well-being, quantitative methods need to be complemented with qualitative methods.

Researchers on rural aging have explored the challenges older adults experience when the need for support increases, but community changes have resulted in health and social care services being closed. This research highlights the strong desire to age in place and the constant negotiations that come with such a decision.

Nevertheless, other researchers have questioned the social sustainability of depopulated areas, arguing that rural aging needs more attention [16] and that knowledge of how home and community factors interact with quality of life in rural areas is lacking.

It has been suggested that older adults are more dependent than younger adults on the home and neighborhood context and are more vulnerable to neighborhood change; however, this has not been empirically supported by recent studies. Contrastingly, it has also been suggested that older adults with lower SES might be more resilient to neighborhood stressors than older adults from areas with high SES [5]. Both of these conclusions are highly generalized, and it is thus important to explore positive aspects of living in disadvantaged areas and critically examine negative images from media to obtain a nuanced picture of the day-to-day life of older adults in disadvantaged areas.

Theoretical Underpinnings

Acknowledging the complex individual–context dynamics and quality of life in disadvantaged areas calls for several theoretical perspectives. We ground our study in a theoretical framework of ecological theories on aging, social networks, human geography, occupational justice, and a perspective of the social life course [17-21].

Early models from Lawton and Nahemow [19] are based on an environmental gerontology perspective that usually includes aspects of the built environment and tries to explain the fit or the congruence between the capabilities of the person and the demands of the environment. We will use the concept of place-making [21], describing how older adults develop “insideness” and the process of belonging and identity in relation to a home or an area. After relocation to a new space, place-making skills might be disrupted if other changes occur as well. If the older adult cannot continue with their day-to-day habits and routines in the new dwelling, the older adult might not develop attachment.

We also add a social layer that includes identity, roles, and the norms that are created and formed within the social context. Moreover, being, acting, and meaning-making are interactive processes between the individual and the social context. The individual takes part in creating the context and the context creates the individual. The complexity of and the forces within social contexts need to be acknowledged to better understand the effects of exclusion and marginalization on disadvantaged areas and the effects of inclusion and creation of community in seemingly harsh areas [22].

The social life-course perspective explains that aging is contextual and that the journey of individuals across the life course is parallel to development and changes in the surrounding society [20]. Individuals age and change while the society they live in ages and changes, too. Older adults are likely to interpret feelings of well-being and belonging in their neighborhood in the light of ideas on the past, present, and future of their life course and the surrounding society. Further, social network theory and theories on social ties will be important in understanding how the context influences quality of life [8,18].

Conceptual Definitions

Quality of Life

We use the World Health Organization Quality of Life Group definition of quality of life as a construct that captures an individual’s physical and psychological health, social relationships, and the environment and defines quality of life as an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns [23].

Participation

The World Health Organization defines participation as an individual’s involvement in life situations that let them take part in society [24], in addition to participation in tasks and activities that are meaningful to them (eg, occupations) and promote health, well-being, and participation in life [17].

Context

We define the environment surrounding the individual as their context, focusing on the home and neighborhood. This context

includes physical factors (eg, buildings and spaces), social factors (eg, family, friends, neighbors, and social networks) and emotional or identity factors (eg, place attachment and belonging).

Study Objective and Research Questions

The study objective is to investigate how home and neighborhood influence participation, quality of life, identity, and belonging of older adults living in urban and rural disadvantaged areas in Sweden, and how these person–context dynamics are experienced by older adults in transitioning neighborhoods. We have three research questions. First, how do older adults in disadvantaged areas reason about their home and neighborhood in relation to their quality of life, and how do they act on concerns regarding their neighborhoods? We will pay particular attention to ways that identity and belonging are manifested, ways that participants relate to the existing media images of the area they live in, participants' thoughts on relocation, and how they place themselves in a transforming neighborhood context. Second, how are observable and self-rated home and neighborhood factors associated with the quality of life of older adults in disadvantaged areas? We will pay particular attention to urban/rural, gender, and Swedish born/non–Swedish born subgroup differences as potential mediators. Third, how can we contribute to existing theoretical perspectives on aging in context by contrasting and integrating knowledge of older adults' quality of life in urban and rural disadvantaged areas?

Methods

Study Design

This baseline study has an explanatory sequential mixed methods design [25] and includes 3 phases. Phase 1, the interview study, includes semistructured interviews and photo-elicitation interviews with 40 subjects). Phase 2, the survey study, will collect quantitative data via telephone survey interviews; 400 subjects will be recruited and added to the 40 phase-1 subjects, for a total of 440 subjects. In phase 3, the integration study, data from the previous phases will be combined and analyzed with a mixed methods analysis approach [25].

Population and Setting

The study population is community-living adults aged 65 years and older who have lived in any of the targeted disadvantaged areas for at least 5 years.

Urban Areas

The urban areas targeted (N=5) are located in 2 smaller cities in the south of Sweden (with populations of 46,000 and 150,000) and are seen as typical examples of how multi-dwelling neighborhoods that were built in the 1960s and 1970s have transitioned over time into disadvantaged neighborhoods, as defined by the Swedish National Police. In recent years, efforts have been made to increase police presence to reduce crime rates and improve safety. In one area, city officials have taken drastic measures to improve housing standards by demolition and new construction, and the neighborhood transition is characterized by gentrification—so far, a rare approach in Sweden.

Rural Areas

The rural areas targeted are rural municipalities in the south of Sweden (with 10,000 to 15,000 inhabitants). The municipalities have been characterized by depopulation for approximately the last 20 years, with the exception of 2015 to 2016, when a large influx of immigrants changed the population structure and increased the population. However, the dependency ratios are still unfavorable. The dependency ratios in these 2 municipalities are between 87% and 91%, compared to 77% in both the south region, Skåne, and in Sweden in general. The municipalities are characterized by several smaller villages, among which there is a "municipality capital" that is usually of similar size to the other villages. Unlike rural municipalities in the central and northern parts of Sweden, these municipalities are within 45 minutes by car of a larger city.

Phase 1: Interview Study

Recruitment

Participants were recruited via community centers serving older adults, libraries, and nonprofit organizations located in the targeted areas. Because of the COVID-19 pandemic, we had to adapt our strategy. Thus, recruitment was also done by mail, after retrieving the addresses of all adults over the age of 65 in each disadvantaged area from the Swedish state personal address register (SPAR). A set of 20 randomly chosen residents received a letter with information about the study that was followed up with a telephone call, a procedure that will be repeated if needed. We aimed for a sample of N=40.

Data Collection

The data collection included semistructured interviews for which we developed an interview guide (Multimedia Appendix 1) based on the aim of the study. At the end of the interview, the participants were instructed to take photographs of the area they lived in and defined as their neighborhood. In urban areas, this was usually the block or the street they lived on, while in the rural areas, the participants usually referred to their village or the neighboring houses. They were instructed to take photographs of places, buildings, or things that they considered important to themselves, either positively or negatively. At the second interview, according to the photo-elicitation technique, the interview focused on the content of the pictures. The interview guide and the data collection procedure were pilot-tested with 3 participants. Only minor adjustments to the interview guide were needed, and the 3 pilot-test participants were thus included in the final sample. Due to the COVID-19 pandemic, interviews were conducted either face-to-face at home, at a community center serving older adults, outside in the garden, in the neighborhood, or remotely via video conferencing software or telephone.

Data Analysis

Data will be analyzed with different qualitative data-analysis approaches, such as the thematic analysis described by Braun and Clarke [26]. Both inductive and deductive approaches will be used, depending on the research question.

Phase 2: Survey Study

Power Calculation, Sample Size and Recruitment

We aim for a sample size of N=400 in phase 2. Power calculations were made based on the World Health Organization 10 Wellbeing index [27], assuming a mean difference of 4.0 with an SD of 10.0 (power 0.80 and $P<.05$), resulting in a recommended sample of at least 98 participants per area. Acknowledging that the power calculation was highly indicative, that the study design was explorative overall, and that we aimed to perform follow-up data collection (if granted funding), we decided to include 200 participants from urban areas and 200 participants from rural areas. To recruit them, we ordered lists of contact information for all adults aged 65 years or older in the targeted urban and rural areas from the SPAR and performed randomization. We will aim for a sample that includes 50% urban participants and 50% rural participants, with 50% being aged 65 to 79 and 50% aged 80 or older. In all, approximately 12,500 adults 65 years or older live in the targeted areas. Anticipating an inclusion rate of 20% or more, the randomized lists will contain a total of 2000 names. Our procedure is to send out information letters and follow up with a telephone call. If the participant meets the inclusion criteria and is willing to participate, we set a date for the telephone interview.

Survey and Data

The survey was developed based on the aim of the study and contains standardized instruments and study-specific questions on quality of life, participation, and health, as well as physical, social, and emotional aspects of housing and neighborhood. Sociodemographic information and information on possible confounders will also be collected. Table 1 shows an overview of all standardized instruments and study-specific questions used in the survey. Study-specific questions and instruments that we adapted for the study are described below [28-35].

Housing satisfaction is measured with 7 study-specific questions regarding housing standards, including size, design, internet, parking, storage, and accommodation of guests, as well as an overall question: “In general, how satisfied are you with your current housing situation?” The questions are answered on a scale from 0 (extremely dissatisfied) to 10 (extremely satisfied). Five questions concern the extent to which the bathroom, kitchen, entrance, bedroom, and living room are practical to use. The questions are answered on a scale from 0 (extremely impractical) to 10 (extremely practical). Five questions concern different aspects of safety at home. The questions are answered on a scale from 0 (extremely unsafe) to 10 (extremely safe). The questions were inspired by a subset of questions from an earlier version of the online self-help tool “Housing Options for Older People” [36,37]. The respondents also respond to 3 statements on housing discomfort with the responses “very true,” “partly true,” or “not true at all.” The statements are as follows: “I often feel alone in my home,” “I often feel that I cannot be left alone/in peace in my home,” and “I often feel bored in my home.”

To capture the emotional aspects of the neighborhood, we use the Person-Place Fit Measure for Older Adults (PPFM-OA), developed by Weil [28]. We used a dual-panel approach to translate the measure into Swedish [38]. In brief, panel 1 consisted of 2 registered occupational therapists with PhD degrees and experience working in both Swedish and US contexts with similar target groups as this study. They individually translated the items, discussed them, and then agreed on a translation. Disagreements, as well as translations that were problematic due to cultural and contextual differences between the United States and Sweden, were discussed with the developer, as well as with an academic panel consisting of 9 graduate students and junior housing and aging researchers. Panel 2 consisted of a selection of potential end responders: 4 older adults (age range 74 to 88 years) who provided feedback on the items and the structure of the translated tool using cognitive interview techniques. After panel 2, final revisions were made and 3 items were excluded due to cultural differences regarding health care and housing options. The participants respond to 41 statements using a Likert scale ranging from 5 (strongly agree) to 1 (strongly disagree).

For the presence and use of services in the neighborhood, we use the Participation in Activities and Places Outside Home Questionnaire (ACT-OUT). ACT-OUT was developed to explore social citizenship through out-of-home participation in activities and places for older adults with and without dementia. We use the first part of ACT-OUT, which registers whether or not the respondent uses 24 types of services and places, including consumer, administrative, and self-care places, places for medical care, social, cultural, and spiritual places, and places for recreational and physical activities [29]. For the current study, we added an initial question on presence—“Does the service exist in your neighborhood?”—before questions regarding previous and current use and the desire for future use of the services listed in ACT-OUT.

For social interaction and activities, the participants respond to questions on how often they do any of 13 activities. The activities include different forms of interacting with friends, relatives, and neighbors, participating in leisure activities, exercising with others, engaging with nonprofit organizations, participating in religious events, discussing or engaging in local politics, and participating in adult education and study groups. Responses include the following: “every day,” “1 to 2 times a week,” “1 to 2 times a month,” “1 to 2 times a year,” and “less than once a year or never.”

Table 1. Survey overview of instruments and study-specific questions.

Area/focus	Instrument	Source
Quality of life		
Quality of Life	World Health Organization Quality of Life Assessment—Brief Scale	World Health Organization Quality of Life Group 1998 [23]
Dwelling		
Year of build	Study-specific	N/A[a]
Number of rooms	Study-specific	N/A
Number of bathrooms	Study-specific	N/A
Number of levels	Study-specific	N/A
Garden/balcony	Study-specific	N/A
Housing satisfaction	Study-specific[b]	N/A
Housing safety	Study-specific[b]	N/A
Housing discomfort	Study-specific	N/A
Neighborhood		
Neighborhood satisfaction/age-friendliness	Person-Place Fit Measure for Older Adults	Weil 2020 [28]
Presence and use of services	Participation in Activities and Places Outside Home for Older Adults[c]	Margot-Cattin 2019 [29]
Participation		
Participation	World Health Organization Disability Assessment Schedule 2.0 (section 6)	Üstün et al 2010 [30]
Social networks	Survey of Health, Ageing and Retirement in Europe	Litwin et al 2013 [31]
Social interactions and activities	Study-specific	N/A
Caregiving	Survey of Health, Ageing and Retirement in Europe[d]	Börsch-Supan et al 2005 [32]
Health and disease		
Disease	Survey of Health, Ageing and Retirement in Europe	Börsch-Supan 2019 [33]
Self-rated health	SF-36	Sullivan et al 1994 [34]
Pain	Study-specific	N/A
Falls	Study-specific	N/A
Hospital stays	Study-specific	N/A
Activities of daily living	ADL[e] staircase	Iwarsson et al 2009 [35]
Receiving care	Survey of Health, Ageing and Retirement in Europe[d]	Börsch-Supan et al 2005 [32]
Sociodemographics		
Age	Study-specific	N/A
Sex	Study-specific	N/A
Number of years living in the neighborhood	Study-specific	N/A
Cohabiting	Study-specific	N/A
Marital status	Study-specific	N/A
Country of origin	Study-specific	N/A
Education	Study-specific	N/A
Work	Study-specific	N/A
Income	Study-specific	N/A
Housing supplement	Study-specific	N/A
Type of dwelling	Study-specific	N/A

Area/focus	Instrument	Source
Housing tenure	Study-specific	N/A
Access to car	Study-specific	N/A

[a]N/A: not applicable.

[b]These questions were inspired by a subset of questions from an earlier version of the online self-help tool "Housing Options for Older People" [36,37].

[c]We added a question on presence—"Does the service exist in your neighborhood?"—prior to questions regarding use of services included in the Participation in Activities and Places Outside Home for Older Adults instrument [29].

[d]These questions were based on the Survey of Health, Ageing and Retirement in Europe [32], but were modified.

[e]ADL: activities of daily living.

For receiving and giving care we use a modified set of questions from the Survey of Health, Ageing and Retirement in Europe (SHARE) [32]. The respondents are asked whether they have received personal care or help with household chores, household maintenance, paperwork, translations, computers and the internet, or transportation in the last 12 months as (1) informal care from someone in the household; (2) informal care from someone outside the household; or (3) formal care. They are also asked whether they have a companion at medical visits. Then, the respondents are asked if the formal or informal care from within or outside the household was received approximately daily, weekly, monthly, or less often. For caregiving, we asked whether the individual had, in the last 12 months, given informal care within or outside the household in the 7 areas mentioned above. The respondents are also asked to estimate how often they provided care.

The survey also asked the participants about pain, as follows: "Have you in the last 30 days been bothered by pain? If yes, how bad is the pain most of the time (mild, moderate, or severe)?" We then asked a question about where in their body they experienced pain. The survey also includes questions about whether or not the respondent has fallen in the last 12 months, where falls occurred, and if the respondent needed medical care due to falls. We also ask about the number of overnight hospital admissions in the last 12 months, regardless of cause.

Data Collection

Data collection was intended to take place at home. However, due to COVID-19 restrictions at the time, we changed this to telephone interviews. The participants return the signed consent form by mail before the phone interview takes place. Questions and scales are mailed to the participants to serve as visual aids during the interview. Answers are recorded by the data collector using RedCap software (Research Electronic Data Capture; Vanderbilt University). Interviews can be completed in Swedish, English, Arabic, Persian, Slavic languages, Polish, or Danish if needed. We will use an interpreter when needed.

Data Quality

Besides the research team doing the interviews (who all have a bachelor's degree or PhD in health science or social science), the data collectors are students in an occupational therapy bachelor's program. All data collectors have received study-specific training. At the start of the study, 3 data collectors performed 2 interviews each (n=6), after which data collection was paused and the data collectors and research teams engaged in a thorough discussion and evaluation. Minor alterations to and clarifications of the instructions were edited into RedCap before the data collection continued. Frequent meetings with the data collectors and the principal investigator of the study will be held throughout the data collection period.

Statistical Data Analysis

For newly translated measures not before used in this context (eg, PPFM-OA [28]), preparatory analyses targeting validity and precision will be conducted before proceeding to primary analyses targeting specific research questions. The survey data will be analyzed with mainstream statistical analyses and SEM to explore and evaluate interactions between quality of life, home and neighborhood factors, and sociodemographic factors. The use of SEM will also support and question theory building.

Phase 3: Integration

In accordance with a mixed methods approach [25,39], phase 3 will be an analytical step comprising integration and synthesis of the data and results from previous phases. This synthesis will generate new knowledge by comparing, contrasting, and positioning a diversity of findings with each other. Data presentation workshops and analysis meetings with researchers, participants, and knowledge users will be the core methodology. Emerging themes will be contrasted against theoretical and empirical scholarly work on aging in context in an iterative process. Preliminary findings will be discussed in a series of workshops with scholars in the field, participants from our study, and potential knowledge users. The integration task is expected to be completed after 3 to 6 months.

Ethics Approval

All participants will sign written consent forms when entering the study. The study was approved by the Swedish Ethical Review Authority (phase 1: Dnr. 2020-03468; phases 2 and 3: Dnr. 2021-03588).

Results

As of the submission of this protocol (August 2022), recruitment for the interview study has been completed (N=39), and 267 participants have been recruited and completed data collection for the survey study. We expect recruitment and data collection to be finalized by December 2022.

Discussion

Anticipated Findings

This study will provide detailed knowledge on what role the home and neighborhood play in older adults' quality of life and their participation in the community and society by focusing on different kinds of disadvantaged areas. By collecting qualitative and quantitative data and addressing physical, social, and emotional aspects of the environment, we will be able to address complex person–environment dynamics [39].

In Sweden, the development of and changes in disadvantaged areas in cities and depopulated areas in rural municipalities are caused by shared challenges on a societal level, such as demographic changes, urbanization, and globalization, but also due to local challenges in Sweden's 290 self-governing municipalities [4]. By including urban and rural areas in this study, we will be able to investigate both similarities and differences in the person–environment dynamics of older adults' quality of life and participation in the community and society.

The study design allows for studying older adults not only as they are affected by the environment, when the neighborhood changes and they have to adapt, but also as active agents, who likely contribute to change in the neighborhood and build the community. The knowledge generated will be useful to better understand the effects of exclusion and marginalization and the effects of inclusion and the creation of community [22].

Inclusive and accessible living environments are fundamental to well-being, and Swedish aging policy states that older adults should be able to age safely, maintain their independence, and continue to lead active lives. The right to be active, live independently, and participate in the community and society can be considered an occupational justice issue, not only an individual health matter, and is important for future research and policy interventions on healthy aging [17].

Limitations

The disadvantaged areas selected for the study are not representative of all disadvantaged areas in Sweden, but they constitute interesting examples that show the diversity of living conditions of older adults. The study was started in 2019, and recruitment, as well as quantitative and qualitative data collection, had to adjust to the COVID-19 pandemic. This likely also influenced the data collected, which we will consider in future analyses and interpretation of results.

Conclusions

With an increasing proportion of older adults, an increasing number of disadvantaged areas, and an increasing dependency ratio in more than 50% of Swedish municipalities, Swedish cities and municipalities are transforming and becoming increasingly segregated. This study will add unique knowledge on what it is like to be older in disadvantaged areas and deepen knowledge on housing and health dynamics in later life. Further, the design of the current study will allow future follow-ups and longitudinal analysis (if granted funding) of aging in a transforming societal context.

Acknowledgments

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Data Availability

The data sets generated during the current study will be made available after data collection is completed upon reasonable request to the corresponding author.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview Guide.
[PDF File (Adobe PDF File), 98 KB - resprot_v11i10e41255_app1.pdf]

Multimedia Appendix 2
Peer-review reports from the Forskningsrådet för hälsa, arbetsliv och välfärd (FORTE, Swedish Research Council for Health, Working Life, and Welfare) (Stockholm, Sweden).
[PDF File (Adobe PDF File), 183 KB - resprot_v11i10e41255_app2.pdf]

References

1. Deprived areas: Social order, criminal structures and challenges for the police force. Utsatta områden - Social ordning, kriminell struktur och utmaningar för polisen. Swedish National Police. 2017. URL: shorturl.at/ehpMU [accessed 2022-09-26]

2. Housing for the elderly in depopulated areas. Swedish National Audit Office. URL: https://www.riksrevisionen.se/en/audit-reports/audit-reports/2014/housing-for-the-elderly-in-depopulated-areas.html [accessed 2022-09-26]
3. Ivert AK, Torstensson Levander M, Mellgren C. The unequal safety net. Den ojämlika tryggheten. Socialvetenskaplig tidskrift 2016 Sep 08;22(3-4):211-229 [FREE Full text] [doi: 10.3384/svt.2015.22.3-4.2338]
4. Jönson H, Szebehely M. Eldercare in Sweden: Local variation and general trends. Äldreomsorger i Sverige: Lokala variationer och generella trender. Malmö, Sweden: Gleerups; 2018.
5. Schafer. (Where) is functional decline isolating? disordered environments and the onset of disability. J Health Soc Behav 2018 Mar;59(1):38-55. [doi: 10.1177/0022146517748411] [Medline: 29281800]
6. Iwarsson S, Horstmann V, Slaug B. Housing matters in very old age - yet differently due to ADL dependence level differences. Scand J Occup Ther 2007 Jul 12;14(1):3-15. [doi: 10.1080/11038120601094732] [Medline: 17366073]
7. Iwarsson S, Löfqvist C, Oswald F, Slaug B, Schmidt S, Wahl H, et al. Synthesizing ENABLE-AGE research findings to suggest evidence-based home and health interventions. J Hous Elderly 2016 Aug 11;30(3):330-343. [doi: 10.1080/02763893.2016.1198742]
8. Henning C, Lieberg M. Strong ties or weak ties? Neighbourhood networks in a new perspective. Scand Hous Plan Res 1996 Jan;13(1):3-26. [doi: 10.1080/02815739608730394]
9. Julien D, Richard L, Gauvin L, Kestens Y. Neighborhood characteristics and depressive mood among older adults: an integrative review. Int Psychogeriatr 2012 Aug;24(8):1207-1225. [doi: 10.1017/S1041610211002894] [Medline: 22300529]
10. Wu Y, Prina AM, Brayne C. The association between community environment and cognitive function: a systematic review. Soc Psychiatry Psychiatr Epidemiol 2015 Mar 3;50(3):351-362 [FREE Full text] [doi: 10.1007/s00127-014-0945-6] [Medline: 25087013]
11. Yen IH, Michael YL, Perdue L. Neighborhood environment in studies of health of older adults: a systematic review. Am J Prev Med 2009 Nov;37(5):455-463 [FREE Full text] [doi: 10.1016/j.amepre.2009.06.022] [Medline: 19840702]
12. Rosso A, Auchincloss A, Michael Y. The urban built environment and mobility in older adults: a comprehensive review. J Aging Res 2011;2011:816106 [FREE Full text] [doi: 10.4061/2011/816106] [Medline: 21766033]
13. Danielewicz AL, Dos Anjos JC, Bastos JL, Boing AC, Boing AF. Association between socioeconomic and physical/built neighborhoods and disability: A systematic review. Prev Med 2017 Jun;99:118-127. [doi: 10.1016/j.ypmed.2017.02.014] [Medline: 28216376]
14. Annear M, Keeling S, Wilkinson T, Cushman G, Gidlow B, Hopkins H. Environmental influences on healthy and active ageing: a systematic review. Ageing Soc 2012 Nov 06;34(4):590-622. [doi: 10.1017/s0144686x1200116x]
15. Meijer M, Röhl J, Bloomfield K, Grittner U. Do neighborhoods affect individual mortality? A systematic review and meta-analysis of multilevel studies. Soc Sci Med 2012 Apr;74(8):1204-1212. [doi: 10.1016/j.socscimed.2011.11.034] [Medline: 22365939]
16. Abramsson M, Hagberg J. What about community sustainability? – dilemmas of ageing in shrinking semi-rural areas in Sweden. Scottish Geogr J 2018 Oct 05;134(3-4):103-121. [doi: 10.1080/14702541.2018.1527941]
17. Durocher E, Gibson B, Rappolt S. Occupational justice: a conceptual review. J Occup Sci 2013 Mar 21;21(4):418-430. [doi: 10.1080/14427591.2013.775692]
18. Granovetter MS. The strength of weak ties. Am J Sociol 1973 May;78(6):1360-1380. [doi: 10.1086/225469]
19. Lawton P, Nahemow L. Ecology and the aging process. In: Eisdorfer C, Lawton P, editors. The psychology of adult development and aging. Washington, DC: American Psychological Association; 1973:619-674.
20. Riley M. On the significance of age in sociology. Am Sociol Rev 1987 Feb;52(1):1-14. [doi: 10.2307/2095388]
21. Rowles G, Watkins J. History, habit, heart and hearth: on making spaces into places. In: Warner Schaie K, Wahl HW, Mollenkopf H, Oswald F, editors. Aging independently: Living arrangements for mobility. New York, NY: Springer Publishing Company; 2003:77-96.
22. Phillipson C. The Role of Community and the Environment in the Lives of Older People. Annu Rev Gerontol Geriatr 2018 Jan 01;38(1):165-181. [doi: 10.1891/0198-8794.38.165]
23. WHOQOL Group. Development of the World Health Organization WHOQOL-BREF Quality of Life Assessment. Psychol Med 1998 May 01;28(3):551-558. [doi: 10.1017/S0033291798006667]
24. International Classification of Functioning, Disability and Health. World Health Organization. 2001. URL: https://www.who.int/standards/classifications/international-classification-of-functioning-disability-and-health [accessed 2022-09-20]
25. Creswell JW, Clark VLP. Designing and conducting mixed methods research. New York, NY: Sage Publications; 2017.
26. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006 Jan;3(2):77-101. [doi: 10.1191/1478088706qp063oa]
27. Tinghög P, Carstensen J. Cross-cultural equivalence of HSCL-25 and WHO (ten) Wellbeing index: findings from a population-based survey of immigrants and non-immigrants in Sweden. Community Ment Health J 2010 Feb 28;46(1):65-76. [doi: 10.1007/s10597-009-9227-2] [Medline: 19636706]
28. Weil J. Developing the person-place fit measure for older adults: broadening place domains. Gerontologist 2020 Nov 23;60(8):548-558. [doi: 10.1093/geront/gnz112] [Medline: 31433829]

29. Margot-Cattin I, Kuhne N, Kottorp A, Cutchin M, Öhman A, Nygård L. Development of a questionnaire to evaluate out-of-home participation for people with dementia. Am J Occup Ther 2019;73(1):7301205030p1-7301205030p10. [doi: 10.5014/ajot.2019.027144] [Medline: 30839258]
30. Ustün TB, Chatterji S, Kostanjsek N, Rehm J, Kennedy C, Epping-Jordan J, WHO/NIH Joint Project. Developing the World Health Organization Disability Assessment Schedule 2.0. Bull World Health Organ 2010 Nov 01;88(11):815-823 [FREE Full text] [doi: 10.2471/BLT.09.067231] [Medline: 21076562]
31. Litwin H, Stoeckel K, Roll A, Shiovitz-Ezra S, Kotte M. Social network measurement in SHARE wave four. In: Malter F, Börsch-Supan A, editors. SHARE Wave 4, innovations and methodology. Munich, Germany: Max-Planck-Institute for Social Law and Social Policy; 2013:18-38.
32. Börsch-Supan A, Jürges H. The Survey of Health, Aging, and Retirement in Europe – Methodology. SHARE Project. 2005. URL: http://www.share-project.org/uploads/tx_sharepublications/SHARE_BOOK_METHODOLOGY_Wave1.pdf [accessed 2022-09-20]
33. Börsch-Supan A. Survey of Health, Ageing and Retirement in Europe (SHARE) Wave 6. SHARE Project. URL: http://www.share-project.org/data-documentation/waves-overview/wave-6.html [accessed 2022-09-20]
34. Sullivan M, Karlsson J, Ware JE. SF-36 ha¨lsoenka¨t : svensk manual och tolkningsguide (Swedish manual and interpretation guide). Go¨teborg, Sweden: Sahlgrenska University Hospital; 1994.
35. Iwarsson S, Horstmann V, Sonn U. Assessment of dependence in daily activities combined with a self-rating of difficulty. J Rehabil Med 2009 Feb;41(3):150-156 [FREE Full text] [doi: 10.2340/16501977-0298] [Medline: 19229447]
36. Heywood F, Oldman C, Means R. Housing and Home in Later Life. Buckingham, UK: Open University Press; 2002.
37. FirstStop Advice. Housing Options (HOOP) Tool. URL: http://www.firststopcareadvice.org.uk/professional/ [accessed 2021-02-12]
38. Hagell P, Hedin P, Meads DM, Nyberg L, McKenna SP. Effects of method of translation of patient-reported health outcome questionnaires: a randomized study of the translation of the Rheumatoid Arthritis Quality of Life (RAQoL) Instrument for Sweden. Value Health 2010 Jun;13(4):424-430 [FREE Full text] [doi: 10.1111/j.1524-4733.2009.00677.x] [Medline: 20070642]
39. Weil J. Research design in aging and social gerontology: Quantitative, qualitative, and mixed methods. New York, NY: Routledge; 2017.

Abbreviations

ACT-OUT: Participation in Activities and Places Outside Home Questionnaire
PPFM-OA: Person-Place Fit Measure for Older Adults
SEM: structural equation modeling
SES: socioeconomic status
SHARE: Survey of Health, Ageing and Retirement in Europe
SPAR: Swedish state personal address register

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Protocol

Dialogic Health Education to Reduce COVID-19 Disparities and Increase Health Literacy in Community and Correctional Settings: Protocol for a Two-Pronged Health Education Program

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Abstract

Background: COVID-19 vaccines significantly reduce rates of hospitalization and death for those infected with the SARS-CoV-2 virus. Those facing social oppression, including people of color, experience heightened risk for COVID-19 and comorbidities, but are often mistrustful of governmental agencies and initiatives, contributing to low vaccine uptake and a reluctance to access vital health care services. Dialogue-based health literacy interventions may mitigate mistrust and increase access to health services and information, subsequently increasing rates of vaccination and other behaviors that reduce COVID-19 risk.

Objective: To improve health literacy and reduce COVID-19 disparities, the Westchester County Department of Health, in partnership with two universities, community- and faith-based organizations, and the Westchester County Department of Correction, co-developed a health education program for community members, correctional officers, and incarcerated jail residents in Westchester, New York. Specific objectives are to increase preventative health behaviors, positive attitudes toward use of public health protocols, full vaccination or intentions to vaccinate, health care information understanding, health provider care access, clear communication with health care providers, and personal health care decision-making.

Methods: Grounded in dialogic learning, the program entails training community-based "trusted messengers" and correctional officers to lead health information sessions in community and correctional settings. During the grant period, the program intends for 80 community-based trusted messengers to receive training from the Department of Health and will be expected to reach a goal of 100 members (N=8000) of their communities. Correctional staff with experience delivering educational programs will be trained to facilitate sessions among 400 correctional facility residents and 600 correctional staff.

Results: Pre-post surveys will assess changes in health behaviors, attitudes, and perceptions. The program has been administered in the correctional facility since February 2022, with information sessions expected to cease for correctional staff and residents in June 2022 and November 2022, respectively. An initial cohort of community-based trusted messengers began training in February 2022, and information sessions have been scheduled in various virtual and community settings since March 2022. As of April 2022, the two-pronged health education program has reached 439 correctional officers, 98 jail residents, and 201 community members countywide. Program evaluation findings will be released in future publications after study implementation is complete.

Conclusions: Few studies have evaluated the combined effects of training-of-trainers (ToT) and dialogical learning models on behavior and health literacy. As the first known COVID-19–specific dialogue-based health education program that applies a ToT model in the community-based, correctional, and virtual settings simultaneously, this study fills a gap in current knowledge about health literacy and health behavior in marginalized populations. Thus, this evidence-based framework can remedy COVID-19 disparities while also addressing risks for a host of health-related issues at the community level, potentially serving as a best-practice model for future health programs.

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KEYWORDS

community engagement; dialogic learning; training of trainers; COVID-19; health literacy; correctional facility health; health equity; racial disparities; community participation

Introduction

Background

Individuals infected with SARS-CoV-2, the virus that causes COVID-19, are significantly less likely to experience death or severe disease when vaccinated [1]. Despite vaccine availability and calls for population-wide COVID-19 vaccination from health care professionals and public health agencies, many individuals in the United States remain unvaccinated [2,3]. Further, groups experiencing various levels of social oppression are not only at heightened risk of COVID-19 morbidity and mortality but are also less likely to receive a COVID-19 vaccine than the population as a whole [4-6].

Sociodemographic characteristics correlated with high COVID-19 positivity at the zip-code level include high percentages of people of color, limited English language proficiency, household crowding, and poverty [7-9]. Reasons for these associations are multidimensional; for example, inequities related to poverty and structural racism can exacerbate comorbidities, thereby increasing risks of COVID-19 severity [10-12]. Moreover, a lack of culturally and linguistically appropriate health communication can thwart contact with the health care system and complicate discernment of reliable health information, such as COVID-19 prevention recommendations [13,14].

Social factors also correspond to low COVID-19 vaccine uptake [15]. Race, ethnicity, and language are linked with vaccine refusal and reduced patient-provider interaction, often due to past experiences of medical discrimination [16,17]. As a result, people of color in the United States are more likely to mistrust health authorities, resulting in lower COVID-19 vaccination rates than the national average [2,18].

Incarcerated individuals face added dimensions of social vulnerability and COVID-19 disparities due to crowding, poor sanitation, and lack of personal protective equipment [19,20]. Although much of the public focus during the pandemic was on state and federal prison systems, with little attention paid to county jails, the jail's transient population creates a disproportionate risk for COVID-19 transmission. This is because new arrests bring infection from the community into the jail, while prisons receive new admissions from a medically cleared jail population [21]. These factors contribute to heightened COVID-19–related risks to the staff and residents of the county jail [22,23].

Despite this disparity, both correctional facility staff and residents demonstrate disproportionately low rates of COVID-19 vaccine uptake [24]. Mistrust toward correctional staff, combined with limited health education in correctional facility settings, can contribute to vaccine skepticism among the incarcerated [25]. In addition, correctional officers more frequently demonstrate vaccine refusal than the population as a whole, with some citing distrust of correctional administrators, beliefs in conspiracy theories, or other misinformation about vaccines [24]. Medical mistrust among both correctional officers and residents may inhibit access, use, and outcomes of health-related interventions that aim to increase vaccination rates.

Advancing Health Literacy

These disparities arise from complex issues occurring over long periods of time; as such, addressing these issues at a population level requires long-term structural solutions [26]. However, health literacy interventions may help to meet more immediate health needs among the underserved. The US Department of Health and Human Services (HHS) National Action Plan to Improve Health Literacy uses a definition of health literacy that underscores health care access, health information understanding, and informed health decision–making [27]. This definition guides the HHS Office of Minority Health's initiative Advancing Health Literacy to Enhance Equitable Community Responses to COVID-19 (AHL). AHL grants fund programs that "demonstrate the effectiveness of working with local community-based organizations to develop health literacy plans to increase the availability, acceptability, and use of COVID-19 public health information and services by racial and ethnic minority populations" [28].

This protocol outlines the guiding principles and methods used to implement an AHL-funded health education program and evaluation of its effectiveness among priority populations in Westchester County, New York.

Theoretical Approach

Educational programs that integrate dialogic learning approaches can give power to learners and acknowledge the value of their experiences and cultures, creating more equitable conditions for sharing information and providing different points of view [29,30]. Studies have shown that discussion-based learning can be more effective in improving health and motivating self-education than a "banking" method of education, which views students as empty vessels to be filled by teachers [29-31].

The program also applies a training-of-trainers (ToT) framework to equip select individuals with the tools and information necessary to facilitate dialogic health information sessions in various settings. Those selected, referred to as "trusted messengers," will be individuals who are considered trustworthy in their communities and can lead culturally sensitive, linguistically appropriate COVID-19–focused information sessions in either correctional facilities or community-based settings. Studies have found that enhanced trust between teachers

and learners can encourage program participants to engage in constructive dialogue, ask questions that enhance understanding, and put health information into practice [29,32-34].

Yet, perceived health expertise is also shown to be important for influencing health behavior and enhancing trust [35,36]. A recent study of vaccine hesitancy among Black Americans found that "medical professionals they were familiar with and trusted could influence their decision to take a COVID-19 vaccine" [35]. Thus, the proposed program engages a team of health professionals who may offer support to trusted messengers who lack prior experience with health education or health care delivery.

Health Education in Correctional Facilities

Health education programs led by trusted individuals in correctional facilities have improved behavior intention and attitudes toward risks related to HIV, tuberculosis, and hepatitis C viral infection [37-40]. This suggests that training those who may be perceived as trusted messengers for jail residents can be equally effective for affecting the same outcomes (attitudes and intended behaviors) for COVID-19–related risks.

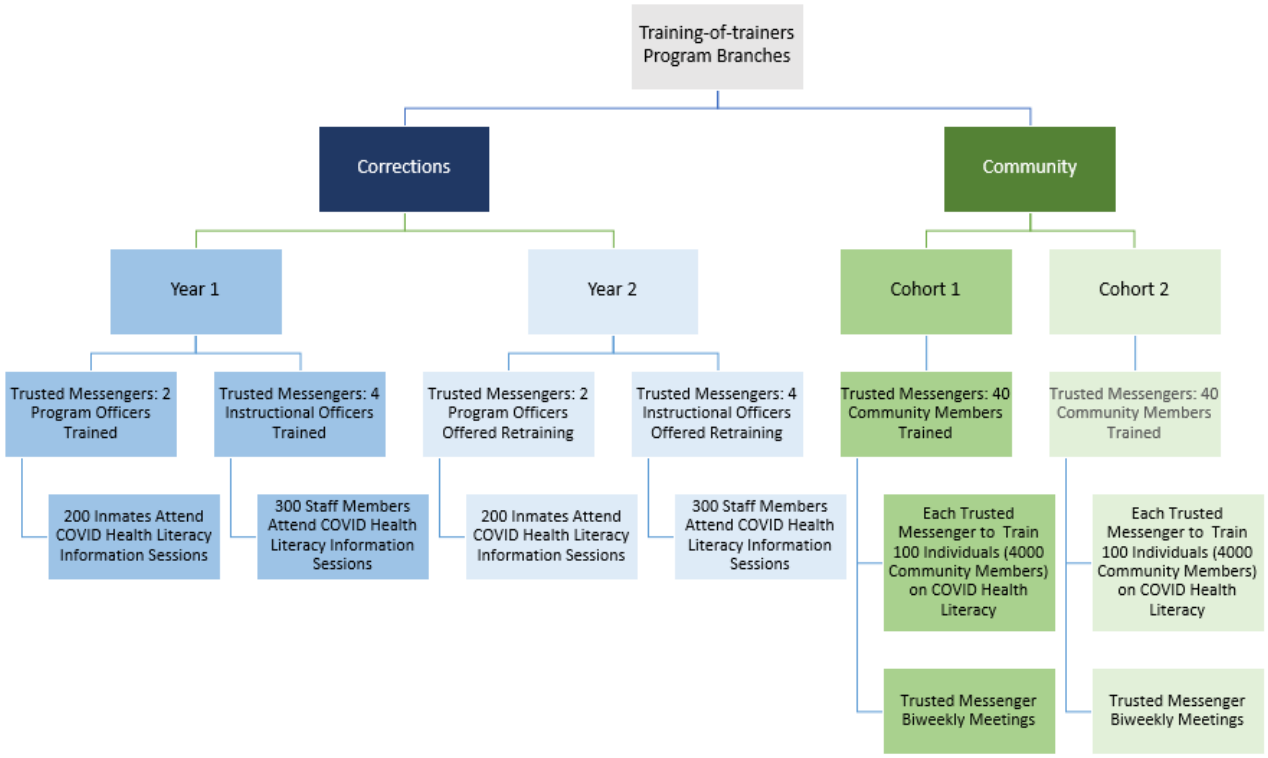
Lessons learned from previous dialogic correctional facility–based HIV programs indicate that "inmate questions and ensuing discussions are an important training ground for applied prevention" [41]. Dialogic education is particularly important in correctional environments, where staff and residents may frequently feel scrutinized, as opening communication between teachers and learners can serve as a rare avenue of personal control and improve individual health decision–making as a result [42].

Overview of the Know Better, Live Better Program

The Westchester County Department of Health (DOH) has designed an AHL-funded program that applies ToT and dialogic learning models of education to correctional officers, jail residents, and community members in geographic areas of focus, relying on trusted messengers to lead health information sessions. Trusted messengers receive training on health information delivery and a semistructured lesson plan for leading a 1-hour information session. The sessions themselves intend to be discussion-based, allowing a bidirectional transmission of information between trusted messengers and program participants.

There are two parallel branches of this program, entitled Know Better, Live Better (KBLB). The first is based in community settings, engaging community- and faith-based organizations (CBOs), and focusing recruitment efforts in neighborhoods with high social vulnerability and COVID-19–related risk. The second branch partners with the Westchester County Department of Correction (DOC) to address health literacy and COVID-19 among correctional officers and jail residents. Figure 1 illustrates the number of trusted messengers participating in ToT and the expected study population per branch.

Figure 1. Overview of Know Better, Live Better program branches, and anticipated reach of community-based and correctional facility–based programs.



Goals and Objectives

We hypothesize that a dialogic learning program, co-developed by CBO partners, will help achieve the overall goals to improve health literacy and reduce COVID-19–related racial and ethnic disparities in Westchester County. After analyzing pre-post survey changes among participants of each information session, we expect increases in preventative health behaviors, positive attitudes toward use of public health protocols, full vaccination or intentions to vaccinate, health care information understanding, health provider care access, clear communication with health care providers, and personal health care decision–making. We

will also use demographic questionnaires to gauge any socioeconomic factors mediating program effectiveness, as measured by these objectives.

Methods

Community-Based Program Design

Overview

We aim to train approximately 80 trusted messengers to reach a goal of 8000 individuals in the geographic area of focus by the end of December 2022. These areas were selected using the Centers for Disease Control and Prevention Social Vulnerability Index (SVI), which encompasses 4 key domains: socioeconomic status, housing and transportation, minority status and language, and household composition. Program staff identified 55 census tracts ranked with the highest social vulnerability in the county. These census tracts overlap with zip codes with high COVID-19–related morbidity and low vaccine uptake; thus, they constitute the geographic area of focus for this project. These are the areas in which program staff will concentrate efforts to recruit all information session participants, trusted messengers, and CBO partners. However, zip code of residence will not be considered among the exclusion criteria for any partner, trusted messenger, or participant to ensure that program benefits are wide-reaching. As of April 2022, 26 trusted messengers completed training and collectively reached 201 community-based participants.

Training of Trainers

All trusted messengers will be screened through an online form and interviews with DOH staff. Applicants must be at least 18 years old, have access to a computer with internet connection, and have sufficient availability to deliver the program to at least 100 participants in geographic areas of focus. Trusted messengers are also required to be vaccinated for COVID-19 before any health information sessions begin. Preference will be given to bilingual trusted messengers who are comfortable giving presentations in other languages, as well as those with strong connections in Westchester communities. Each trusted messenger will receive a stipend for completing required program activities.

Program staff facilitate 6-hour trainings spread over 1 week to provide trusted messengers with information to prepare them for discussion facilitation. This includes COVID-19–related health information, skills related to dialogic learning, and the curriculum outline. Each trusted messenger receives a handbook that contains this information in written form. Trusted messengers will participate in biweekly, 1-hour check-in meetings with program staff to provide opportunities to discuss challenges they have incurred.

Study Settings

Community-based information sessions are designed to be either virtual or in person, in order to reach those with limited internet access, and will be limited to 30 individuals to foster productive and engaging discussions [43,44]. Partnering CBOs may host in-person sessions so that attendees can engage with health information in familiar community settings such as churches and cultural centers. Virtual sessions will be hosted through the Cisco WebEx video conferencing system with a DOH account.

Health Information Session Development

The proposed information sessions cover issues related to COVID-19, such as disease prevention measures and barriers to vaccine acceptance. These topics are contextualized in a broader discussion about health literacy, which includes accessing health care, understanding health information, and making individual health decisions. Trusted messengers will be provided with standardized resources that are necessary for program delivery, including presentation slides and handouts. The information sessions will be piloted with academic partners and CBOs to ensure appropriateness, applicability, and quality.

Participant Recruitment

CBOs and DOH program staff will assist trusted messengers with recruitment and locating meeting spaces for in-person sessions. Trusted messengers and/or CBOs are to ensure that recruitment efforts are made before the scheduled session. Trusted messengers and/or CBOs will make initial contact with the participants, depending on who has identified them as an interested participant.

For virtual sessions, program staff will provide trusted messengers with a WebEx video conferencing link to share with their intended audience. Registration links will also be made publicly available on the program website. In-person participants may learn about scheduled sessions in any language through personal referral, public notice, and other promotional efforts that DOH program staff and partners make.

Health Care Professional Support Team

Because health care professionals who are trusted in their communities can effectively influence health perceptions and behavior, a support team comprised mainly of DOH-employed registered nurses and nurse practitioners will be present for all sessions (virtual and in person) as an additional source of support for trusted messengers who lack health expertise.

Data Collection

Data will be collected during this project using multiple instruments, as outlined in Figure 2. First, a presurvey will be distributed prior each information session. This questionnaire is designed to assess knowledge, attitudes, and behaviors regarding COVID-19 protocols and vaccines. There will also be questions related to health literacy, such as participants' ability to navigate the health care system, discern reliable health information, and use health information to make decisions. The included questions were adapted from previously validated tools: European Health Literacy Survey (HLS-EU) Questionnaire and the Understanding America Study (UAS230) [45,46]. Demographic items will include race/ethnicity, gender, age group, marital status, and employment.

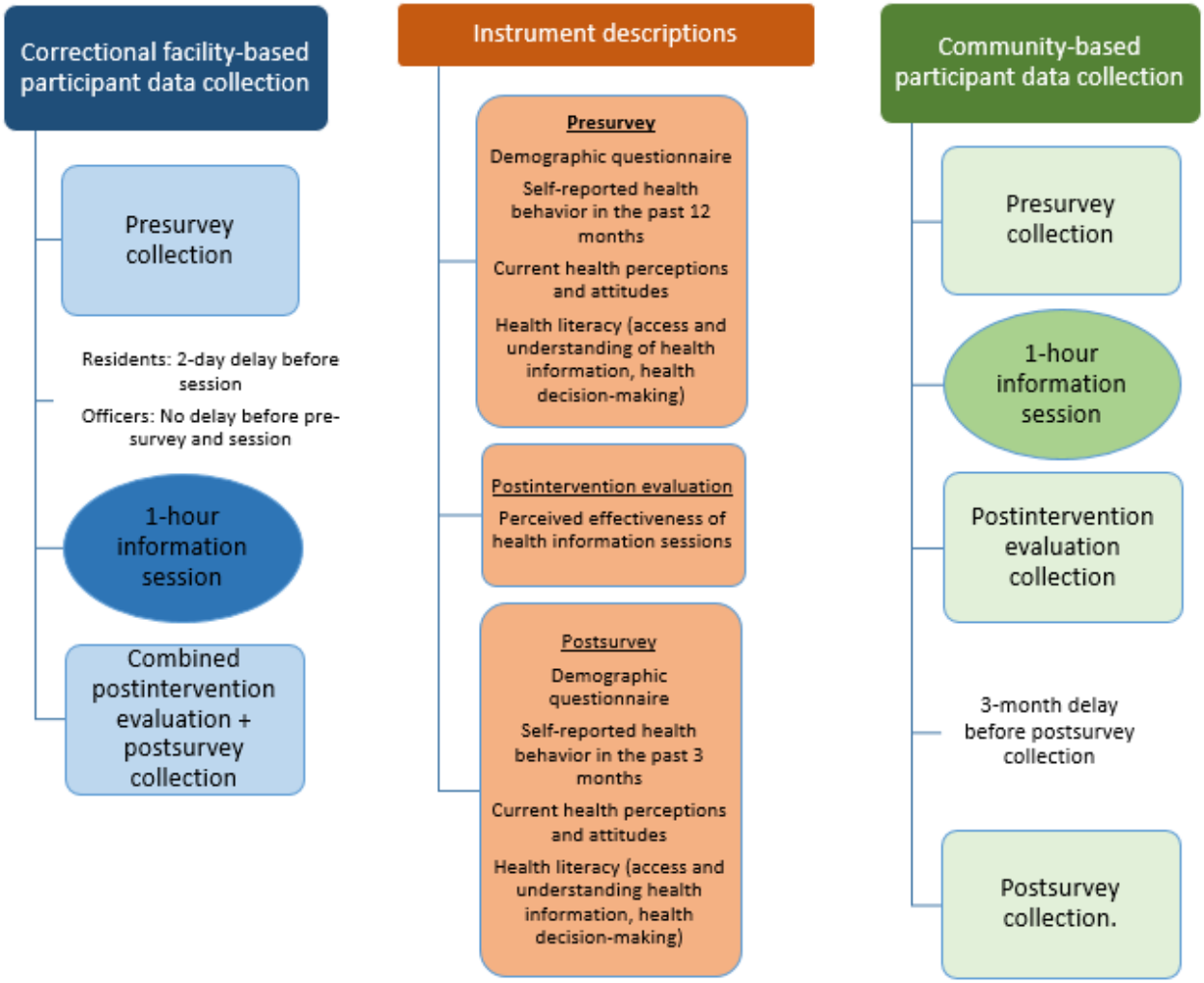
Immediately following the information session, program staff will distribute a short questionnaire ("postintervention evaluation") that asks participants to assess the perceived efficacy of the 1-hour session. The questionnaire consists of 7 Likert items asking whether the session had impact in terms of

health information understanding, health information access, and health care decision–making.

Participants in the in-person information sessions will be offered paper surveys. Virtual program participants will complete the surveys from an open link from Research Electronic Data Capture (REDCap), a secure, web-based application designed to support data capture for research studies [47]. In-person participants will receive paper versions that will be collected by select program staff and entered manually into REDCap.

In addition to collecting data through surveys, program staff will be present at each information session to track general information about the session logistics. Staff will also use an observation guide to document the broad themes that arise during the facilitated discussions, providing a source of qualitative data.

Figure 2. Data collection time points and instruments used in each program branch.



Supplementary Data Collection

DOH research staff will assess the broader public health influence of the AHL program by monitoring public health surveillance data at the zip-code level, comparing changes in geographic areas of focus to the rest of the county throughout the grant period. These data include COVID-19 positivity rates, calculated using test results reported to the New York State Electronic Clinical Laboratory Reporting System. Data from the New York State Immunization Information System will also track vaccine registration rates across zip codes in the county. Staff will take into account any national, state, or local policy changes, and other potential reasons for changes in COVID-19 positivity and vaccination rates.

To evaluate the effect of the AHL program on primary care access, staff will compile a list of primary care providers located in geographic areas of focus. They will request information from a subset of providers on new patient visits and service utilization throughout the grant period on a monthly basis.

Incentives

The use of incentives in research encourages innovation, provides motivation, and promotes strategic decision-making [48]. Evidence-based incentivization through nonmonetary means is linked to increased data sharing, specifically when individuals are provided with a badge or certificate [49]. Therefore, all participants will receive a certificate of completion for attending the health information session.

Individuals receiving a financial incentive for immunization were three times more likely to become immunized compared to those not receiving an incentive [50]. Thus, to encourage program participation, individuals will be provided a US $10

gift card incentive as compensation for their time spent at the session. A US $10 electronic gift card will also be provided to those who complete the optional 3-month postintervention survey.

Research Ethics and Approval

The materials and methods of the community-based portion of the project were reviewed and approved by the Mercy College Institutional Review Board (IRB; Project #21-82) on February 8, 2022.

Correctional Facility–Based Program Design

Overview

DOH staff will train program officers and instructional officers to educate 400 correctional facility residents and 600 correctional staff, respectively, during the 2-year grant period. While the officers will lead information sessions, DOH program staff will attend to provide administrative assistance and complete informed consent. The training and 1-hour lesson plans will closely resemble those designed for the community-based branch of the AHL program, with further tailoring to meet audience-specific needs, including COVID-19 protocols and special health care resources. As of April 2022, the correctional facility–based education program has reached 439 correctional officers and 98 jail residents.

In the correctional facility, there are two sets of discussion leaders, who play the same role as trusted messengers in community-based sessions. Program officers with experience delivering health programs to jail resident comprise the first group. Although they are uniformed officers, the relationships they have with residents are more positive than those of other officers, owing to their roles as program leaders. The second group consists of correctional officers who typically act as instructors for fellow officers during annual training days. Thus, the two sets of learners for the correctional facility–based program are residents and correctional officers. All discussion leaders will be required to be vaccinated for COVID-19.

Training of Trainers

Program staff will provide approximately 6 hours of training to both program and instructional officers. Training sessions will cover COVID-19–related information, AHL program goals, informed consent, and advice for moderating discussions among residents and officers. Like community-based trusted messengers, program and instructional officers will receive necessary resources, including a trainer manual, pilot session recordings, and access to medical support via video conference during the information sessions for any health questions.

Study Settings

All correctional facility–based sessions will occur in person at a Westchester County–based jail. The jail consists of the Jail and Penitentiary Divisions. The Jail Division houses individuals aged 18 years and older, including men and women awaiting sentencing and women sentenced to terms of 1 year or less. The Penitentiary Division houses men aged 18 years and older sentenced to terms of 1 year or less. The DOC operates the jail and is accredited by the American Correctional Association with the medical operations accredited by the National Commission on Correctional Health Care.

Health information sessions for correctional staff will be held in a training academy classroom during annually scheduled training days. Participating staff members will be asked to voluntarily complete a presurvey immediately before the information session and a postsurvey immediately afterward. A program staff member and a member of the health care professional support team will be virtually present at all sessions.

Health information sessions for residents will take place in the housing units' recreational rooms. Due to COVID-19, there is an anticomingling policy between housing units. Therefore, the program will be offered to each unit individually to ensure complete jail coverage and minimize disease spread. Per DOC request, all residents who would like to participate will be allowed to attend with potential discussion group sizes of up to 40 individuals.

Health Information Session Planning

The correctional facility–based curriculum, after undergoing CBO partner review, will be tailored to address needs and specific concerns for officers and residents based on recent literature. These tailored versions will be reviewed by a health educator and members of DOC leadership, each with experience delivering programs in correctional facilities. Residents will also receive a list of local health care providers who can be accessed upon release.

Participant Recruitment

Correctional officers will participate in KBLB health information sessions as part of their annual "pay back" days, dedicated for training purposes. DOC leadership has dedicated 1 hour of open training time to the KBLB program to increase health literacy and address COVID-19 vaccine resistance among staff.

To recruit residents, program officers will provide information about the KBLB program to residents ahead of the scheduled lessons. Per DOC protocols, residents must write their name on a sign-up sheet if they are interested in participating so that the officers may account for all residents during scheduled session times. This also ensures that participants receive their incentive, voluntary presurvey, and informed consent.

Data Collection

Data will be collected during the correctional facility–based component of this program using two instruments: the "presurvey" and the "postsurvey." The presurvey will be distributed prior to the discussion sessions, while the postsurvey will be distributed immediately following the discussion session. Neither is required to participate in the discussion. These surveys are based on the same instruments that were used for the community-based education program (Figure 2).

Unlike the community-based branch, the correctional facility branch of the program will combine the 3-month postsurvey with the postdiscussion evaluation. The postsurvey is identical to the presurvey, including all Likert scales, so that pre-post changes can be accurately assessed. Open-ended questions will

be used to understand primary concerns regarding COVID-19 vaccines and other public health prevention recommendations before and after the sessions. All surveys will be paper-based and responses will be manually entered into REDCap.

Like the community-based component, program staff will complete an observation guide detailing the number of participants in attendance and documenting characteristics of the correctional facility–based discussion session. Staff will record common themes discussed during the sessions, unique features of each session, questions that arise, and discussion topics. The observational guide will include both qualitative and quantitative elements to capture a more complete and detailed depiction of each session.

Incentives

Correctional staff will participate in the program during work hours. They will receive either breakfast or lunch during the session in addition to their regular hourly pay.

Incentives for residents will be a US $10 voucher to the jail commissary for food and beverages, or a US $10 prepaid phone card. All participants will receive an incentive regardless of whether they complete surveys.

Research Ethics and Approval

The materials and methods of the correctional facility–based portion of the project were reviewed and approved by the Pace University IRB (Project #1843825-2) on February 11, 2022.

Results

Analysis of Community-Based Program Data

All survey data will be analyzed with descriptive statistics. Investigators will use *t*-tests and χ^2 analyses for pre-post discussion session changes and a multivariable regression analysis to adjust for covariates such as race, ethnicity, age, and other demographic variables.

Pre- and postsurveys do not include person identifiers and subsequently will not be matched individually. However, as they will be given to a correlated group of individuals, the mean of the pretest variables will be used as a threshold score for the comparison of the post-test variables using a one-sample *t*-test. The postsurvey scores will be compared to the individual mean score of the presurvey. The surveys will be analyzed for changes in behavior or behavior intentions, attitudes, and perceptions with the following potential mediator-moderator domains: gender, age, race, ethnicity, zip code, education level, and marital status.

For item nonresponse, response rates for each question will be stratified by demographic factors to ensure systematic bias is not present due to nonrandom missing variables. If variables are found to be missing at random, imputation of items will occur.

The qualitative components of the observational guides completed by program staff will be analyzed for emergent themes using a data-driven thematic coding scheme that will be iteratively developed by the analytic team in accordance with grounded theory analysis [51,52].

Census tracts comprising the geographic areas of focus, as determined by the SVI, will be mapped to overlapping zip codes. Population counts from the US Census Bureau and data extracted from disease reporting systems will allow for zip code–level computation of outcome rates, vaccination registration rates, and COVID-19 positivity rates. To quantify disparities between zip codes that fall within geographic areas of focus and the rest of the county, a time-trend analysis will be performed, using outcome rates calculated monthly over the course of the 2-year grant period. This will allow assessment of whether changes in outcome rates in the geographic areas of focus correspond to changes in the number of AHL program sessions collectively occurring in those zip codes in a given month, while also comparing rate changes to county zip codes in which information sessions did not take place.

Analysis of Correctional Facility–Based Program Data

The analysis plan for pre- and postsurvey changes and adjustment for covariates will not differ from the analyses performed on community-based surveys detailed above. In addition, the observation guides used for observing correctional facility–based information sessions will not differ from those guides applied to community-based sessions. Therefore, the analysis of all observation guides will also adhere to the same procedures. Analysis of open-ended responses on pre- and postsurveys will follow similar thematic analysis to the qualitative components of the observation guides.

Discussion

Projected Significance

While there is a body of literature examining sociodemographic predictors of poor health literacy, few studies integrate peer support and dialogic learning models, two evidence-based frameworks that can have sustainable effects on health behavior and knowledge, with COVID-19–focused health education. To our knowledge, this is the first COVID-19–specific dialogue-based education program that applies a ToT model in community-based, virtual, or correctional settings to undergo longitudinal evaluation over multiple months. We hypothesize that pre-and postsurvey analyses for all participants in all settings will demonstrate an increase in the following key outcomes: preventative health behaviors, positive attitudes toward use of public health protocols, full vaccination or intentions to vaccinate, health care information understanding, health provider care access, clear communication with health care providers, and personal health care decision–making improvement.

Expected Benefits

In addition to meeting our outcome objectives, we anticipate that the AHL-funded KBLB program will have several benefits for both community- and correctional facility–based participants. First, engaging CBO partners at multiple stages of KBLB planning and implementation can make participant recruitment efforts more equitable, allow community perspectives to inform

an educational approach, and help develop sustainable partnerships that sustain program effectiveness [53,54].

Trusted messengers can foster a learning environment in which participants feel comfortable being candid and relaying questions or concerns. For attendees with minimal contact with the health care system, access to a member of the health care professional support team may be a rare opportunity to interact with health experts in a setting that is less intimidating than a clinic or private physician practice.

The emphasis on dialogic learning also allows attendees to discuss health concerns about COVID-19, discerning reliable health information, and other issues directly to a trustworthy peer. Attendees at information sessions are also encouraged to share knowledge about barriers to health improvement and health care access in their respective communities. The information exchanged during facilitated discussions is expected to illuminate underlying reasons for health-related attitudes and/or behaviors among diverse Westchester residents who, by virtue of geographic location in high-risk zip codes, experience varying levels of social oppression.

By having both trusted messengers and health care professionals present at each of the health information sessions, the program may increase the likelihood that participants will share messages learned. Throughout the pandemic, individuals reported stronger intentions to share messages from leaders compared to citizens [55]. Therefore, the trusted messenger framework is used to encourage active participation to create a more dynamic and interactive learning environment, while the health care professional lends credibility to all information shared.

Challenges

Potential obstacles must be considered during program implementation and evaluation. Studies have shown that dialogic learning approaches are highly dependent on the attitudes of instructors and the physical environment in which learning takes place [56]. Program staff must use the trusted messenger recruitment process to carefully vet individuals who are invested in collaborative learning, as well as those who are trusted and well-connected in the geographic areas of focus. Because certain issues related to the COVID-19 pandemic may be contentious, such as vaccination mandates, fear of being judged or criticized may hinder participation. Furthermore, information sessions held over a virtual conferencing system may pose an additional barrier to participant interaction. Thus, the ToT must emphasize discussion facilitation strategies that encourage participation and promote a safe, inclusive environment for discussion [57,58].

It will be difficult to recruit a cohort of community-based trusted messengers that is entirely representative of a diverse county population. Hard-to-reach populations may include individuals who prefer languages other than English and Spanish, individuals with disabilities, the deaf community, the LGBTQ community, elderly persons, and others. Without participating trusted messengers, CBOs, or program staff who have existing relationships with these subpopulations, participation recruitment may lack breadth; as a result, health information sessions may lack critical perspectives.

Health departments and other agencies that coordinate community-based participatory health interventions may encounter administrative obstacles during program planning and implementation phases. For instance, ToT models and CBO partnerships generally require formal agreements between funders, awardees, and partners. Grassroots organizations lacking legal departments and other administrative support may not have the capacity to properly vet proposed agreements, afford liability insurance, or provide other types of documentation that government agencies may require. Similar challenges are present for informal groups and associations that are organized by community members rather than formal institutions. Such barriers can slow down onboarding processes and delay program implementation. Monthly CBO workgroups may act as resource-sharing opportunities for large, well-equipped organizations to assist more resource-limited groups.

Some challenges specific to the correctional facility setting are related to special restrictions and policies that may interfere with best practices for health program delivery. For example, due to the COVID-19–related anticomingling policy, informational sessions for residents must take place in housing units of 35 to 40 people. Depending on the number of voluntary participants per housing unit, discussion group sizes may exceed the recommended maximum size of 30 learners per unit. To ensure that quality of the discussion is maintained, program officers who are experienced in leading larger discussions among residents will lead health information sessions. Similarly, correctional officers leading discussions for fellow officers are accustomed to instructing large groups in this setting. Finally, because the rate of vaccine uptake among correctional officers is generally low, it is a challenge to recruit discussion leaders who support vaccination and other health measures that are emphasized in the program curriculum.

Despite these challenges, program implementation may have lasting effects that result in long-term health improvement and subsequent cost savings. For example, establishing trust and understanding can aid effective health communication and resource-sharing in future health emergencies. In addition, investing in programs that motivate health literacy skills through dialogue can lead to more preventive health behaviors at the population level, reducing the potential costs associated with emergency services utilization [59]. Findings from this study will be used to make recommendations and develop best practices for future health programs.

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Community Responses to COVID-19 program seeks to demonstrate the effectiveness of local government implementation of evidence-based health literacy strategies that are culturally appropriate to enhance COVID-19 testing, contact tracing, and/or other mitigation measures (eg, public health prevention practices and vaccination) in racial and ethnic minority populations and other socially vulnerable populations, including racial and ethnic minority rural communities. OMH expects the awardee projects to demonstrate the effectiveness of working with local community-based organizations to develop health literacy plans to increase the availability, acceptability, and use of COVID-19 public health information and services by racial and ethnic minority populations. Recipients are also expected to leverage local data to identify racial and ethnic minority populations at the highest risk for health disparities and low health literacy, as well as populations not currently reached through existing public health campaigns.

Authors' Contributions

FK and SK led the overall program and study design resulting in the successful HHS grant application, led the writing of the application for Mercy College IRB and Pace University IRB approval, and led the writing of this manuscript. MC made contributions to the overall study design, survey instrument design, data collection procedures for the community-based branch of the program, application for Mercy College IRB approval, and the editing of this manuscript. KC-C made contributions to the overall study design and data collection procedures for the correctional facility–based branch of the program, application for Pace University IRB approval, and the editing of this manuscript. CD and AW made contributions to the overall study design, survey instrument design, and the editing of this manuscript. DHJ is the principal investigator of this project, providing supervision on all program design and evaluation planning documents, and edited this protocol paper. All authors read, edited, and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Externally reviewed by: Office of Minority Health, United States Department of Health and Human Services.
[PDF File (Adobe PDF File), 121 KB - resprot_v11i10e37713_app1.pdf]

References

1. Griffin JB, Haddix M, Danza P, Fisher R, Koo TH, Traub E, et al. SARS-CoV-2 infections and hospitalizations among persons aged ≥16 years, by vaccination status - Los Angeles County, California, May 1-July 25, 2021. MMWR Morb Mortal Wkly Rep 2021 Aug 27;70(34):1170-1176. [doi: 10.15585/mmwr.mm7034e5] [Medline: 34437525]
2. COVID Data Tracker Weekly Review.22 January. Centers for Disease Control and Prevention. 2022 Jan 20. URL: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html [accessed 2022-01-26]
3. American Hospital Association. AHA, AMA, ANA urge for widespread vaccination and booster shots during holiday season as Omicron variant spreads. PR Newswire. 2021 Dec 21. URL: https://tinyurl.com/dbjxz88s [accessed 2022-01-26]
4. Coustasse A, Kimble C, Maxik K. COVID-19 and vaccine hesitancy: a challenge the United States must overcome. J Ambul Care Manage 2021;44(1):71-75. [doi: 10.1097/JAC.0000000000000360] [Medline: 33165121]
5. Nguyen L, Joshi A, Drew D, Merino J, Ma W, Lo C, et al. Racial and ethnic differences in COVID-19 vaccine hesitancy and uptake. medRxiv. 2021 Feb 28. URL: https://www.medrxiv.org/content/10.1101/2021.02.25.21252402v1 [accessed 2022-01-26]
6. Paul E, Steptoe A, Fancourt D. Attitudes towards vaccines and intention to vaccinate against COVID-19: implications for public health communications. Lancet Reg Health Eur 2021 Feb;1:100012 [FREE Full text] [doi: 10.1016/j.lanepe.2020.100012] [Medline: 33954296]
7. Chen J, Krieger N. Revealing the unequal burden of COVID-19 by income, race/ethnicity, and household crowding: US county versus zip code analyses. J Public Health Manag Pract 2021;27 Suppl 1, COVID-19 and Public Health: Looking Back, Moving Forward:S43-S56. [doi: 10.1097/PHH.0000000000001263] [Medline: 32956299]
8. Martin CA, Jenkins DR, Minhas JS, Gray LJ, Tang J, Williams C, Leicester COVID-19 consortium. Socio-demographic heterogeneity in the prevalence of COVID-19 during lockdown is associated with ethnicity and household size: Results from an observational cohort study. EClinicalMedicine 2020 Aug;25:100466 [FREE Full text] [doi: 10.1016/j.eclinm.2020.100466] [Medline: 32840492]
9. Vahidy FS, Nicolas JC, Meeks JR, Khan O, Pan A, Jones SL, et al. Racial and ethnic disparities in SARS-CoV-2 pandemic: analysis of a COVID-19 observational registry for a diverse US metropolitan population. BMJ Open 2020 Aug 11;10(8):e039849 [FREE Full text] [doi: 10.1136/bmjopen-2020-039849] [Medline: 32784264]
10. Bailey ZD, Feldman JM, Bassett MT. How structural racism works - racist policies as a root cause of U.S. racial health inequities. N Engl J Med 2021 Feb 25;384(8):768-773. [doi: 10.1056/NEJMms2025396] [Medline: 33326717]

11. Kabarriti R, Brodin NP, Maron MI, Guha C, Kalnicki S, Garg MK, et al. Association of race and ethnicity with comorbidities and survival among patients with COVID-19 at an urban medical center in New York. JAMA Netw Open 2020 Sep 01;3(9):e2019795 [FREE Full text] [doi: 10.1001/jamanetworkopen.2020.19795] [Medline: 32975574]
12. Yearby R, Mohapatra S. Law, structural racism, and the COVID-19 pandemic. J Law Biosci 2020 Jan;7(1):lsaa036 [FREE Full text] [doi: 10.1093/jlb/lsaa036] [Medline: 32879732]
13. Feinberg IZ, Owen-Smith A, O'Connor MH, Ogrodnick MM, Rothenberg R, Eriksen MP. Strengthening culturally competent health communication. Health Secur 2021 Jun 01;19(S1):S41-S49. [doi: 10.1089/hs.2021.0048] [Medline: 33961489]
14. Choi S, Davis C, Cummings S, Van Regenmorter C, Barnett M. Understanding service needs and service utilization among older Kurdish refugees and immigrants in the USA. Int Soc Work 2013 Jun 05;58(1):63-74. [doi: 10.1177/0020872812471694]
15. McFadden SM, Demeke J, Dada D, Wilton L, Wang M, Vlahov D, et al. Confidence and hesitancy during the early roll-out of COVID-19 vaccines among Black, Hispanic, and undocumented immigrant communities: a review. J Urban Health 2022 Feb 23;99(1):3-14 [FREE Full text] [doi: 10.1007/s11524-021-00588-1] [Medline: 34940933]
16. Savoia E, Piltch-Loeb R, Goldberg B, Miller-Idriss C, Hughes B, Montrond A, et al. Predictors of COVID-19 vaccine hesitancy: socio-demographics, co-morbidity, and past experience of racial discrimination. Vaccines 2021 Jul 09;9(7):767 [FREE Full text] [doi: 10.3390/vaccines9070767] [Medline: 34358184]
17. Spencer MS, Chen J. Effect of discrimination on mental health service utilization among Chinese Americans. Am J Public Health 2004 May;94(5):809-814. [doi: 10.2105/ajph.94.5.809] [Medline: 15117705]
18. Artiga S, Hill L, Haldar S. COVID-19 cases and deaths by race/ethnicity: current data and changes over time. Kaiser Family Foundation. 2021. URL: https://www.kff.org/racial-equity-and-health-policy/issue-brief/covid-19-cases-and-deaths-by-race-ethnicity-current-data-and-changes-over-time/ [accessed 2022-01-26]
19. Valway SE, Greifinger RB, Papania M, Kilburn JO, Woodley C, DiFerdinando GT, et al. Multidrug-resistant tuberculosis in the New York State prison system, 1990-1991. J Infect Dis 1994 Jul 01;170(1):151-156. [doi: 10.1093/infdis/170.1.151] [Medline: 8014491]
20. Williams B, Ahalt C, Cloud D, Augustine D, Rorvig L, Sears D, et al. Correctional facilities in the shadow of COVID-19: unique challenges and proposed solutions. Health Aff 2020 Mar 26:10 [FREE Full text] [doi: 10.1377/forefront.20200324.784502]
21. Collica-Cox K, Molina L. A case study of the Westchester County New York's jail response to COVID-19: controlling COVID while balancing service needs for the incarcerated-A national model for jails. Victims Offenders 2020 Oct 21;15(7-8):1305-1316. [doi: 10.1080/15564886.2020.1820923]
22. Reinhart E, Chen DL. Association of jail decarceration and anticontagion policies with COVID-19 case growth rates in US counties. JAMA Netw Open 2021 Sep 01;4(9):e2123405 [FREE Full text] [doi: 10.1001/jamanetworkopen.2021.23405] [Medline: 34473257]
23. Malloy GSP, Puglisi L, Brandeau ML, Harvey TD, Wang EA. Effectiveness of interventions to reduce COVID-19 transmission in a large urban jail: a model-based analysis. BMJ Open 2021 Feb 17;11(2):e042898 [FREE Full text] [doi: 10.1136/bmjopen-2020-042898] [Medline: 33597139]
24. Lewis N, Sisak M. "Hell No": Correctional officers are declining the coronavirus vaccine en masse. The Marshall Project. 2021. URL: https://www.themarshallproject.org/2021/03/15/hell-no-correctional-officers-are-declining-the-coronavirus-vaccine-en-masse [accessed 2022-01-26]
25. Barsky BA, Reinhart E, Farmer P, Keshavjee S. Vaccination plus decarceration - stopping Covid-19 in jails and prisons. N Engl J Med 2021 Apr 29;384(17):1583-1585. [doi: 10.1056/NEJMp2100609] [Medline: 33657290]
26. Dada D, Djiometio JN, McFadden SM, Demeke J, Vlahov D, Wilton L, et al. Strategies that promote equity in COVID-19 vaccine uptake for Black communities: a review. J Urban Health 2022 Feb 11;99(1):15-27 [FREE Full text] [doi: 10.1007/s11524-021-00594-3] [Medline: 35018612]
27. National Action Plan to improve health literacy. Office of Disease Prevention and Health Promotion. U.S. Department of Health and Human Services. 2021 Aug 24. URL: https://health.gov/our-work/national-health-initiatives/health-literacy/national-action-plan-improve-health-literacy [accessed 2022-01-26]
28. FY 2021 Notice of Funding Opportunities. US Department of Health and Human Services Office of Minority Health. URL: http://www.minorityhealth.hhs.gov/omh/Content.aspx?ID=21530&lvl=2&lvlid=102 [accessed 2022-01-26]
29. Freire P. Pedagogy of the oppressed. New York: Bloomsbury Academic; 1970:87-97.
30. Giroux HA. Culture, power and transformation in the work of Paulo Freire. In: Schultz F, editor. S.O.U.R.C.E.S: Notable Selections in Education. New York: McGraw-Hill; 2001:77-86.
31. Wiggins N. Popular education for health promotion and community empowerment: a review of the literature. Health Promot Int 2012 Sep 11;27(3):356-371. [doi: 10.1093/heapro/dar046] [Medline: 21835843]
32. Lee S, Schorr E, Hadidi NN, Kelley R, Treat-Jacobson D, Lindquist R. Power of peer support to change health behavior to reduce risks for heart disease and stroke for African American men in a faith-based community. J Racial Ethn Health Disparities 2018 Oct 1;5(5):1107-1116. [doi: 10.1007/s40615-018-0460-7] [Medline: 29392680]
33. McGinnies E, Ward CD. Better Liked than Right. Pers Soc Psychol Bull 2016 Jul 02;6(3):467-472. [doi: 10.1177/014616728063023]

34. Reznitskaya A, Kuo L, Clark A, Miller B, Jadallah M, Anderson RC, et al. Collaborative reasoning: a dialogic approach to group discussions. Cambridge J Educ 2009 Nov 13;39(1):29-48. [doi: 10.1080/03057640802701952]
35. Momplaisir F, Haynes N, Nkwihoreze H, Nelson M, Werner R, Jemmott J. Understanding drivers of coronavirus disease 2019 vaccine hesitancy among Blacks. Clin Infect Dis 2021 Nov 16;73(10):1784-1789 [FREE Full text] [doi: 10.1093/cid/ciab102] [Medline: 33560346]
36. Iyasere J, Garcia A, Prabhu D, Procaccino A, Spaziani K. Trustworthy and trusted: strategies to improve confidence in Covid-19 vaccines. NEJM Catalyst Innovations in Care Delivery 2021 Apr 01;2(2):1-7 [FREE Full text] [doi: 10.1056/CAT.21.0046]
37. Datiko DG. Peer education in prisons to improve tuberculosis case finding. Lancet Glob Health 2019 Apr;7(4):e396-e397 [FREE Full text] [doi: 10.1016/S2214-109X(18)30566-7] [Medline: 30824365]
38. Thornton K, Sedillo ML, Kalishman S, Page K, Arora S. The New Mexico Peer Education Project: filling a critical gap in HCV prison education. J Health Care Poor Underserved 2018;29(4):1544-1557. [doi: 10.1353/hpu.2018.0111] [Medline: 30449762]
39. Wright N, Bleakley A, Butt C, Chadwick O, Mahmood K, Patel K, et al. Peer health promotion in prisons: a systematic review. Int J Prison Health 2011;7(4):37-51. [doi: 10.1108/17449201111256899] [Medline: 25757711]
40. South J, Bagnall A, Hulme C, Woodall J, Longo R, Dixey R, et al. A systematic review of the effectiveness and cost-effectiveness of peer-based interventions to maintain and improve offender health in prison settings. Health Serv Deliv Res 2014;2(35):1-217. [doi: 10.3310/hsdr02350]
41. Dubik-Unruh S. Peer education programs in corrections: curriculum, implementation, and nursing interventions. J Assoc Nurses AIDS Care 1999;10(6):53-62. [doi: 10.1016/S1055-3290(06)60321-X] [Medline: 10546174]
42. Ross MW. Pedagogy for prisoners: an approach to peer health education for inmates. J Correct Health Care 2011 Jan 01;17(1):6-18. [doi: 10.1177/1078345810378251] [Medline: 20810874]
43. Arbaugh J, Benbunan-Fich R. Contextual factors that influence ALN effectiveness. In: Hiltz SR, Goldman R, editors. Learning together online: Research on asynchronous learning networks. Milton Park, UK: Routledge; 2005:123-144.
44. Fox S. Optimal class size for online education in Pasifika contexts. Micronesian Educator 2021;30:69-73. [doi: 10.4135/9781483318332.n62]
45. Sørensen K, Pelikan JM, Röthlin F, Ganahl K, Slonska Z, Doyle G, HLS-EU Consortium. Health literacy in Europe: comparative results of the European health literacy survey (HLS-EU). Eur J Public Health 2015 Dec 05;25(6):1053-1058 [FREE Full text] [doi: 10.1093/eurpub/ckv043] [Medline: 25843827]
46. Understanding America Study. UAS230 Survey Questionnaire. University of South California. URL: https://uasdata.usc.edu/index.php [accessed 2021-04-20]
47. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009 Apr;42(2):377-381 [FREE Full text] [doi: 10.1016/j.jbi.2008.08.010] [Medline: 18929686]
48. Fu X. How does openness affect the importance of incentives for innovation? Research Policy 2012 Apr;41(3):512-523. [doi: 10.1016/j.respol.2011.12.011]
49. Rowhani-Farid A, Allen M, Barnett AG. What incentives increase data sharing in health and medical research? A systematic review. Res Integr Peer Rev 2017;2:4 [FREE Full text] [doi: 10.1186/s41073-017-0028-9] [Medline: 29451561]
50. Achat H, McIntyre P, Burgess M. Health care incentives in immunisation. Aust N Z J Public Health 1999 Jun;23(3):285-288. [doi: 10.1111/j.1467-842x.1999.tb01257.x] [Medline: 10388173]
51. Corbin JM, Strauss A. Grounded theory research: Procedures, canons, and evaluative criteria. Qual Sociol 1990;13(1):3-21. [doi: 10.1007/bf00988593]
52. Strauss A, Corbin J. Grounded theory methodology: an overview. In: Denzin NK, Lincoln YS, editors. Handbook of qualitative research. Thousand Oaks, CA: Sage Publications; 1994:273-281.
53. Cheadle A, Hsu C, Schwartz PM, Pearson D, Greenwald HP, Beery WL, et al. Involving local health departments in community health partnerships: evaluation results from the partnership for the public's health initiative. J Urban Health 2008 Mar 8;85(2):162-177 [FREE Full text] [doi: 10.1007/s11524-008-9260-4] [Medline: 18259870]
54. Bloemraad I, Terriquez V. Cultures of engagement: The organizational foundations of advancing health in immigrant and low-income communities of color. Soc Sci Med 2016 Sep;165:214-222 [FREE Full text] [doi: 10.1016/j.socscimed.2016.02.003] [Medline: 26898114]
55. Everett J, Colombatto C, Chituc V, Brady W, Crockett M. The effectiveness of moral messages on public health behavioral intentions during the COVID-19 pandemic. PsyArXiv. 2020. URL: https://psyarxiv.com/9yqs8/ [accessed 2022-01-26]
56. Wiggins N, Pérez A. Using popular education with health promotion students in the USA. Health Promot Int 2017 Aug 01;32(4):660-670. [doi: 10.1093/heapro/dav121] [Medline: 26851226]
57. Repper J, Aldridge B, Gilfoyle S, Gillard S, Perkins R, Rennison J. Peer support workers: theory and practice. Centre for Mental Health. 2013 Jun 05. URL: https://www.centreformentalhealth.org.uk/publications/peer-support-workers-theory-and-practice [accessed 2022-01-26]
58. Mormina M, Pinder S. A conceptual framework for training of trainers (ToT) interventions in global health. Global Health 2018 Oct 22;14(1):100 [FREE Full text] [doi: 10.1186/s12992-018-0420-3] [Medline: 30348183]

59. Johansson T, Keller S, Sönnichsen AC, Weitgasser R. Cost analysis of a peer support programme for patients with type 2 diabetes: a secondary analysis of a controlled trial. Eur J Public Health 2017 Apr 01;27(2):256-261. [doi: 10.1093/eurpub/ckw158] [Medline: 27694160]

Abbreviations

AHL: Advancing Health Literacy to Enhance Equitable Community Responses to COVID-19
CBO: community- and faith-based organization
DOC: Department of Correction
DOH: Department of Health
HHS: US Department of Health and Human Services
HLS-EU: European Health Literacy Survey
IRB: Institutional Review Board
KBLB: Know Better, Live Better
OMH: Office of Minority Health
REDCap: Research Electronic Data Capture
SVI: social vulnerability index
ToT: training of trainers

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Protocol

Community-Engaged Intervention Mapping for Cardiovascular Disease Prevention in Black and Latinx Sexual Minority Men With HIV in New York City: Protocol for a Web-Based Mixed Methods Study

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Abstract

Background: Approximately every 37 seconds, someone in the United States dies of cardiovascular disease (CVD). It has emerged as an important contributor to morbidity among persons with HIV. Black and Latinx sexual minority men are at higher risk of both HIV and CVD when compared to heterosexual, nonethnic or minority men. Persons with HIV have a 1.5 to 2-times risk of having CVD than do HIV-negative persons. Data suggest that by the year 2030, an estimated 78% of persons with HIV will have CVD. The relationship between HIV and CVD in marginalized populations is not well understood because overall awareness of HIV and CVD as comorbid conditions is low, which further heightens risk. This has created a critically pressing issue affecting underrepresented ethnic and racial populations with HIV and requires immediate efforts to mitigate risk.

Objective: The purpose of this formative, mixed methods study is to use a community-engaged approach to map a behavioral intervention for CVD prevention in Black and Latinx sexual minority men with HIV in New York City.

Methods: Literature reviews focused on behavioral prevention studies using intervention mapping. In Aim 1, we will use qualitative interviews with HIV program managers and community members to understand facilitators and barriers to CVD prevention, chronic illnesses of concern, and early design elements needed for a web-based CVD prevention intervention. In Aim 2, we will conduct qualitative interviews and administer cross-sectional validated surveys with 30 Black and Latinx sexual minority men with HIV. We will assess illness perceptions of chronic conditions, such as HIV, hypertension, and diabetes. A total of 40 participants (program managers and community members) for Aims 1 and 2 will be enrolled to participate. To develop the protocol, we will follow steps 1 through 3 (needs assessment, change objectives, implementation strategy) of intervention mapping, using mixed methods.

Results: The study was approved by New York University Institutional Review Board in February 2021 (IRB-FY2021-4772) and also by the Yale University Institutional Review Board in June 2022 (#2000031577). We anticipate completing data collection on or before December 2022. Early analyses suggested concerns about illnesses outside of HIV and associated comorbid conditions, such as COVID-19 and monkeypox. Additionally, we noted a strong interest in using a web-based platform for CVD prevention education.

Conclusions: Web-based, behavioral, CVD prevention interventions may be promising modalities to closing the cardiovascular health disparities gap in Black and Latinx sexual minority men with HIV by extending the reach of prevention interventions using community-informed approaches and technological modalities that have been underused in this population.

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KEYWORDS

intervention mapping; CVD; eHealth intervention; HIV; sexual minority men; Black men; Latinx; community engagement; men who have sex with men; community based; qualitative; survey

Introduction

Background

Cardiovascular disease (CVD) and HIV are 2 chronic conditions that are often comorbid in the presence of HIV. Persons with HIV are at higher risk of CVD than are HIV-negative persons. Specifically, persons with HIV have a 1.5 to 2-times higher risk of CVD [1]. In the United States, a person dies of CVD approximately every 37 seconds [2]. According to 2018 data, it is the leading cause of death in the United States and accounts for more deaths than does cancer and chronic respiratory illnesses combined [2]. In 2019, it was estimated that over 18 million deaths were due to CVD [2]. The consequences of CVD are also costly, with average expenditures in 2016-2017 estimating upward of US $364 billion dollars [2]. Although the costs of CVD are high, these costs exponentially increase when combined with other chronic conditions, such as HIV.

Higher CVD risk in those with HIV is linked to increased inflammation and hyperstimulation of the immune system [3]. The analysis of 3 large international HIV treatment trials suggested that higher interleukin 6 and D-dimer levels reflecting inflammation and coagulation associated with HIV are also associated with an increased risk of fatal CVD and a greater risk of death following a nonfatal CVD event [3]. Recent publications linked CVD with inflammation and antiretroviral treatment associated with HIV [4,5]. Furthermore, risk factors of coronary heart disease (eg, smoking, diet) as well as nontraditional risk factors (eg, hepatitis C, substance use) should also be considered in persons with HIV [5,6]. A 2020 study noted the existence of promising treatments and medications for inflammation and atherosclerotic CVD (ASCVD); however, these treatments have yet to show similar significant results for treating HIV-associated CVD [5]. Estimated 10-year CVD risk is highest in Black men (8.3%) and Latinx men (4.4%) with HIV when compared to nonminoritized HIV-negative individuals [7] and remains a significant pressing health issue toward cardiovascular health equity.

HIV Health Disparities Impacting Advancement of Cardiovascular Health in Sexual Minority Men

Over the course of 9 years (2010-2019), the incidence in HIV diagnoses has shifted disproportionally in racial and ethnic populations [8]. For example, in 2021, sexual minority men (herein referring to persons who identify as nonheterosexual, gay, bisexual, queer, or same-gender loving) accounted for two-thirds of all new HIV infections [8]. Black and Latinx populations have shown little to no decrease in HIV diagnoses [8].Whereas, the number of new HIV infections in White persons decreased from 7500 to 5100 (per 100,000 people) [8]. Data trends suggest that HIV prevention efforts have fared better in nonminoritized ethnic and racial populations. By the year 2030, an estimated 78% of persons with HIV will have CVD [9]. A 2016 study examining CVD risk in a West African population showed that for every 10 participants in their 256 person sample, 8 had at least 2 CVD risk factors [10]. The prevalence of CVD in persons of color is significant and calls for immediate interventions [11], especially within sexual minority men of color with HIV. To address this, interventions must be focused on improving cardiovascular health and be tailored to communities who are at highest risk.

Matrices of Cardiovascular Risk

The American Heart Association created the Life's Simple 7 (LS7), a tool developed to assess cardiovascular health risks. The overall goal of this tool is to promote cardiovascular health related to 4 modifiable lifestyle risk factors (diet, smoking, BMI, physical activity) and 3 biometric measures (blood pressure, cholesterol, and blood sugar) [11]. Each category is divided into 3 scoring levels (poor = 0, intermediate =1, ideal =2) with an optimal total score of 11 to 14, an average score of 9 to 10, and an inadequate score of 0 to 8. By using this tool, areas for improvement in cardiovascular health can be identified in those with HIV who carry high CVD risk.

A longitudinal study comparing the different risk factors of ASCVD within persons with HIV observed that age, diabetes mellitus, current smoking status, hypertension, and dyslipidemia were associated with an elevated risk of ASCVD [12]. Another study showed the use of LS7 lowered CVD risks by roughly 78% compared to those that did not follow any of the metrics [13]. The Reprieve study, a prospective, double-blind, placebo-controlled, multicenter, phase III efficacy trial, observed CVD risk factors in a sample of over 7500 persons with HIV. Findings suggested that ideal cardiovascular health was driven by lower BMI and less smoking [12]. HIV-specific risk

prediction models have also been in use to study persons with HIV. The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) model, developed in 2010, provides additional CVD risk factors that include CD4 counts, use of abacavir, and cumulative use of nucleoside reverse transcriptase inhibitors and protease inhibitors [14,15]. Although the D:A:D study incorporated a persons-with-HIV cohort that was predominantly European [7], it is important to note the additional factors that should be considered in this population, specifically assessing diverse populations, genders, and populations in low-and middle-income countries with HIV [16]. LS7 and the D:A:D model are promising tools to facilitate improvements in cardiovascular health and CVD risk in persons with HIV [16,17].

Formative Development of a Community-Engaged, Web-Based CVD Prevention Protocol for Persons With HIV

To address the prevention of CVD and improve the cardiovascular health equity in Black and Latinx sexual minority men who are at the greatest risk, this study will use a tailored, community-engaged approach. Specifically, the study will be formative and intended to develop a protocol for a web-based, CVD behavioral intervention. The premise for this study originates from qualitative data from a larger parent study where preliminary findings suggest that sexual minority men of color with HIV are interested in technology-based, health-related, prevention education [18,19]. Additionally, there are limited studies using nonpharmacologic behavioral interventions to prevent CVD in sexual minority men of color with HIV [20]. To accomplish this goal, the study will be guided by intervention mapping. Intervention mapping prioritizes active participation of relevant stakeholders in the development process and acknowledges the complex intersectionality of influences (eg, individual, interpersonal, organizational, societal) on health outcomes [21]. Additionally, intervention mapping has been used in HIV research to foster collaboration between the researchers and the participants, allowing researchers to develop interventions that appeal to the needs of those they aimed to help [22]. These factors are key for the intervention program currently being developed, as levels of collaboration and common understanding between researchers and participants will help ensure that the partner communities are actively engaged in the intervention process. Intervention mapping consists of 6 steps but is by no means a linear process. The process is iterative and bidirectional with program developers moving between steps as they gain new information and perspective [23].

Study Objectives

Acknowledging the lack of interventions to promote cardiovascular health equity in sexual minority men of color with HIV, we propose a tailored, community-engaged, web-based approach to prevention. Over the years, there has been an increase in web-based behavioral interventions. Given the ubiquity of technology, even among very low-income communities, web-based interventions have shown great promise as a modality for behavioral interventions. Using intervention mapping, participants will inform the researchers of intervention components that are necessary for engagement and knowledge building using a web-based platform. We have two aims: (1) engage 10 HIV program managers already engaged in health-related programming in New York City to explore the facilitators and barriers to developing a web-based, intervention mapping protocol for CVD prevention; and (2) develop a community-engaged, intervention mapping protocol for CVD prevention with 30 Black and Latinx sexual minority men. We anticipate that this formative work will result in a relevant and actionable protocol to be implemented using a web-based platform. The study design and objectives are advantageous to addressing the critical health equity gap in CVD incidence. They are also advantageous to increasing engagement and potential for behavioral change, as the protocol is informed by community members and not exclusively by empirical work. We expect that this will make the web-based content more relevant to the needs of participants, which in turn may increase recruitment, retention, and behavioral outcomes.

Framework

Intervention mapping is an approach in which researchers design interventions through exploring the needs of the community [21]. Intervention mapping uses six steps: (1) develop a deeper understanding of the population and problem being studied, (2) determine the main issues of the overall problem and identify the best possible outcome if changes were made, (3) create intervention methods based on the identified issues in order to reach the positive outcomes, (4) use the intervention methods to create an intervention program, (5) implement the intervention program in the studied community, and (6) analyze the results of the program in order to determine the efficacy of the interventions [23].

Intervention mapping has been used to develop interventions and methods of care for a variety of diseases throughout different populations, ranging from HIV in young adult men [24] to diabetes in African American adults [25]. Researchers often combine the evidence learned from intervention mapping with other conceptual models, such as social cognitive theory or the transtheoretical model, to determine new avenues of preventative care [26]. In certain cases, the process of intervention mapping has been used as a reference to create new tools for more specific intervention development [26]. This study will incorporate formative steps 1 through 3.

Steps to Intervention Mapping

Step 1: Logical Model of the Problem (Needs Assessment)

This step focuses on discussing the foundations of the issue being addressed to begin identifying possible changes for which interventions can be made. In this study, we focused on developing a community-engaged protocol to prevent CVD in Black and Latinx sexual minority men with HIV.

Step 2: Program Outcomes and Objectives—Logic Model of Change (Change Objectives)

This step focuses on needed changes and persons who are involved in improving the chosen health-related issue, which is CVD prevention. At this point, expected program outcomes are established through the identification of specified behaviors

[27,28] required for increasing cardiovascular health. Environmental and behavioral outcomes are then differentiated into program objectives, and changeable determinants of behavior are selected for each program objective. For each expected program outcome, program objectives are aligned with the changeable determinants in a matrix design to identify the needed changes, or the change objectives. In this study, the researchers will construct a matrix based on prior literature reviews and the data collected during both study aims with HIV program managers and community members.

Step 3: Intervention Development (Framework Strategy)

A fundamental premise of the intervention mapping process is that all developed intervention methods are grounded in theory [28]. Having specified the objectives of the intervention based on the needs assessment in step 1 and the developed matrices of change in step 2, a relevant theoretical framework will be selected as the foundation of the intervention methods and strategies to create effective matrices of change.

Diffusion of Innovations

Given the study's focus on adoption of new ideas and behaviors, diffusion of innovations is an appropriate theory and will serve as a guide for this study. Diffusion of innovations [27] is an iterative process theory that focuses on understanding how "new ideas, practices and technologies" are spread through social networks and grow in familiarity to best facilitate adopting the innovation [29,30]. The theory proposes that there are five key [27] components to the successful uptake of innovative behavior: (1) the attributes of the innovation; (2) the adopters and their degree of innovativeness (ie, earliness to adoption); (3) the structure of the target social system and its opinion leaders, who can influence others' attitudes or behaviors with relative frequency; (4) the individual adoption process; and (5) the diffusion system, comprising the change agency and its agents who introduce the desired innovation to the social system [29]. A change agency is a conglomerate of individuals (ie, change agents) that act as influencers for acceptance of the proposed innovation [27,31]. The influencers are often external to the targeted social network in which they are encouraging uptake of the proposed innovation [32,33].

Five categories of adopters exist in this theory: (1) innovators, (2) early acceptors, (3) early majority, (4) late majority, and (5) laggards [27]. Innovators, who often have high tolerance for ambiguity and often take more risk, are the very first people to adopt an innovation [27]. Early acceptors are next to adopt an innovation after judicious appraisal of an innovation's advantages and disadvantages [27]. The early majority subsequently adopt an innovation due to social pressure, exhibiting an imitative effect [27]. The late majority are similarly influenced through social pressure but tend to be more skeptical and cautious [27]. Laggards, who are less susceptible to social pressure, take their time before adopting an innovation and may even resist the proposed innovation [27].

The theory has previously been applied across various innovative health interventions, such as an online-offline hybrid sexual health intervention among high-risk youth [34], a culturally specific individual-level peer navigation intervention among sexual minority men of color [35], and a peer-led social media–based intervention of HIV pre-exposure prophylaxis adoption [36]. For this study, the 5 key components of the diffusion of innovations theory are best suited to describe stages of adoption toward cardiovascular health.

Methods

Ethics Approval

All procedures performed in this study are in accordance with the ethical standards of the institutional and national research committee, the 1964 Helsinki Declaration and its later amendments, or comparable ethical standards. This study was funded by the National Heart, Lung, and Blood Institute (#R25HL105446) as a subaward through the SUNY Downstate Medical Center and through the Fund for Gay and Lesbian Studies (FLAGS), LGBT Studies at Yale University. Approval was obtained from the New York University Institutional Review Board in February 2021 (IRB-FY2021-4772) and by the Yale University Institutional Review Board in June 2022 (#2000031577). Informed consent will be obtained from all participants who meet the eligibility criteria and agree to participate. All participants who complete either Aim 1 or 2 will receive a US $45 gift card.

Study Design

We are conducting a 2-phase, mixed methods, community-informed study in New York City.

Eligibility criteria includes the following: identifying as a sexual minority male (nonheterosexual), living with HIV, being a community member engaged in HIV programming in New York City, being 30 to 65 years old, having internet access, and self-identifying as being from a racial or ethnic minoritized background. It is documented that chronic illness is becoming diagnosed at earlier stages of life, with the highest prevalence at ages 50 years and above [37]. Data from the Million Hearts study found that more than 30% of life-changing cardiac events were in adults as young as 35 years of age [38]. Our sample age range is appropriate given the changing age demographic of chronic illness.

Participant Recruitment

We are partnering with a premier urban health institute in New York City whose mission is to directly address health disparities through community-engagement and partnership to facilitate behavior change and informed health decision-making. Participants will be recruited from community-based organizations within New York City. Program managers will inform clients about the study through word of mouth, during activities with clients, and through posted or digital flyers. Interested persons who meet eligibility criteria will be scheduled to be consented and participate in the qualitative interviews. We anticipate that we will be able to successfully recruit a diverse sample by partnering with a community-based organization and because of the diversity of the New York City demographics. New York City (inclusive of its boroughs) is one of the most ethnic and racially diverse cities in the nation. According to the 2021 Census, New York City is 28.9% Hispanic and 23.8% Black [39]. The Bronx borough is 56.4%

Hispanic and 43.8% Black, the Brooklyn borough is 18.8% Hispanic and 33.3% Black, and the Queens borough is 28.1% Hispanic and 20.7% Black [39]. Moreover, Behavioral Risk Factor Surveillance System (BRFSS) data suggest that 9.2% of adults in New York City self-identify as lesbian, gay, bisexual, or other [40].

Procedures

Aim 1

In Aim 1, web-based focus group interviews using Zoom (Zoom Video Communications) with 10 key informants, including HIV program managers and community members at both the organizational and community levels, will be used to explore community-level barriers and facilitators to CVD prevention. Program managers are able to provide expert, public health–and community-informed perspectives about risk and external factors affecting prevention efforts. They can also address tailored strategies that may be helpful to mitigate CVD risk. It is important to include program managers and community members in Aim 1 to ensure both perspectives coalesce to provide a thorough and unbiased understanding of risk and community needs. A qualitative interview guide with 5 open-ended questions will be used, for example, "Tell me about how health-related community needs have been addressed in the past? How have strategies been most successful?" After completion of Aim 1, we will have identified barriers and facilitators (needs assessment) to community-based CVD prevention. These data will be used in the preliminary design (program objectives) of the intervention mapping protocol. Previous qualitative research approaches suggest that data saturation is reached when there is no longer new emerging data.

Aim 2

In Aim 2, web-based semistructured interviews will be conducted using Zoom with up to 30 community members, who will be individually interviewed, and will explore HIV-related chronic conditions of concern, barriers, and facilitators to CVD prevention. Qualitative interviews will explore technology-enabled design strategies and intervention components and materials that are responsive to identified community needs. After qualitative data collection for Aim 2, we will expect to have collected the necessary data (practical strategies, program components, and materials) for a tailored, behavioral, CVD prevention study. Additionally, to further examine health perceptions, engagement in physical activity, and nicotine use, we will administer survey questionnaires. Based on qualitative frameworks, our community members (N=30) is within standard sample size to achieve saturation [41,42] and to also provide sufficient descriptive data on HIV illness perceptions in order to make cautious inference using a small sample [43].

Measures

International Physical Activity Questionnaire (Short Form)

The International Physical Activity Questionnaire (Short Form) is a 7-item questionnaire used in populations of adults between the ages of 15 and 64 years old. The questions are open-ended and require individuals to self-report their physical activity within the past 7 days. It has been used in several diverse populations internationally with young and middle-aged adults. An example question from this measure includes the following: "During the last 7 days, on how many days did you do vigorous physical activities like heavy lifting, digging, aerobics, or fast bicycling?" It has high reliability with a Cronbach α of <.80 and predictive validity [44].

Smoking Behaviors: The BRFSS

The BRFSS, is a 2-part telephone survey developed by the Centers for Disease Control and Prevention (CDC) to collect information regarding chronic conditions and health risk behaviors [45,46]. It is a survey used nationally as a tool to assess public health needs and priorities. We included questions on tobacco and e-cigarette use. Example questions included the following: "Have you smoked at least 100 cigarettes in your entire life?" "Have you ever used an e-cigarette or other electronic "vaping" product, even just one time, in your entire life?"

Illness Perception Questionnaire-Revised HIV

The Illness Perception Questionnaire-Revised (IPQ-R) for HIV has been adapted from the original IPQ by replacing illness with HIV [47]. The IPQ-R-HIV is an 83-item questionnaire that uses a Likert scale (1 = strongly disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, and 5 =strongly agree). The IPQ-R-HIV has a Cronbach α of .90 of and is reported to have acceptable internal consistency. The IPQ-R-HIV asks questions about views of living with HIV, symptoms associated with HIV, and symptoms associated with combination therapy. An example question from this measure includes the following: "Anti-HIV medication can control the progress of my HIV infection?" This measure has been previously tested in HIV studies with sexual minority men.

IPQ-R for Hypertension

The IPQ-R for Hypertension has been adapted from the original IPQ by replacing illness with hypertension [47]. The IPQ-R-Hypertension is an 80-item questionnaire that uses a Likert scale (1 = strongly disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, and 5 = strongly agree). The IPQ-R-Hypertension has a Cronbach α of 0.75 and is reported to have demonstrated good test - retest reliability, and predictive, concurrent, and discriminant validity. The IPQ-R-Hypertension asks questions about hypertension representation, cause, and identity. An example question includes the following: "Having this high blood pressure makes me feel anxious?" This measure has been studied in populations at risk for atrial fibrillation and other related chronic conditions.

IPQ-R for Diabetes

The IPQ-R-Diabetes has been adapted from the original IPQ by replacing illness with diabetes [47]. The IPQ-R-Diabetes is a 64-item questionnaire that uses a Likert scale (1 = strongly disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, and 5 = strongly agree). The IPQ-R-Diabetes has a Cronbach α of >0.7 of and is reported to have sufficient internal consistency. The IPQ-R-Diabetes asks questions about views

on living with diabetes and symptoms associated with diabetes. An example question from this measure includes the following: "I have experienced pain since my diabetes?" This measure has been used in international studies with populations of individuals diagnosed with type 2 diabetes.

Data Analysis

In Aim 1 and Aim 2, focus groups and semistructured interviews will be analyzed using content analysis in NVivo version 12 (QSR International). Qualitative content analysis is consistent with a formative study, as it is an inductive process and is used to develop themes using either focus groups or interviews [48].

For aim 2 questionnaires, quantitative data will be analyzed using SPSS version 28 (IBM Corp). Descriptive statistics (frequencies, means, SDs) will be used to characterize participants reported illness perceptions, 7-day physical activity, and nicotine use. We will use bivariate statistics to examine relationships between participant characteristics and reported illness perceptions. Since this is formative and noninterventional work, power analyses are not warranted.

Results

This study was approved by New York University Institutional Review Board in February 2021 (IRB-FY2021-4772) and by the Yale University Institutional Review Board in June 2022 (#2000031577). As of July 2022, we have completed data collection on over 90% of our anticipated sample and expect to compete all data collection on or before December 2022. We expect that the qualitative data will be robust and inform the necessary components for a community-informed and tailored intervention mapping protocol for CVD prevention in persons with HIV. The quantitative data will provide additional context into illness perceptions about HIV and also hypertension and diabetes, if applicable. Physical activity and nicotine use will provide further context on self-reported behavioral cardiovascular risk. Early qualitative analyses suggests concerns about conditions outside of HIV, hypertension, and diabetes, such as cancer, breathing problems, COVID-19, and monkeypox. We will have clearer insights once data collection has ended and data are analyzed on the complete sample.

Discussion

Expected Findings

The overarching aim of this formative study is to develop a community-engaged intervention mapping protocol for a web-based CVD prevention intervention in Black and Latinx sexual minority men with HIV ages 30 to 65 years. As Black and Latinx sexual minority men with HIV are at a higher relative risk for CVD, culturally competent and relevant interventions are necessary. There is a gap in the literature regarding culturally competent CVD preventative interventions for lesbian, gay, bisexual, transgender, queer, and others (LGBTQ+) populations, and this formative study addresses this cardiovascular health equity gap. We anticipate that the qualitative and quantitative data will inform us of the necessary information required for designing content for a CVD prevention, sexual minority–focused, web-based intervention in order to have maximal impact. Specifically, by using mixed methods, we will have a stronger understanding on how to tailor a CVD prevention intervention and also gain new knowledge about HIV, hypertension, diabetes, and other illness priorities in Black and Latinx men.

Technology-enabled interventions can be leveraged as innovative tools to mitigate chronic illness, as 62% of adults living with 1 or more chronic disease use online resources [49]. Technology-enabled, behavioral, CVD prevention interventions may be promising modalities to closing the cardiovascular health disparities gap in Black and Latinx sexual minority men with HIV. The Pew Research Center reported that the proportion of adults who have smartphones (and live in households with incomes less than US $30,000 thousand dollars per year) has increased by more than half [49]. Recent literature indicates that regardless of income level, a majority of persons have access to and are using the internet. According to the Williams Institute, 56% of Black LGBT adults live in low-income households (those which are below 200% of the United States federal poverty level) compared to 49% of Black heterosexual households [50]. Additionally, 37% of LGBT Latinx adults reside in a household with an annual income below US $24,000 per year [50]. This suggests increased uptake, accessibility, and use in smartphones and underscores the importance of using digital technologies to meet the increasing need of health education among Black and Latinx LGBT populations.

Strengths and Limitations

The risk of CVD in Black and Latinx sexual minority men is a pressing health challenge. We address this challenge using a community-informed approach leveraging mixed methods data collection techniques and an established intervention mapping framework. Additionally, using a community-informed approach centers the perspectives of Black and Latinx sexual minority men with HIV, who have been historically been left-out of informing the design of CVD prevention interventions. We believe that using intervention mapping will result in the design of a tailored intervention strategy that will have relevance and increase engagement. By partnering with a community-based organization serving sexual minority men of color, we are able to develop an intervention strategy that focuses on the needs of the community and that is not based in the traditional clinical setting, as engagement may vary. We believe that these are strengths of the study. Moreover, the findings from this study will be disseminated back to the community through a verbal presentation and poster of the study findings. We also plan to disseminate study results in a high-impact journal and through scientific meeting presentations.

This study is not without limitations. First, generalizability is limited given the small sample size. However, although small, the sample size is within the recommended limits for qualitative and quantitative formative inquiry. Second, qualitative data collection using focus groups are subject to group dynamics which could influence external validity [51]. However, we are mitigating bias with having a trained moderator facilitate discussions. Third, self-reported measures are subject to social desirability and response bias. We are mitigating the potential for bias and missing data by having a trained investigator.

Despite these limitations, the benefits of this study are an early, yet necessary step, in addressing a critical health disparity issue in persons with HIV.

Conclusions

Formative, mixed methods approaches to developing web-based, community-engaged, behavioral interventions for CVD prevention in ethnic and racial sexual minority men with HIV hold much promise given the uptake of technology and internet use. Conventional approaches to CVD prevention, such as traditional patient teaching in the clinical setting, in overlooked, minoritized populations may not be feasible or sustainable given the differences in social determinants, culture, and overall health priorities.

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Data Availability

The data that support the findings of this study will be available from the corresponding author (SRR) after data collection and dissemination activities have concluded. The data may be made available upon reasonable request.

Conflicts of Interest

None declared.

References

1. American Heart Association. As HIV patients live longer, heart disease might be their next challenge. https://www.heart.org/en/news/2019/06/03/as-hiv-patients-live-longer-heart-disease-might-be-their-next-challenge. 2019. URL: https://www.heart.org/en/news/2019/06/03/as-hiv-patients-live-longer-heart-disease-might-be-their-next-challenge [accessed 2022-05-10]
2. Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS, et al. Heart disease and stroke statistics' 2022 update: a report from the American Heart Association. Circulation 2022 Feb 22;145(8):e153-e639 [FREE Full text] [doi: 10.1161/CIR.0000000000001052] [Medline: 35078371]
3. Nordell AD, McKenna M, Borges ÁH, Duprez D, Neuhaus J, Neaton JD, INSIGHT SMART, ESPRIT Study Groups, SILCAAT Scientific Committee. Severity of cardiovascular disease outcomes among patients with HIV is related to markers of inflammation and coagulation. J Am Heart Assoc 2014 May 28;3(3):e000844 [FREE Full text] [doi: 10.1161/JAHA.114.000844] [Medline: 24870935]
4. Baker J, Sharma S, Achhra A, Bernardino J, Bogner J, Duprez D, et al. Changes in cardiovascular disease risk factors with immediate versus deferred antiretroviral therapy initiation among HIV?positive participants in the START (Strategic Timing of Antiretroviral Treatment) Trial. JAHA 2017 May 05;6(5):e004987. [doi: 10.1161/jaha.116.004987]
5. Titanji B, Gavegnano C, Hsue P, Schinazi R, Marconi V. Targeting inflammation to reduce atherosclerotic cardiovascular risk in people with HIV infection. JAHA 2020 Feb 04;9(3):e014873. [doi: 10.1161/jaha.119.014873]
6. Freiberg MS, So-Armah K. HIV and cardiovascular disease: we need a mechanism, and we need a plan. J Am Heart Assoc 2016 Mar 24;4(3):e003411 [FREE Full text] [doi: 10.1161/JAHA.116.003411] [Medline: 27013540]
7. Liang Y, Ketchum NS, Turner BJ, Flores J, Bullock D, Villarreal R, et al. Cardiovascular risk assessment varies widely by calculator and race/ethnicity in a Majority Latinx cohort living with HIV. J Immigr Minor Health 2020 Apr;22(2):323-335. [doi: 10.1007/s10903-019-00890-w] [Medline: 31004259]
8. CDC. HIV and gay and bisexual men differences in knowledge of status, prevention, treatment, and stigma exist by race/ethnicity. Vital Signs 2021. URL: https://www.cdc.gov/vitalsigns/hivgaybimen/index.html [accessed 2022-06-29]
9. Smit M, Brinkman K, Geerlings S, Smit C, Thyagarajan K, Sighem AV, et al. Future challenges for clinical care of an ageing population infected with HIV: a modelling study. The Lancet Infectious Diseases 2015 Jul;15(7):810-818. [doi: 10.1016/s1473-3099(15)00056-0]
10. Commodore‐Mensah Y, Hill M, Allen J, Cooper LA, Blumenthal R, Agyemang C, et al. Sex differences in cardiovascular disease risk of Ghanaian and Nigerian born west African immigrants in the United States: the Afro Cardiac study. JAHA 2016 Feb 23;5(2):e002385. [doi: 10.1161/jaha.115.002385]
11. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van HL, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through

2020 and beyond. Circulation 2010 Feb 2;121(4):586-613 [FREE Full text] [doi: 10.1161/CIRCULATIONAHA.109.192703] [Medline: 20089546]
12. Douglas, Umbleja T, Bloomfield GS, Fichtenbaum CJ, Zanni MV, Overton ET, et al. Cardiovascular Risk and Health Among People With Human Immunodeficiency Virus (HIV) Eligible for Primary Prevention: Insights From the REPRIEVE Trial. Clin Infect Dis 2021 Dec 06;73(11):2009-2022 [FREE Full text] [doi: 10.1093/cid/ciab552] [Medline: 34134131]
13. Feinstein MJ, Hsue PY, Benjamin LA, Bloomfield GS, Currier JS, Freiberg MS, et al. Characteristics, Prevention, and Management of Cardiovascular Disease in People Living With HIV: A Scientific Statement From the American Heart Association. Circulation 2019 Jul 09;140(2):e98-e124. [doi: 10.1161/cir.0000000000000695]
14. Monforte A, Reiss P, Ryom L, El-Sadr W, Dabis F, De Wit S, et al. Atazanavir is not associated with an increased risk of cardio- or cerebrovascular disease events. AIDS 2013 Jan 28;27(3):407-415. [doi: 10.1097/QAD.0b013e32835b2ef1] [Medline: 23291539]
15. Ryom L, Lundgren J, El-Sadr W, Reiss P, Kirk O, Law M, et al. Cardiovascular disease and use of contemporary protease inhibitors: the D:A:D international prospective multicohort study. The Lancet HIV 2018 Jun;5(6):e291-e300. [doi: 10.1016/S2352-3018(18)30043-2]
16. Achhra AC, Lyass A, Borowsky L, Bogorodskaya M, Plutzky J, Massaro JM, et al. Assessing Cardiovascular Risk in People Living with HIV: Current Tools and Limitations. Curr HIV/AIDS Rep 2021 Aug;18(4):271-279 [FREE Full text] [doi: 10.1007/s11904-021-00567-w] [Medline: 34247329]
17. Sanchez E. Life's Simple 7: vital but not easy. J Am Heart Assoc 2018 May 17;7(11):9324 [FREE Full text] [doi: 10.1161/JAHA.118.009324] [Medline: 29773574]
18. Ramos SR, Johnson C, Melkus G, Kershaw T, Gwadz M, Reynolds H, et al. Cardiovascular Disease Prevention Education Using a Virtual Environment in Sexual-Minority Men of Color With HIV: Protocol for a Sequential, Mixed Method, Waitlist Randomized Controlled Trial. JMIR Res Protoc 2022 May 17;11(5):e38348 [FREE Full text] [doi: 10.2196/38348] [Medline: 35579928]
19. Ramos SR, Warren R, Shedlin M, Melkus G, Kershaw T, Vorderstrasse A. A Framework for Using eHealth Interventions to Overcome Medical Mistrust Among Sexual Minority Men of Color Living with Chronic Conditions. Behav Med 2019 Jul 25;45(2):166-176 [FREE Full text] [doi: 10.1080/08964289.2019.1570074] [Medline: 31343963]
20. Ramos SR, O'Hare OM, Hernandez Colon A, Kaplan Jacobs S, Campbell B, Kershaw T, et al. Purely Behavioral: A Scoping Review of Nonpharmacological Behavioral and Lifestyle Interventions to Prevent Cardiovascular Disease in Persons Living With HIV. J Assoc Nurses AIDS Care 2021 Jan 20;32(5):536-547. [doi: 10.1097/jnc.0000000000000230]
21. Fernandez ME, Ruiter RAC, Markham CM, Kok G. Intervention mapping: theory-and evidence-based health promotion program planning: perspective and examples. Front Public Health 2019;7:209 [FREE Full text] [doi: 10.3389/fpubh.2019.00209] [Medline: 31475126]
22. Mikolajczak J, Kok G, Hospers H. Queermasters: Developing a Theory- and Evidence- Based Internet HIV Prevention Intervention to Promote HIV Testing among Men who have Sex with Men (MSM). Applied Psychology 2008;57(4):681-697. [doi: 10.1111/j.1464-0597.2008.00342.x]
23. Kok G, Gottlieb N, Bartholomew L, Parcel G. Planning Health Promotion Programs an Intervention Mapping Approach. San Francisco: Jossey-Bass; 2013.
24. Pachankis JE, McConocha EM, Reynolds JS, Winston R, Adeyinka O, Harkness A, et al. Project ESTEEM protocol: a randomized controlled trial of an LGBTQ-affirmative treatment for young adult sexual minority men's mental and sexual health. BMC Public Health 2019 Aug 09;19(1):1086 [FREE Full text] [doi: 10.1186/s12889-019-7346-4] [Medline: 31399071]
25. Cherrington A, Martin M, Hayes M, Halanych J, Wright M, Appel S, et al. Intervention mapping as a guide for the development of a diabetes peer support intervention in rural Alabama. Prev Chronic Dis 2012;9:E36 [FREE Full text] [doi: 10.5888/pcd9.110053] [Medline: 22239751]
26. Millard T, Dodson S, McDonald K, Klassen KM, Osborne RH, Battersby MW, et al. The systematic development of a complex intervention: HealthMap, an online self-management support program for people with HIV. BMC Infect Dis 2018 Dec 04;18(1):615 [FREE Full text] [doi: 10.1186/s12879-018-3518-6] [Medline: 30509195]
27. Rogers E, Singhal A, Quinlan M. Diffusion of Innovations. New York: Routledge; 2014.
28. Eldredge L, Markham C, Ruiter R, Fernández M, Kok G, Parcel G. Planning Health Promotion Programs: An Intervention Mapping Approach. San Francisco: John Wiley & Sons; 2016.
29. Dearing JW. Applying Diffusion of Innovation Theory to Intervention Development. Res Soc Work Pract 2009 Sep 01;19(5):503-518 [FREE Full text] [doi: 10.1177/1049731509335569] [Medline: 20976022]
30. Cain M, Mittman R. Diffusion of Innovation in Health Care. Oakland, CA: California Healthcare Foundation; 2002.
31. Lustig M, Koester J, Halualani R. Intercultural Competence: Interpersonal Communication Across Cultures. Boston: Pearson/A and B; 2006.
32. Roberts C, Edwards R, Barker L. Intrapersonal Communication Processes. Scottsdale, AZ: Gorsuch Scarisbrick Publishing; 1987.
33. Gouws T, Rheede van Oudtshoorn GP. Correlation between brand longevity and the diffusion of innovations theory. J. Public Affairs 2011 Sep 06;11(4):236-242. [doi: 10.1002/pa.416]

34. Williamson A, Barbarin A, Campbell B, Campbell T, Franzen S, Reischl TM, et al. Uptake of and Engagement With an Online Sexual Health Intervention (HOPE eIntervention) Among African American Young Adults: Mixed Methods Study. J Med Internet Res 2021 Jul 16;23(7):e22203 [FREE Full text] [doi: 10.2196/22203] [Medline: 34269689]
35. Johnson AK, Buenrostro R, Soberanis G, McCarn B, Magner B, Maiorana A. Salud y Orgullo Mexicano: Development of a Culturally Specific Transnational Linkage and Retention in Care Intervention for Mexican Men Who Have Sex with Men Living with HIV in Chicago. J Immigr Minor Health 2021 Apr 16:1-7. [doi: 10.1007/s10903-021-01185-9] [Medline: 33860874]
36. Patel VV, Ginsburg Z, Golub SA, Horvath KJ, Rios N, Mayer KH, et al. Empowering With PrEP (E-PrEP), a Peer-Led Social Media-Based Intervention to Facilitate HIV Preexposure Prophylaxis Adoption Among Young Black and Latinx Gay and Bisexual Men: Protocol for a Cluster Randomized Controlled Trial. JMIR Res Protoc 2018 Aug 28;7(8):e11375 [FREE Full text] [doi: 10.2196/11375] [Medline: 30154071]
37. Pew Research Center.: Pew Research Center; 2013 Nov. URL: https://www.pewresearch.org/science/2013/11/26/the-diagnosis-difference/ [accessed 2022-05-20]
38. Ritchey MD, Wall HK, Owens PL, Wright JS. Vital Signs: State-Level Variation in Nonfatal and Fatal Cardiovascular Events Targeted for Prevention by Million Hearts 2022. MMWR Morb Mortal Wkly Rep 2018 Sep 07;67(35):974-982 [FREE Full text] [doi: 10.15585/mmwr.mm6735a3] [Medline: 30188881]
39. QuickFacts New York city, New York. US Census. 2021. URL: https://www.census.gov/quickfacts/newyorkcitynewyork [accessed 2022-09-27]
40. BRFSS. BRFSS brief– Orientation and gender identity: demographics and health indicators New York State Adults, 2019-2020. New York State Department of Health. 2020. URL: https://health.ny.gov/statistics/brfss/reports/docs/2022-16_brfss_sogi.pdf [accessed 2022-09-27]
41. Sandelowski M. Sample size in qualitative research. Res Nurs Health 1995 Apr;18(2):179-183. [doi: 10.1002/nur.4770180211] [Medline: 7899572]
42. Francis JJ, Johnston M, Robertson C, Glidewell L, Entwistle V, Eccles MP, et al. What is an adequate sample size? Operationalising data saturation for theory-based interview studies. Psychol Health 2010 Dec;25(10):1229-1245 [FREE Full text] [doi: 10.1080/08870440903194015] [Medline: 20204937]
43. Islam MR. Sample size and its role in Central Limit Theorem (CLT). IJPM 2018:1-7 [FREE Full text] [doi: 10.31295/pm.v1n1.42]
44. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003 Aug;35(8):1381-1395. [doi: 10.1249/01.MSS.0000078924.61453.FB] [Medline: 12900694]
45. Pierannunzi C, Hu SS, Balluz L. A systematic review of publications assessing reliability and validity of the Behavioral Risk Factor Surveillance System (BRFSS), 2004-2011. BMC Med Res Methodol 2013 Mar 24;13:49 [FREE Full text] [doi: 10.1186/1471-2288-13-49] [Medline: 23522349]
46. Yore M, Ham SA, Ainsworth BE, Kruger J, Reis JP, Kohl HW, et al. Reliability and validity of the instrument used in BRFSS to assess physical activity. Med Sci Sports Exerc 2007 Aug;39(8):1267-1274. [doi: 10.1249/mss.0b013e3180618bbe] [Medline: 17762359]
47. Moss-Morris R, Weinman J, Petrie K, Horne R, Cameron L, Buick D. The Revised Illness Perception Questionnaire (IPQ-R). Psychology & Health 2002 Jan;17(1):1-16 [FREE Full text] [doi: 10.1080/08870440290001494]
48. Elizabeth R, Lenz PRF, Carolyn F, Waltz PRF, Ora Lea Strickland PRF. Measurement in nursing and health research. 5th edition. Yale University Library. URL: https://search-ebscohost-com.yale.idm.oclc.org/login.aspx?direct=true&db=nlebk&AN=1288050&site=ehost-live&scope=site [accessed 2022-06-30]
49. Chronic diseases and the internet. Pew Research Center. 2010 Mar 24. URL: https://www.pewresearch.org/internet/2010/03/24/chronic-disease-and-the-internet[accessed [accessed 2022-06-29]
50. Latinx LGBT Adults in the US. Williams Institute. 2021. URL: https://williamsinstitute.law.ucla.edu/publications/latinx-lgbt-adults-in-the-us/ [accessed 2022-06-30]
51. Leung F, Savithiri R. Spotlight on focus groups. Can Fam Physician 2009 Feb;55(2):218-219 [FREE Full text] [Medline: 19221085]

Abbreviations

ASCVD: atherosclerotic cardiovascular disease
BRFSS: Behavioral Risk Factor Surveillance System
CDC: Centers for Disease Control and Prevention
CVD: cardiovascular disease
D:A:D: Data collection on Adverse events of anti-HIV Drugs
FLAG: Fund for Gay and Lesbian Studies
IPQ-R: Illness Perception Questionnaire-Revised
LGBTQ+: Lesbian, gay, bisexual, transgender, queer, and others

LS7: Life's Simple 7

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Protocol

Understanding Racial Disparities in COVID-19–Related Complications: Protocol for a Mixed Methods Study

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Abstract

Background: In the United States, the COVID-19 pandemic has magnified the disproportionate and long-standing health disparities experienced by Black communities. Although it is acknowledged that social determinants of health (SDOH) rather than biological factors likely contribute to this disparity, few studies using rigorous analytic approaches in large, information-rich community-based data sets are dedicated to understanding the underlying drivers of these racial disparities.

Objective: The overall aim of our study is to elucidate the mechanisms by which racial disparities in severe COVID-19 outcomes arise, using both quantitative and qualitative methods.

Methods: In this protocol, we outline a convergent parallel mixed methods approach to identifying, quantifying, and contextualizing factors that contribute to the dramatic disparity in COVID-19 severity (ie, hospitalization, mortality) in Black versus white COVID-19 patients within the integrated health care system of Kaiser Permanente Georgia (KPGA). Toward this end, we will generate two quantitative cohorts of KPGA members with a confirmed COVID-19 diagnosis between January 1, 2020, and September 30, 2021: (1) an electronic medical record (EMR) cohort including routinely captured data on diagnoses, medications, and laboratory values, and a subset of patients hospitalized at Emory Healthcare to capture additional in-hospital data; and (2) a survey cohort, where participants will answer a range of questions related to demographics (eg, race, education), usual health behaviors (eg, physical activity, smoking), impact of COVID-19 (eg, job loss, caregiving responsibilities), and medical mistrust. Key outcomes of interest for these two cohorts include hospitalization, mortality, intensive care unit admission, hospital readmission, and long COVID-19. Finally, we will conduct qualitative semistructured interviews to capture perceptions of and experiences of being hospitalized with COVID-19 as well as related interactions with KPGA health care providers. We will analyze and interpret the quantitative and qualitative data separately, and then integrate the qualitative and quantitative findings using a triangulation design approach.

Results: This study has been funded by a Woodruff Health Sciences grant from December 2020 to December 2022. As of August 31, 2022, 31,500 KPGA members diagnosed with COVID-19 have been included in the EMR cohort, including 3028 who were hospitalized at Emory Healthcare, and 482 KPGA members completed the survey. In addition, 20 KPGA members (10 Black and 10 white) have been interviewed about their experiences navigating care with COVID-19. Quantitative and qualitative data cleaning and coding have been completed. Data analysis is underway with results anticipated to be published in December 2022.

Conclusions: Results from this mixed methods pilot study in a diverse integrated care setting in the southeastern United States will provide insights into the mechanisms underpinning racial disparities in COVID-19 complications. The quantitative and qualitative data will provide important context to generate hypotheses around the mechanisms for racial disparities in COVID-19, and may help to inform the development of multilevel strategies to reduce the burden of racial disparities in COVID-19 and its ongoing sequelae. Incorporating contextual information, elucidated from qualitative interviews, will increase the efficacy, adoption, and sustainability of such strategies.

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KEYWORDS

COVID-19; social determinants of health; race; mixed methods; equity; disparity; health; pandemic; disease severity; mortality; racial; ethnicity; complications

Introduction

Background

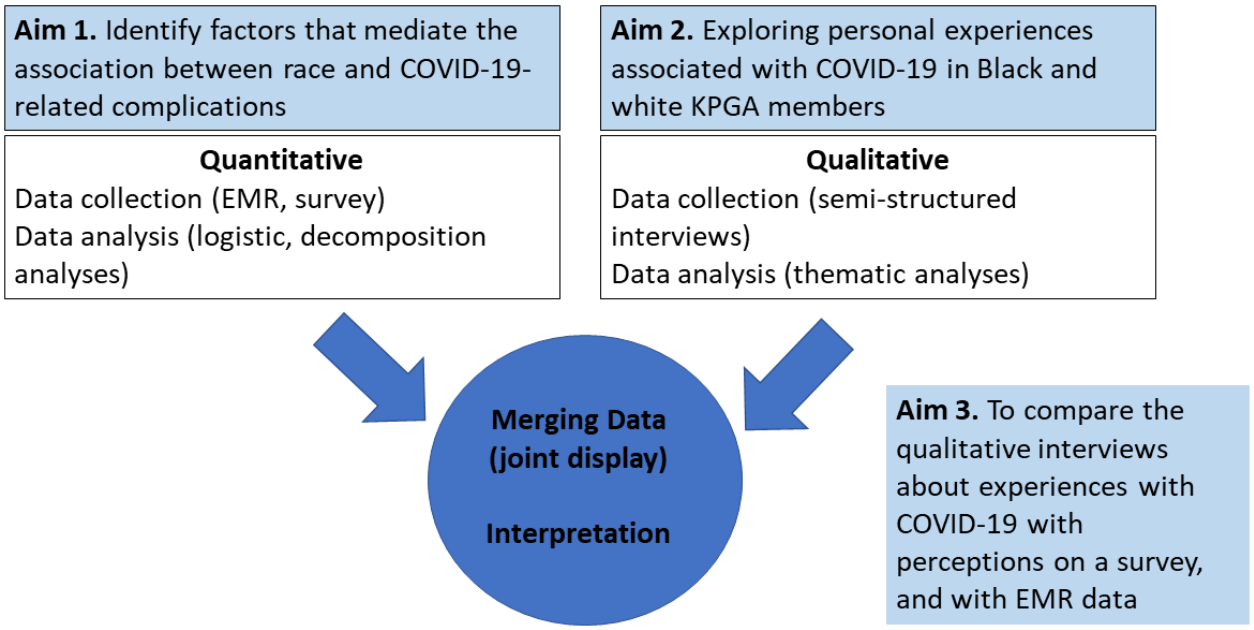
In the United States, the COVID-19 pandemic has magnified the disproportionate and long-standing health disparities experienced by Black communities. Substantive data now demonstrate that Black Americans experience infection, hospitalization, and death from COVID-19 at disproportionality high rates [1-5]. For example, in the state of Georgia, Black Americans represent 31% of the population, yet they account for approximately 40% of total COVID-19 deaths [6]. Now, as we approach our third year of the pandemic, an abundance of extant literature points to the heavily racialized effects of COVID-19, yet there has been scarce discourse and few interventions addressing the disproportionate toll among Black populations due to a lack of actionable evidence needed to inform such responses. Unpacking the role of structural racism (through the multilevel processes that interact with one another to generate and reinforce disparities faced by racialized communities) on the risk of COVID-19 complications, including severe COVID-19 infections requiring hospitalization and "long COVID-19," remains crucial to inform pandemic responses among Black communities.

Social determinants of health (SDOH), rather than biological differences, are hypothesized to impose a greater risk for both infection and severe disease from COVID-19 (ie, hospitalization) among Black communities [7]. These include a myriad of factors operating at the level of the individual (eg, chronic disease burden), interpersonal (eg, patient-provider relationship), community (eg, health care availability), and social and economic structure (eg, poverty rate, racial segregation). Although it is acknowledged that these factors likely contribute, few studies using rigorous analytic approaches in large, information-rich community-based data sets are dedicated to understanding the underlying drivers of these racial disparities.

Objective

In this protocol, we outline a mixed methods approach to identifying, quantifying, and contextualizing the specific medical and SDOH factors that contribute to the dramatic disparity in COVID-19 complications in Black versus white COVID-19 patients within an integrated health care system. The specific aims of this planned research are to: (1) quantitatively examine the individual, community, and structural factors contributing to (ie, mediating) disparities in COVID-19 complications in Black versus white COVID-19 patients using electronic medical record (EMR) data and primary survey data; (2) conduct semistructured qualitative interviews among Black and white patients hospitalized with COVID-19 to explore personal experiences with COVID-19, and contextualize factors that facilitate and impede health-seeking behaviors at the interpersonal, family, community, and health care levels; and (3) compare and contrast the qualitative interviews about personal experiences with COVID-19 with perceptions on the quantitative survey and routinely collected EMR data (Figure 1). This mixed methods approach will provide a robust understanding of the multifactorial challenges faced by adults diagnosed with COVID-19, and compare these challenges between Black and white patients to inform future interventions and policies that may reduce barriers and improve equity.

Figure 1. Convergent parallel mixed methods design to understand racial disparities in COVID-19–related complications. EMR: electronic medical record; KPGA: Kaiser Permanente Georgia.



Methods

Conceptual Framework

Our approach is informed by the National Institute of Minority Health and Health Disparities (NIMHD) Research Framework (Table 1) [8]. This framework considers the complex interplay among individual, interpersonal, community, and structural factors that influence health and health outcomes. In this study, the NIMHD Framework informed our quantitative EMR cohort and survey development, as well as the qualitative interview guide.

Table 1. The National Institute on Minority Health and Health Disparities Research Framework [8].

Levels of influence	Domains of influence				
	Biological	Behavioral	Physical/built environment	Sociocultural environment	Health care system
Structural	Population exposure	Policies and laws (eg, social distancing)	Societal structure	Societal norms; society; structural discrimination; media	Quality of care; health care policies
Community	Community exposure	Community functioning	Community environment; community resources	Community norms; local structural discrimination	Availability of health services; safety net services
Interpersonal	Family microbiome; caregiver-child interaction	Family functioning; school/work functioning	Household environment; school/work environment	Social networks; family/peer norms; interpersonal discrimination	Patient-provider relationship; medical decision-making
Individual	Preexisting conditions	Health behaviors (including social distancing); coping strategies	Personal environment	Sociodemographic; cultural identity; response to discrimination	Insurance coverage; health literacy; trust in health care system

Community Advisory Board

Evidence suggests that a community-engaged approach leads to the development of more efficacious and readily adoptable interventions [9], the long-term objective of our work. For this study, we have formed a community advisory board (CAB; N=5) comprised of patients, caregivers, and researchers. CAB members were recruited through established community engagement networks, academic institutions, local community organizations, and health care systems. The composition of the CAB is 70% women and 100% nonwhite. To date, the CAB has helped inform the development of the qualitative interviews. It is anticipated that results arising from the study will be disseminated to the CAB, which will be essential to contextualizing results and informing the development future multilevel intervention studies to reduce COVID-19–related racial disparities.

Study Population and Data Sources

Kaiser Permanente Georgia

Kaiser Permanente Georgia (KPGA) is a large health insurance database of more than 260,000 current adult members (>40% Black) across 2230 US Census tracts in the metropolitan Atlanta area as well as North Georgia. To be enrolled in the database, participants must have insurance with KPGA. The large

proportion of Black members (in the general Georgia population, the proportion of people identifying as Black is 32.6%) and variability in SDOH indices (household income, social vulnerability index) will allow us to investigate racial disparities and effect modification by individual circumstances, health care site, and neighborhood. KPGA has an extensive EMR data repository, including information related to patient demographics (with some individual measures of SDOH such as insurance status), diagnoses, procedures, claims, lab values, and prescribed medications. In addition, community-level SDOH variables were drawn from an extensive database of characteristics at the county, census-tract, and zip code levels to characterize social vulnerability factors at the community and system levels. Data on community- and system-level factors were obtained from publicly available sources (eg, American Community Survey), which were geocoded and linked to patient EMR data using information of the patient address.

EMR Cohort (Quantitative)

To develop the EMR cohort, all adult (aged ≥18 years) members enrolled in KPGA as of January 1, 2020, with a minimum of 1-month continuous enrollment and with a confirmed diagnosis of COVID-19 were included (N=31,500). COVID-19 was defined by a positive COVID-19 polymerase chain reaction test or an International Classification of Diseases-10th revision (ICD-10) diagnosis code (U07.1, B97.29, B34.2, B97.21, or J12.81). To ascertain granular information on in-hospital outcomes (eg, intensive care unit [ICU] admission), KPGA EMR data were linked to Emory Healthcare for the subset of KPGA members hospitalized with COVID-19 at Emory Healthcare (n=3028). KPGA does not offer inpatient services and Emory Healthcare represents >50% of all hospitalizations among KPGA members in metropolitan Atlanta. Linkage of KPGA to Emory Healthcare data was done using an algorithm of date of birth, first name, last name, and sex, with a linkage rate greater than 90%.

COVID-19 Survey Cohort (Quantitative)

For the COVID-19 survey, adult (aged ≥18 years) KPGA members with a confirmed COVID-19 diagnosis; a valid email address; and current KPGA enrollment with a minimum of 1-month continuous enrollment as of June 1, 2021, were invited to participate via email. The cohort eligible for the survey was populated on June 1, 2021, and research staff began emailing eligible adults a recruitment email with an embedded survey link. Emails were sent in batches of 500 between July 1, 2021, and August 15, 2021. In total, 482 people completed the survey with a response rate of 3%, similar to other Kaiser Permanente email-administered surveys. All participants provided informed consent.

Interview Cohort (Qualitative)

For semistructured interviews, Black and white adult (aged ≥18 years) KPGA members with a confirmed COVID-19 diagnosis and hospitalized with COVID-19 with a discharge date between March 2020 and March 2021 were eligible to be recruited. KPGA members were recruited via the KPGA patient portal (Health Connect), email, phone, and mail. Upon initial contact, we additionally screened individuals to ensure we only recruited those who self-identify as Black or white and ensured an equal distribution of participants by race (ie, 10 Black and 10 white participants). Using this recruitment method, and anticipating a 10%-20% response rate [10], we invited approximately 200 KPGA members to achieve our sample size of 20. Based on guidance, completing 20 interviews among a racially balanced cohort will be adequate for ensuring an appropriate saturation of themes [11].

Table 2 describes the four distinct populations in this study, and respective measurements and study outcomes.

Table 2. Study populations, measurements, and outcomes of interest.

Study population	Study population description	Participants, n	Measurement(s)	Outcome(s)
Quantitative				
EMR[a] cohort	All adult KPGA[b] members diagnosed with COVID-19 between January 1, 2020, and June 1, 2021	31,500	EMR data, including demographics, neighborhood-level SDOH[c], comorbidities, medications, and lab values	Hospitalization within 30 days of COVID-19 diagnosis; readmission (30, 60, and 90 days); mortality; long COVID
Survey cohort	We invited those in the EMR cohort with a valid email address (n=~17,500) to complete a COVID-19 survey	482	Survey questions related to demographics (eg, race, education), usual health behaviors (eg, physical activity, smoking), impact of COVID-19 (eg, job loss, caregiving responsibilities), and medical mistrust. Survey data were supplemented with EMR data	Hospitalization within 30 days of COVID-19 diagnosis; readmission (30, 60, and 90 days); mortality; long COVID
KPGA-Emory cohort	All adult KPGA members hospitalized at Emory Healthcare with COVID-19 between January 1, 2020, and June 1, 2021	3028	KPGA EMR data, supplemented with data on in-hospital medications and lab values from Emory Healthcare	In-hospital outcomes: mechanical ventilation, COVID-19 treatment, ICU[d] admission, ECMO[e] use
Qualitative: interview cohort	We invited those in the EMR cohort with a valid email address (n=~17,500) to participate in a 60-minute one-on-one interview	10	Semistructured interviews	Themes

[a]EMR: electronic medical record.

[b]KPGA: Kaiser Permanente Georgia.

[c]SDOH: social determinants of health.

[d]ICU: intensive care unit.

[e]ECMO: extracorporeal membrane oxygenation.

Quantitative Methods and Analysis: EMR Cohort

Primary Exposure: Race

Race is a social construct describing groups that have associated racial meanings that affect their economic, political, and social lives [7,12]. Racial inequalities are influenced by class differences and SDOH [12,13]. In this study, the primary independent variable will be race, determined from KPGA patient self-report data, and will focus on Black and white adults. Based on guidance by Ioannidis et al [14] and Lin and Kesley [15], the use of race in the current context is appropriate, as other SDOH factors often fail to associate (with sufficient precision) when race is used as the placeholder, and the development of our models will carefully consider other explanatory biological and sociologic variables that may explain race-based signals. Further, due to persistent structural inequities that exist across multiple levels, studying the magnitude of disparities between Black and white individuals in EMR data is often difficult because of missing race/ethnicity data. Therefore, to address missing data on self-identified race (~24% among adults in KPGA), we will apply a Bayesian method integrating surname and geocoded information to impute self-reported race [16]. This approach has previously shown high correlation (76%) with self-reported race with other Kaiser Permanente databases [16]. Analyses will be performed with and without imputed race. Quantitative findings of factors contributing to racial disparities will be merged with the perceptions and experiences from semistructured interviews using a triangulation design. Of note, the current study protocol is restricted to examine differences between Black and white individuals and does not include other racial or ethnic groups, or those identifying as multiracial. This is because the reasons for racial and ethnic disparities in health outcomes across groups are complex and must be carefully considered against each group's historical, social, and economic circumstances. Here, we focus on Black versus white disparities to better ensure that the research provides specific and actionable insight for this important subgroup. Future work will incorporate other racial and ethnic groups.

Covariates

A list of the multilevel variables that will be considered as confounders and/or mediators based on our conceptual model, along with their respective data sources, is detailed in Table 3. We will consider these variables in the context of individual-, community-, and system-level factors, but acknowledge that these are not always mutually exclusive and that many risk factors have upstream causes for which solutions should also be upstream.

Table 3. Quantitative study variables and data sources.

Independent variables	Data Source
Individual-level factors	
Demographics (eg, race, age, sex, ethnicity)	KPGA[a] EMR[b]
Insurance coverage	KPGA EMR
Primary language spoken at home	KPGA EMR
COVID-19 diagnosis date	KPGA EMR
Pre-existing conditions	KPGA EMR
Medical treatment	KPGA EMR
Vital signs and lab data	KPGA EMR
In-hospital lab values	Emory Healthcare
In-hospital medications	Emory Healthcare
Marital status	COVID-19 Survey
SDOH[c] (eg, education, household income)	COVID-19 Survey
Locus of control	COVID-19 Survey
Health behaviors (eg, exercise, smoking, drinking) pre- and post-COVID-19	COVID-19 Survey
COVID-19 symptoms	COVID-19 Survey
Health care–seeking behavior	COVID-19 Survey
Impacts of COVID-19 pandemic (eg, job loss)	COVID-19 Survey
Vaccine hesitancy	COVID-19 Survey
Medical mistrust	COVID-19 Survey
Community- and structural-level factors	
Neighborhood deprivation index	American Community Survey
Median household income	American Community Survey
Social vulnerability index	American Community Survey
Outcome variables	
30-day hospitalization	KPGA EMR
Readmission (30-day, 60-day, 90-day)	KPGA EMR
ICU[d] admission	Emory Healthcare
Mechanical ventilator use	Emory Healthcare
COVID-19 treatment	Emory Healthcare
ECMO[e] use	Emory Healthcare
Long COVID complications: cardiovascular (CAD[f], HF[g], MI[h], stroke, PVD[i]); respiratory (fibrotic lung disease, bronchiectasis, pulmonary vascular disease; mental health (depression, anxiety, substance abuse)	KPGA EMR
Mortality	KPGA EMR

[a]KPGA: Kaiser Permanente Georgia.

[b]EMR: electronic medical record.

[c]SDOH: social determinants of health.

[d]ICU: intensive care unit.

[e]ECMO: extracorporeal membrane oxygenation.

[f]CAD: coronary artery disease.

[g]HF: heart failure.

[h]MI: myocardial infarction.

[i]PVD: peripheral vascular disease.

Outcomes

COVID-19–Related Hospitalizations

Hospitalizations will be considered to be COVID-19–related if they occurred within 30 days of the COVID-19 diagnosis date and include an ICD-10 code for COVID-19.

Hospital Readmissions

Hospital readmissions will be defined as readmissions at 30, 60, and 90 days following the first hospital discharge date.

In-Hospital Outcomes

ICU admission, COVID-19 treatment, and ventilator status will be defined based on KPGA and Emory Healthcare data

Long COVID

Long COVID will be defined through multiple outcome domains: cardiovascular (coronary artery disease, heart failure, myocardial infarction, stroke, peripheral vascular disease); metabolic (diabetes); kidney (acute kidney injury); respiratory (fibrotic lung disease, bronchiectasis, pulmonary vascular disease); mental health (depression, anxiety, substance abuse). Long COVID outcomes will be defined using ICD-10 codes as appropriate. To minimize misclassification of acute COVID-19 complications, as well as previously undiagnosed conditions, long COVID will be defined as symptoms >30 days following the initial COVID-19 infection date.

Mortality

Vital status is updated on a quarterly basis by a dedicated team at KPGA. We will consider COVID-19–specific deaths and all-cause deaths in this group (Tables 2-3).

Statistical Analysis

Overview

In this open cohort study, we will follow individuals in our cohort from the date of first COVID-19 infection, through to each outcome of interest (ie, hospitalization, postacute sequelae of COVID-19, death, or end of enrollment). All primary analyses will consider time to first event (ie, first COVID-19–related event). In sensitivity analyses, we will consider multiple events (ie, >1 event). In addition, given the various waves of COVID-19 (ie, emergence of the Delta and Omicron variants), all analyses will be stratified by calendar period.

Summary Statistics

The study population characteristics will be described with summary statistics as appropriate for the EMR cohort. The χ^2, *t*, and Wilcoxon rank-sum tests will be used to test for differences in baseline characteristics by race as appropriate. We will fit multivariable Poisson regression models, negative binomial regression, and generalized Poisson regression to estimate the excess risk of COVID-19 outcomes in Black versus white adults, and determine the multilevel factors associated with this excess risk using a stepwise approach [17]. All models will consider variability across calendar time. Given the known sex disparity in COVID-19 (ie, men have higher risk of severe COVID-19 compared with women) [18], we will additionally stratify all results by sex. Findings will also be stratified by age and vaccination status to examine the effect modification on their association with severe COVID-19 outcomes. Study variables obtained from EMR data, excluding race, are expected to be available for >95% of participants based on prior analyses. Therefore, our primary approach will be a complete case analysis. However, we will perform sensitivity analyses using hot-deck imputation, replacing missing values with imputed values as estimated from respondents with matching covariates [19].

Decomposition Analysis

Following a social-ecological approach, we will apply the Oaxaca-Blinder decomposition technique to quantify the contribution of individual, community, and structural exposures to racial disparities in COVID-19 outcomes. This regression-based counterfactual method was originally developed in economics with recent applications in epidemiology [20,21]. We will use this method to partition the disparity in outcomes between Black and white KPGA members into the portion that is explained by differences in the levels of exposures across race, differences in the associations of the exposures across race, and the portion that is unexplained by exposures included in the model (ie, other unmeasured factors such as racism). The output from the decomposition analysis will provide insight on the expected residual disparity in outcome if Black and white adults experienced the same level of exposures (eg, equal health care access), sample exposure effects (eg, equal effects on outcomes once health care is accessed), and the interaction between level and effects of exposures. This technique will enable us to quantify the confounder-adjusted potential impact of targeting specific exposures and exposure combinations (which may be differentially distributed by race but also have differential effects on outcomes for each race) on the Black-white disparity in study outcomes. This quantification can be used to prioritize future intervention efforts. Finally, effect modification by area-level characteristics will be evaluated through stratified decomposition analysis among adults residing in counties with high and low vulnerability scores following established percentile-based indices (high: >75th percentile). All analyses will be performed using Stata version 16.1 (StataCorp).

Sample Size and Power Calculation

The EMR cohort is expected to follow 31,500 adults (~47.2% Black). For the rarest outcome, COVID-19 mortality (159 per 100,000 white adults) [22], we expect to be able to detect relative risks (between Black and white adults) of 1.4 with 0.9 power at the 5% significance level. Based on previous applied studies using decomposition analysis (sample size range 24 to 22,666,142), our study will have a modest sample size to conduct decomposition analysis, and based on a range of uncertainty estimates, we anticipate having 80% assurance for 80% power or higher [23].

Quantitative Methods and Analysis: COVID-19 Survey Cohort

Survey Development

We collected additional individual-level patient information on COVID-19–positive patients via an electronic survey to explore specific factors, including SDOH, that may be associated with

COVID-19 complications not captured in EMR data. Variables included in the survey (see Multimedia Appendix 1 and Table 3) were based on a priori knowledge as well as emerging questions specific to COVID-19, and obtained from a variety of sources, including the National Institute of Health's Office of Behavioral and Social Sciences Research resource list of COVID-19–relevant domains for clinical or population research [24]. The survey, administered through Emory University's RedCap system, was pilot-tested among a sample (N=15) of non-COVID-19 non-KPGA members, and estimated to take, on average, 8 (range 5-10) minutes to complete.

Race

Race, as described above for the EMR cohort, will be collected via self-report on the survey. We will define individuals as non-Hispanic Black and non-Hispanic white. Within the design of the survey, all individuals must answer questions on race before progressing in the survey. Therefore, we do not have any missing data on race for the COVID-19 survey.

Outcome

KPGA members who completed the COVID-19 survey were linked to the KPGA EMR using name, date of birth, and medical record number with an almost 100% match rate. This means that all COVID-19 survey participants will also have EMR data on comorbidities, lab values, and medications as per the EMR cohort. The primary outcome for COVID-19 survey participants will be 30-day hospitalization as ascertained by the KPGA EMR (Table 3).

Statistical Analysis

Overview

The analytic approach for the COVID-19 survey cohort will be similar to that described for the EMR cohort under the Summary Statistics subsection above. We do not have sufficient power to perform a decomposition analysis on this sample.

Sample Size and Power Calculation

Using a Poisson regression for our primary outcome of COVID-19–related hospitalization within 30 days of infection among 482 survey participants, 38.6% of whom identify as Black, we estimate having 93% power at a .05 significance level to detect a minimum relative risk of 1.4. This sample size estimate is adjusted for covariates of age, gender, neighborhood vulnerability index, and median income.

Qualitative Methods and Analysis

Overview

Examining racial disparities in COVID-19 using large EMR systems such as KPGA will provide quantitative data to explore the contribution of several multilevel factors to known racial disparities. However, this approach in isolation may overlook the complex interaction of contextual factors, cultural and personal values, social resources, and individual motivations that influence a person's ability to seek health care and navigate the health care system. Therefore, this mixed methods project concurrently conducted in-depth semistructured interviews, guided by the theoretical framework outlined in Table 1 and with feedback from the CAB, to capture perceptions of and experiences of being hospitalized with COVID-19 as well as related interactions with KPGA health care providers. Qualitative methods such as this are well-suited to produce rich, contextual information from individuals deemed knowledgeable about specific issues [25]. Furthermore, capturing the patient experience and integrating this information into the design and development of future interventions, as our long-term objective, is known to increase the efficacy, adoption, and sustainability of such interventions [26].

Data Collection

Semistructured interviews were conducted among a cohort of 10 Black and 10 white participants diagnosed with COVID-19. According to the principles of qualitative research, we believe that a sample size of 20 will be sufficient to reach saturation for thematic analyses [27]. All interviews were conducted via telephone and audio-recorded. Each interview lasted ~60 minutes and was conducted by trained social behavioral scientists at KPGA with extensive experience in qualitative interviewing. The interview guide focused on factors related to health disparities and the multilevel factors associated with racial disparities in health and health care. This includes social environment (neighborhood-level access to quality care), medical mistrust, patient-provider interaction, and changes in employment or housing circumstances (Multimedia Appendix 2). We included a process for referring participants to counseling through KPGA's Behavioral Health Department for any patients who report challenges during the interview. The interview guide and procedures were pilot-tested with a subset (n=2-3) of the study population prior to enrolling study participants. Participants were offered a nominal financial incentive (US $20 Amazon gift card) for participating in the interview.

Data Analysis

Semistructured interviews were audio-recorded and transcribed verbatim by two trained research assistants (one identifying as Black and the other as white) and overseen by a trained social behavioral scientist (identifying as Black). A random sample of transcripts were checked against the audio recordings for accuracy. We then developed a codebook using open coding to identify themes that emerged, followed by axial coding to categorize the themes that emerged to code the interview transcripts [26]. Two coders independently coded each interview transcript and any discordance between the primary coders was discussed with the group until a resolution was reached. Intercoder agreement will be assessed using κ values. We used NVivo 12.0 software to code data and organize results. Thematic analysis will be used to describe themes within the study domains and constructs. We will use modeling techniques to visualize relationships between themes that emerge among each group of participants.

Mixed Methods Integration

This study will follow the checklist for mixed methods research proposed by Fetters and Molina-Azorin [28]. We will analyze and interpret quantitative and qualitative data separately, and then integrate the qualitative and quantitative findings using a triangulation design approach to directly compare and contrast quantitative statistical results with qualitative findings, and to

validate quantitative findings with qualitative data. We will present quantitative data and qualitative data separately, and together in a joint display table (Figure 1).

Ethics Approval and Dissemination

The KPGA Institutional Review Board (IRB; #00000406) and Emory University IRB (#MOD004-STUDY00001631) reviewed and approved this study. Online informed consent was obtained from all participants in the survey cohort. Verbal informed consent was obtained from all participants involved in qualitative interviews.

The Emory and KPGA IRBs waived the requirement of written Privacy Rule Authorization for use of protected health information for recruitment purposes, for the secondary data analysis portion of the study, and waived the requirement of written Privacy Rule authorization and the requirement to obtain a signed consent form for the survey and interview portions of the study.

Study findings will be disseminated with key stakeholders, including CAB members, KPGA, and Emory Healthcare, and will be presented at academic conferences and published in peer-reviewed journals.

Data and Material Availability

The data that support the findings of this study are available from KPGA, but restrictions apply to the availability of these data, which were used under license for this study and so are not publicly available. However, data are available from the authors upon reasonable request and with permission of KPGA.

Results

This study has been funded by a Woodruff Health Sciences grant from December 2020 to December 2022. As of August 31, 2022, 31,500 KPGA members diagnosed with COVID-19 between January 1, 2020, and September 30, 2021, have been included in the EMR cohort, including 3028 who were hospitalized at Emory Healthcare, and 482 KPGA members completed the survey. In addition, 20 KPGA members (10 Black and 10 white) have been interviewed about their experiences navigating care with COVID-19. Quantitative and qualitative data cleaning and coding have been completed. Data analysis is underway with results anticipated to be published in December 2022.

Table 4 describes the basic demographics of our three distinct study populations. In brief, the EMR cohort was more likely to be Black, female, and younger as compared to the general KPGA population. The survey cohort was less likely to be Black and male, and more likely to be older as compared to the general KPGA population. Finally, the interview cohort was more likely to be Black and male relative to the general KPGA population.

Table 4. Demographic characteristics of the three unique study populations diagnosed with COVID-19 included in this mixed methods study as compared to the general KPGA population

Characteristics	EMR[a] cohort	Survey cohort	Interview cohort	KPGA[b] population
Participants recruited, n	31,500	482	20	264,681
Black, n (%)	14,868 (47.2)	186 (38.6)	10 (50.0)	110,107 (41.6)
Men, n (%)	13,261 (42.1)	157 (32.5)	12 (60.0)	120,430 (45.5)
Aged>60 years, n (%)	5260 (16.7)	192 (39.8)	0 (0)	63,259 (23.9)

[a]EMR: electronic medical record.

[b]KPGA: Kaiser Permanente Georgia.

Discussion

Principal Findings

Results from this mixed methods pilot study in a diverse integrated care setting in the southeastern United States will provide insights into the mechanisms underpinning racial disparities in COVID-19 complications. We hypothesize that Black KPGA members will have an increased risk for COVID-19–related complications such as hospitalization, ICU admission, and ventilator use relative to white KPGA members. We also anticipate that a higher proportion of comorbidities among Black KPGA members will explain some, but not all, of the observed disparities, and that SDOH, including racism, will also contribute significantly to race-based disparities. The quantitative and qualitative data in this study will provide important context to generate hypotheses around the mechanisms for racial disparities in COVID-19, and may help to inform the development of multilevel strategies to reduce the burden of racial disparities in COVID-19 and its ongoing sequelae. Incorporating contextual information, elucidated from qualitative interviews, will increase the efficacy, adoption, and sustainability of such strategies.

Comparison to Prior Work

Previous work examining racial disparities in COVID-19–related outcomes has largely been limited to quantitative approaches describing the relative risk of COVID-19 or COVID-19–related outcomes in one race or ethnic group relative to another. Few studies to date have employed a mixed methods approach to comprehensively explore the underlying mechanisms of racial disparities in COVID-19–related outcomes. One known study, using data from the “Health, Ethnicity and Pandemic Survey” (N=2506), a nationally representative survey conducted in October 2020, reported that Black respondents were 6 times more likely to report experiences of racism during COVID-19 [29]. The experience of racism was related to where people lived (eg, “red” vs “blue” states, and racially homogenous neighborhoods), as well as individual-level factors such as being male, low education, and lack of access to the internet [29].

This study highlighted the importance of examining the multilevel factors contributing to racism, but did not expand this research to examine mechanisms and associations with COVID-19–related outcomes, a focus of the current research.

Strengths and Limitations

The key strength of this study is the use of a large integrated health care system (KPGA) with a rich EMR data infrastructure that includes individual, interpersonal, community, and structural factors, providing a unique opportunity to disentangle the key multilevel mechanisms underscoring racial disparities in COVID-19 for which few other data sets are equipped to address. Furthermore, KPGA is a longitudinal data set, and includes inpatient, outpatient, and general health encounters, leading to greater generalizability than most hospital-based COVID-19 studies performed to date. Our research team has extensive expertise using EMR data for research purposes [30-35], including validation studies [36], and is well-equipped to address the nuances of EMR data in research settings.

However, there are some limitations of this study to consider. First, KPGA has a higher proportion of Black adults compared to the Georgia population (41.6% and 32.6%, respectively), higher socioeconomic status (ie, median income and social vulnerability) [37], and does not include uninsured or Medicaid patients. Therefore, results from this study cannot be generalized to the broader Georgia population, but rather to those within an integrated health care system such as KPGA. Despite this, pervasive racial, ethnic, and socioeconomic disparities exist within the KPGA population. For example, Kaiser Permanente has previously reported racial and socioeconomic disparities with respect to health and well-being [38], gastric cancer [39], smoking cessation [40], and diabetes care [41], and preliminary evidence suggests that Black members are twice as likely to experience housing instability, indicating that a social gradient exists within this integrated health system. Understanding the underlying mechanisms contributing to racial disparities in COVID-19 in a population with comparatively uniform access to care is the focus of this work, for which the KPGA data infrastructure is well-suited.

Second, there are known limitations to the use of EMR data for research purposes, not least of which pertains to diagnosis bias: there is likely a race-based bias in terms of who is being screened, tested, and subsequently diagnosed with comorbidities. However, EMR data outperform claims and self-reported data. Moreover, the use of EMR data from a large population allows us to tease out underlying mechanisms of racial disparities in COVID-19 that would not be possible in a smaller, more select cohort population.

Third, our survey response rate was only 3%, similar to other email-based recruitment surveys. Consequently, our survey population is more likely to be white, female, and older as compared to the general KPGA population, thus limiting the external generalizability of our findings. However, the internal validity of our analyses examining the relative contribution of various SDOH factors and COVID-19–related disparities within this population is unlikely to be comprised by this selection bias, and thus the results will still be informative and generate important hypotheses for future work.

Finally, qualitative findings will be limited to a small number of COVID-19–related contexts due to the sample size. Here, we have prioritized understanding the context of health care navigation among Black and white KPGA members with COVID-19, as interventions to improve access, and thus reduce racial disparities, within an integrated health care system may be more readily addressed.

Future Directions

In this pilot study, we hope to generate new knowledge regarding underlying mechanisms of race-based disparities in COVID-19 outcomes to inform the development of future multilevel interventions aimed at reducing inequalities within integrated care settings. Further, KPGA shares the same data infrastructure with 18 other health systems across the United States (in 13 states and serving >28.4 million patients). This will allow us to expand our work to a multisite study across the United States examining the impact of COVID-19 in communities of color in the southeast and nationally.

Conclusion

In conclusion, this study will investigate race-based disparities in COVID-19 outcomes, and the contributing roles and mediating pathways of individual-level and social (eg, structural racism, neighborhood environment) factors among a racially and socioeconomically diverse population of people enrolled within an integrated health system. A rigorous examination of social contexts and racial disparities in COVID-19 outcomes will contribute to the identification of factors that can inform continuing efforts to address racial disparities in the United States in the context of COVID-19.

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Authors' Contributions

JLH conceptualized the study, contributed to design, and wrote the manuscript. SAP, JG, and TD contributed to conceptualization, study design, and reviewed/edited the manuscript. REP, BM, DW-W, RJ, and LT contributed to study design and reviewed/edited the manuscript. All authors have read and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Quantitative survey questions.
[PDF File (Adobe PDF File), 220 KB - resprot_v11i10e38914_app1.pdf]

Multimedia Appendix 2
Qualitative interview guide.
[PDF File (Adobe PDF File), 156 KB - resprot_v11i10e38914_app2.pdf]

References

1. Azar KMJ, Shen Z, Romanelli RJ, Lockhart SH, Smits K, Robinson S, et al. Disparities in outcomes among COVID-19 patients in a large health care system In California. Health Aff 2020 Jul 01;39(7):1253-1262. [doi: 10.1377/hlthaff.2020.00598] [Medline: 32437224]
2. Gold JAW, Wong KK, Szablewski CM, Patel PR, Rossow J, da Silva J, et al. Characteristics and clinical outcomes of adult patients hospitalized with COVID-19 - Georgia, March 2020. MMWR Morb Mortal Wkly Rep 2020 May 08;69(18):545-550. [doi: 10.15585/mmwr.mm6918e1] [Medline: 32379729]
3. Killerby ME, Link-Gelles R, Haight SC, Schrodt CA, England L, Gomes DJ, CDC COVID-19 Response Clinical Team. Characteristics associated with hospitalization among patients with COVID-19 - Metropolitan Atlanta, Georgia, March-April 2020. MMWR Morb Mortal Wkly Rep 2020 Jun 26;69(25):790-794. [doi: 10.15585/mmwr.mm6925e1] [Medline: 32584797]
4. Mahajan U, Larkins-Pettigrew M. Racial demographics and COVID-19 confirmed cases and deaths: a correlational analysis of 2886 US counties. J Public Health 2020 Aug 18;42(3):445-447 [FREE Full text] [doi: 10.1093/pubmed/fdaa070] [Medline: 32435809]
5. Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and mortality among Black patients and white patients with Covid-19. N Engl J Med 2020 Jun 25;382(26):2534-2543 [FREE Full text] [doi: 10.1056/NEJMsa2011686] [Medline: 32459916]
6. COVID-19 United States cases by county. Johns Hopkins University and Medicine Coronavirus Research Center. URL: https://coronavirus.jhu.edu/us-map [accessed 2020-04-17]
7. Webb Hooper M, Nápoles AM, Pérez-Stable EJ. COVID-19 and racial/ethnic disparities. JAMA 2020 Jun 23;323(24):2466-2467 [FREE Full text] [doi: 10.1001/jama.2020.8598] [Medline: 32391864]
8. NIMHD Minority Health and Health Disparities Research Framework. National Institutes of Health National Institute on Minority Health and Health Disparities. URL: https://www.nimhd.nih.gov/about/overview/research-framework.html [accessed 2021-03-15]
9. Minkler M, Wallerstein N. Community-based participatory research: from process to outcomes. San Francisco, CA: Jossey-Bass; 2008.
10. Kelly-Pumarol IJ, Henderson PQ, Rushing JT, Andrews JE, Kost RG, Wagenknecht LE. Delivery of the research participant perception survey through the patient portal. J Clin Transl Sci 2018 Jun 21;2(3):163-168 [FREE Full text] [doi: 10.1017/cts.2018.32] [Medline: 30370068]
11. Hennink M, Hutter I, Bailey A. Qualitative research methods. New York, NY: SAGE Publications Limited; 2020.
12. Krieger N. Discrimination and health inequities. Int J Health Serv 2014;44(4):643-710. [doi: 10.2190/HS.44.4.b] [Medline: 25626224]
13. Krieger N, Waterman PD, Kosheleva A, Chen JT, Carney DR, Smith KW, et al. PLoS One 2011 Nov 18;6(11):e27636 [FREE Full text] [doi: 10.1371/journal.pone.0027636] [Medline: 22125618]
14. Ioannidis JPA, Powe NR, Yancy C. Recalibrating the use of race in medical research. JAMA 2021 Feb 16;325(7):623-624. [doi: 10.1001/jama.2021.0003] [Medline: 33492329]
15. Lin SS, Kelsey JL. Use of race and ethnicity in epidemiologic research: concepts, methodological issues, and suggestions for research. Epidemiol Rev 2000 Jan 01;22(2):187-202. [doi: 10.1093/oxfordjournals.epirev.a018032] [Medline: 11218371]
16. Elliott M, Fremont A, Morrison P, Pantoja P, Lurie N. A new method for estimating race/ethnicity and associated disparities where administrative records lack self-reported race/ethnicity. Health Serv Res 2008 Oct;43(5 Pt 1):1722-1736 [FREE Full text] [doi: 10.1111/j.1475-6773.2008.00854.x] [Medline: 18479410]
17. Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. Source Code Biol Med 2008 Dec 16;3(1):17 [FREE Full text] [doi: 10.1186/1751-0473-3-17] [Medline: 19087314]

18. Garg S, Kim L, Whitaker M, O'Halloran A, Cummings C, Holstein R, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019 - COVID-NET, 14 States, March 1-30, 2020. MMWR Morb Mortal Wkly Rep 2020 Apr 17;69(15):458-464. [doi: 10.15585/mmwr.mm6915e3] [Medline: 32298251]
19. Andridge RR, Little RJ. The use of sample weights in hot deck imputation. J Off Stat 2009;25(1):21-36 [FREE Full text] [Medline: 21691591]
20. Isong I, Rao S, Bind M, Avendaño M, Kawachi I, Richmond T. Racial and ethnic disparities in early childhood obesity. Pediatrics 2018 Jan;141(1):e20170865 [FREE Full text] [doi: 10.1542/peds.2017-0865] [Medline: 29269386]
21. Jackson J, VanderWeele T. Decomposition analysis to identify intervention targets for reducing disparities. Epidemiology 2018 Nov;29(6):825-835 [FREE Full text] [doi: 10.1097/EDE.0000000000000901] [Medline: 30063540]
22. Racial Data Dashboard. The COVID Tracking Project at The Atlantic. 2021. URL: https://covidtracking.com/race/dashboard [accessed 2021-03-10]
23. Liu X, Wang L. Sample size planning for detecting mediation effects: a power analysis procedure considering uncertainty in effect size estimates. Multivariate Behav Res 2019 Apr 15;54(6):822-839. [doi: 10.1080/00273171.2019.1593814] [Medline: 30983425]
24. COVID-19 OBSSR Research Tools. National Institute of Health Office of Behavioral and Social Science Research. 2020. URL: https://obssr.od.nih.gov/research-resources [accessed 2021-08-11]
25. Sanders EB, Stappers PJ. Co-creation and the new landscapes of design. CoDesign 2008 Mar;4(1):5-18. [doi: 10.1080/15710880701875068]
26. Lewis S. Qualitative inquiry and research design: choosing among five approaches. Health Promotion Practice 2015 Apr 02;16(4):473-475. [doi: 10.1177/1524839915580941]
27. Francis JJ, Johnston M, Robertson C, Glidewell L, Entwistle V, Eccles MP, et al. What is an adequate sample size? Operationalising data saturation for theory-based interview studies. Psychol Health 2010 Dec;25(10):1229-1245. [doi: 10.1080/08870440903194015] [Medline: 20204937]
28. Fetters MD, Molina-Azorin JF. A checklist of mixed methods elements in a submission for advancing the methodology of mixed methods research. J Mixed Method Res 2019 Oct 10;13(4):414-423. [doi: 10.1177/1558689819875832]
29. Su D, Alshehri K, Ern J, Chen B, Chen L, Chen Z, et al. Racism experience among American adults during COVID-19: a mixed-methods study. Health Equity 2022 Aug 01;6(1):554-563 [FREE Full text] [doi: 10.1089/heq.2022.0070] [Medline: 36081888]
30. Harding J, Andes L, Rolka D, Imperatore G, Gregg EW, Li Y, et al. National and state-level trends in nontraumatic lower-extremity amputation among U.S. medicare beneficiaries with diabetes, 2000-2017. Diabetes Care 2020 Oct;43(10):2453-2459. [doi: 10.2337/dc20-0586] [Medline: 32723844]
31. Harding J, Benoit S, Gregg E, Pavkov M, Perreault L. Trends in rates of infections requiring hospitalization among adults with versus without diabetes in the U.S., 2000-2015. Diabetes Care 2020 Jan;43(1):106-116. [doi: 10.2337/dc19-0653] [Medline: 31615853]
32. Harding J, Shaw J, Peeters A, Cartensen B, Magliano D. Cancer risk among people with type 1 and type 2 diabetes: disentangling true associations, detection bias, and reverse causation. Diabetes Care 2015 Feb;38(2):264-270. [doi: 10.2337/dc14-1996] [Medline: 25488912]
33. Harding J, Shaw J, Peeters A, Guiver T, Davidson S, Magliano D. Mortality trends among people with type 1 and type 2 diabetes in Australia: 1997-2010. Diabetes Care 2014 Sep;37(9):2579-2586. [doi: 10.2337/dc14-0096] [Medline: 24947787]
34. Schrager JD, Patzer RE, Kim JJ, Pitts SR, Chokshi FH, Phillips JS, et al. Racial and ethnic differences in diagnostic imaging utilization during adult emergency department visits in the United States, 2005 to 2014. J Am Coll Radiol 2019 Aug;16(8):1036-1045. [doi: 10.1016/j.jacr.2019.03.002] [Medline: 31092354]
35. Wiley Z, Ross-Driscoll K, Wang Z, Smothers L, Mehta A, Patzer R. Racial and ethnic differences and clinical outcomes of patients with coronavirus disease 2019 (COVID-19) presenting to the emergency department. Clin Infect Dis 2022 Feb 11;74(3):387-394 [FREE Full text] [doi: 10.1093/cid/ciab290] [Medline: 33822023]
36. Loh V, Harding J, Koshkina V, Barr E, Shaw J, Magliano D. The validity of self-reported cancer in an Australian population study. Aust N Z J Public Health 2014 Feb 04;38(1):35-38. [doi: 10.1111/1753-6405.12164] [Medline: 24494943]
37. QuickFacts Georgia. U.S. Census Bureau. URL: https://www.census.gov/quickfacts/GA [accessed 2021-03-14]
38. Stiefel MC, Gordon NP, Wilson-Anumudu FJ, Arsen EL. Sociodemographic determinants of health and well-being among adults residing in the Combined Kaiser Permanente Regions. Perm J 2019;23:18-091 [FREE Full text] [doi: 10.7812/TPP/18-091] [Medline: 31050642]
39. Bautista MC, Jiang S, Armstrong MA, Kakar S, Postlethwaite D, Li D. Significant racial disparities exist in noncardia gastric cancer outcomes among Kaiser Permanente's patient population. Dig Dis Sci 2015 Apr 30;60(4):984-995. [doi: 10.1007/s10620-014-3409-7] [Medline: 25354832]
40. Young-Wolff KC, Adams SR, Tan AS, Adams AS, Klebaner D, Campbell CI, et al. Disparities in knowledge and use of tobacco treatment among smokers in California following healthcare reform. Prev Med Rep 2019 Jun;14:100847 [FREE Full text] [doi: 10.1016/j.pmedr.2019.100847] [Medline: 31024786]

41. Marshall CJ, Rodriguez HP, Dyer W, Schmittdiel JA. Racial and ethnic disparities in diabetes care quality among women of reproductive age in an integrated delivery system. Womens Health Issues 2020 May;30(3):191-199. [doi: 10.1016/j.whi.2020.03.003] [Medline: 32340896]

Abbreviations

CAB: community advisory board
EMR: electronic medical record
ICD-10: International Classification of Diseases, 10th revision
ICU: intensive care unit
IRB: Institutional Review Board
KPGA: Kaiser Permanente Georgia
NIMHD: National Institute of Minority Health and Health Disparities
SDOH: social determinants of health

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Protocol

Biomarkers of Exposure and Potential Harm in Exclusive Users of Nicotine Pouches and Current, Former, and Never Smokers: Protocol for a Cross-sectional Clinical Study

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Abstract

Background: Tobacco harm reduction (THR) aims to reduce the health burden of cigarettes by encouraging smokers to switch to using alternative tobacco or nicotine products. Nicotine pouches (NPs) are smokeless, tobacco-free, oral products that may be beneficial as part of a THR strategy.

Objective: This 2-center, cross-sectional confinement study conducted in Denmark and Sweden aimed to determine whether biomarkers of exposure (BoEs) to tobacco toxicants and biomarkers of potential harm (BoPHs) in exclusive users of NPs show favorable differences compared with current smokers.

Methods: Participants were healthy NP users (target n=100) and current, former, or never smokers (target n=40 each), as confirmed by urinary cotinine and exhaled carbon monoxide concentrations. During a 24-hour confinement period, participants were asked to use their usual product (NP or cigarette) as normal, and BoEs and BoPHs were measured in blood and 24-hour urine samples, with compliance determined using anabasine, anatabine, and N-(2-cyanoethyl)valine. BoEs and BoPHs were compared between NP users and current, former, and never smokers. Urinary total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (BoE to nicotine-derived nitrosamine ketone) and urinary 8-epi-prostaglandin F2α type III, exhaled nitric oxide, blood carboxyhemoglobin, white blood cell count, soluble intercellular adhesion molecule-1, and high-density lipoprotein cholesterol (BoPHs) were evaluated as primary outcomes. Other measures included urinary 11-dehydrothromboxane B2, forced expiratory volume, carotid intima-media thickness, self-reported quality of life, and oral health.

Results: The results of this study were received in mid-2022 and will be published in late 2022 to early 2023.

Conclusions: The results of this study will provide information on toxicant exposure and biomarkers associated with the development of smoking-related diseases among users of NPs compared with smokers, as well as on the potential role of NPs in THR.

Trial Registration: International Standard Randomised Controlled Trial Number (ISRCTN) ISRCTN16988167; https://www.isrctn.com/ISRCTN16988167

International Registered Report Identifier (IRRID): DERR1-10.2196/39785

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KEYWORDS

biomarkers of exposure; biomarkers of potential harm; nicotine pouches; tobacco harm reduction; cross-sectional clinical study

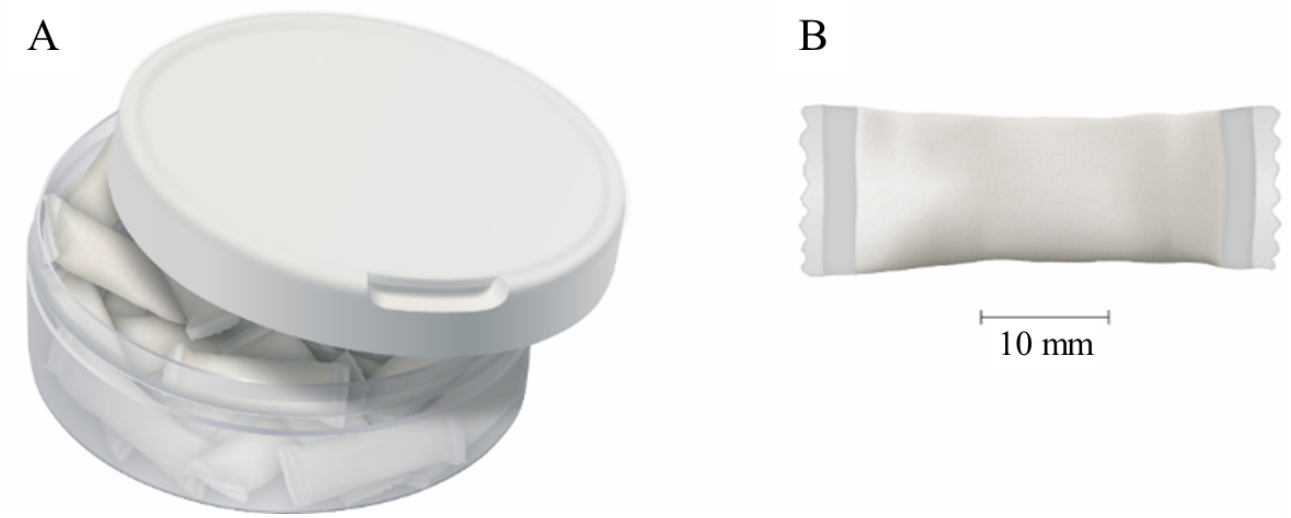
Introduction

Background

Cigarette smoking is associated with several health risks, including the development of lung cancer and cardiovascular disease [1]. Although the addictive properties of cigarette smoking are primarily due to the tobacco constituent nicotine [2,3], its disease mechanisms, including DNA damage and oxidative stress [4,5], are associated with the long-term inhalation of smoke from the combusted tobacco [1,6]. This knowledge has led to the concept of tobacco harm reduction (THR), whereby smokers are encouraged to replace cigarette smoking with the use of alternative nicotine products with potentially fewer health risks [7]. Such an approach might reduce the health burden of tobacco use [8] and is currently supported by a number of health and regulatory bodies [9-11], although THR is not universally implemented or accepted [12]. Furthermore, for THR to realize its full potential, complete switching from the more harmful product, typically tobacco cigarettes, to the less harmless product is required [13].

Commercially available since the mid-2010s, nicotine pouches (NPs; Figure 1) are nicotine-containing oral, smokeless, tobacco-free pouches [14,15]. Although NPs are growing in popularity [16,17], use of NPs is relatively low; in a representative monthly survey of British adults conducted between November 2020 and October 2021, only 0.26% used NPs [18]. Similar to Swedish snus, which is a smokeless tobacco product that has been recognized to have reduced health risks compared with combustible cigarettes [19,20], NPs are placed between the gum and top lip, where nicotine is released from the cellulose matrix in the pouch and absorbed through the oral mucosa.

Figure 1. Illustration of a typical nicotine pouch: (A) as sold in container with lid, and (B) individual pouch. It is from "Chemical characterization of tobacco-free "modern" oral nicotine pouches and their position on the toxicant and risk continuums" by David Azzopardi, Chuan Liu & James Murphy David Azzopardi, Chuan Liu & James Murphy (2021) taken from Drug and Chemical Toxicology (2022), Vol45:5, Informa UK Limited, trading as Taylor & Francis Group (2022), reprinted by permission of the publisher.



Because of their relatively simple composition, that is, pharmaceutical-grade nicotine added to a cellulose-based matrix rather than a nicotine-containing tobacco matrix, NPs contain fewer toxicants compared with snus and may therefore present similar or fewer health risks. This has been demonstrated in a recent toxicant analysis in which 24 to 26 compounds (23 to 25 of which were harmful and potentially harmful constituents [HPHCs]) were measured in snus, NPs, and a nicotine replacement therapy (NRT) gum and lozenge. In total, 22 out of 25 of the measured HPHCs were not quantified in the NPs, whereas only 11 out of 23 HPHCs were not quantified in Swedish snus [15]. In addition, studies have demonstrated that extracts from NPs are significantly less toxicologically active in vitro than extracts from Swedish snus or cigarette smoke [21,22].

The aforementioned findings indicate that NPs may have a potential role to play in a THR approach, as recently suggested by Palmer et al [23]. However, at present, there are no data on a user's actual exposure to toxicants from these products. It should be noted that a reduction in toxicant exposure from alternative nicotine product use compared with continued smoking may not correspond to a reduction in overall harm, and further studies on longer-term use of these products are required to support this. In this regard, clinical studies measuring biomarkers in human samples can provide information on whether NP users are exposed to reduced levels of toxicants and whether this translates to a potential for reduced risk compared with continued smoking. In particular, biomarkers of exposure (BoEs), which indicate a user's internal exposure to tobacco toxicants, and biomarkers of potential harm (BoPHs), which reflect changes in their wider biological system [24], are now being used to evaluate the risk reduction potential of e-cigarettes and tobacco heating products [25-29].

Objectives

The aim of this study was to assess whether the lower number and levels of toxicants found in NPs compared with those found in tobacco smoke translate to lower levels of selected BoEs as well as favorable differences in selected BoPHs and physiological measures of health between adults who use NPs and adult current, former, and never smokers.

The primary objective was to quantitatively assess differences between NP users and current smokers in one BoE (total 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol [NNAL]) and six BoPHs (fractional exhaled nitric oxide [FeNO], 8-epi-prostaglandin F2α type III [8-epi-PGF2α type III], carboxyhemoglobin [COHb], white blood cell (WBC) count, soluble intercellular adhesion molecule-1 [sICAM-1], and high-density lipoprotein [HDL]).

The secondary objectives were to quantitatively assess differences between NP users and current smokers in the BoEs' total nicotine equivalents (nicotine, cotinine, 3-hydroxycotinine, and their glucuronide conjugates); monohydroxybutenylmercapturic acid; 3-hydroxy-1-methylpropylmercapuric acid (HMPMA); 3-hydroxypropylmercapturic acid; total N-nitrosonornicotine; 3-hydroxybenzo[a]pyrene; S-phenylmercapturic acid; the BoPH 11-dehydrothromboxane B2 (11-dTX B2); the physiological measures forced expiratory volume in 1 second as percentage of predicted (FEV_1%pred), carotid intima-media thickness (CIMT), and oral health; and a quality-of-life questionnaire. In addition, all study end points were compared between NP users and former smokers and between NP users or former smokers and never smokers.

Methods

Study Design

This cross-sectional multicenter confinement study was conducted among exclusive NP users and current, former, and never smokers attending 1 of 2 centers in Herlev, Denmark, and Uppsala, Sweden, between March 2021 and January 2022. Written informed consent was obtained from all participants before screening and enrollment.

Ethics Approval

Ethics approval for the study was obtained from the Scientific Ethics Committees for the Capital Region, Denmark (H-21021424) and the Ethical Review Authority, Sweden (2021-01810). The study was conducted in accordance with the Declaration of Helsinki and will be reported based on the guidelines of the International Council on Harmonisation. The trial has been registered on the ISRCTN registry (ISRCTN16988167).

Biomarker Selection

The BoEs chosen for analysis are based on the 9 priority smoke toxicants recommended for mandatory lowering by the World Health Organization [30], which provide an indication of exposure to toxicants present in the gas and particulate phases of tobacco smoke (Table 1). For two of these toxicants (acetaldehyde and formaldehyde), there are no reliable BoEs at present; therefore, levels of crotonaldehyde were assessed (through HMPMA) instead. The BoPHs 11-dTX B2 [31-33], 8-epi-PGF2α type III [34,35], CIMT [36-38], COHb [39-41], FeNO [35,42], FEV_1%pred [43], HDL [44-46], sICAM-1 [47-49], and WBC count [50-53] were selected to cover a range of associated smoking-related diseases, including lung cancer, cardiovascular disease, and chronic obstructive pulmonary disease, as well as underlying disease processes such as oxidative stress (Table 2). Note that urinary NNAL, a biomarker for nicotine-derived nitrosamine ketone exposure, is also considered a BoPH associated with lung cancer [54,55].

Table 1. Biomarkers of exposure measured in the study.

Biomarker of exposure	Associated toxicant	Matrix	Method	References
Primary end point				
Total NNAL[a]	NNK[b]	24-hour urine	LC-MS/MS[c]	[54-57]
Secondary end points				
3-HPMA[d]	Acrolein	24-hour urine	LC-MS/MS	[56,58]
3-OH-B[a]P[e]	B[a]P[f]	24-hour urine	LC-MS/MS	[59]
HMPMA[g]	Crotonaldehyde	24-hour urine	LC-MS/MS	[56,58]
MHBMA[h]	1,3-Butadiene	24-hour urine	LC-MS/MS	[56,58]
S-PMA[i]	Benzene	24-hour urine	LC-MS/MS	[58]
TNeq[j]	Nicotine	24-hour urine	LC-MS/MS	[56]
Total NNN[k]	NNN	24-hour urine	LC-MS/MS	[56]

[a]NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol. Urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol is associated with lung cancer risk [57]; therefore, it is also considered a biomarker of potential harm for lung cancer [54,55].

[b]NNK: nicotine-derived nitrosamine ketone.

[c]LC-MS/MS: liquid chromatography with tandem mass spectrometry.

[d]3-HPMA: 3-hydroxypropylmercapturic acid.

[e]3-OH-B[a]P: 3-hydroxybenzo[a]pyrene.

[f]B[a]P: benzo[a]pyrene.

[g]HMPMA: 3-hydroxy-1-methylpropylmercapuric acid.

[h]MHBMA: monohydroxybutenylmercapturic acid.

[i]S-PMA: S-phenylmercapturic acid.

[j]TNeq: total nicotine equivalents (nicotine, cotinine, 3-hydroxycotinine, and their glucuronide conjugates).

[k]NNN: N-nitrosonornicotine.

Table 2. Biomarkers of potential harm measured in the study.

Biomarker of potential harm	Associated biological process	Matrix	Method	References
Primary end points				
8-Epi-PGF2α type III[a]	Oxidative stress	24-hour urine	LC-MS/MS[b]	[34,35,60]
COHb[c]	CVD[d]	Whole blood	HS GC-MS[e]	[39-41,61]
FeNO[f]	Airway inflammation	Exhaled breath	Chemical field-effect transistor	[35,42,62]
HDL[g]	CVD	Blood	Enzyme colorimetric	[28,44-46]
sICAM-1[h]	CVD	Serum	ELISA[i]	[28,47-49]
WBC[j] count	Inflammation	Blood	Flow cytometry	[50-53,63]
Secondary end points				
11-dTX B2[k]	CVD	24-hour urine	LC-MS/MS	[31-33,60]
CIMT[l]	CVD	Physiological measurement	Ultrasound	[36-38,64]
FEV_1%pred[m]	COPD[n]	Physiological measurement	Spirometry	[43,65,66]

[a]8-Epi-PGF2α type III: 8-Epi-prostaglandin F2α type III.

[b]LC-MS/MS: liquid chromatography with tandem mass spectrometry.

[c]COHb: carboxyhemoglobin.

[d]CVD: cardiovascular disease.

[e]HS GC-MS: headspace gas chromatography–mass spectrometry.

[f]FeNO: fractional exhaled nitric oxide.

[g]HDL: high-density lipoprotein.

[h]sICAM-1: soluble intercellular adhesion molecule-1.

[i]ELISA: enzyme-linked immunosorbent assay.

[j]WBC: white blood cell.

[k]11-dTX B2: 11-dehydrothromboxane B2.

[l]CIMT: carotid intima-media thickness.

[m]FEV_1%pred: forced expiratory volume in 1 second as percentage of predicted.

[n]COPD: chronic obstructive pulmonary disease.

Study Participants

All participants were healthy adult men or women aged 19 to 55 years. For all other inclusion and exclusion criteria, refer to Textbox 1. Exclusive NP users as well as current, former, and never smokers were recruited in Sweden and Denmark, with an equal split of Swedish and Danish participants in each arm. Participants were selected either from a database of individuals who were registered at the participating clinics for the purpose of undertaking clinical studies or through study-specific advertising (eg, social media). Because of difficulties in recruiting NP users by the study clinics alone, an external recruitment agency assisted in identifying potential participants from its database and referred interested individuals to the study clinics without releasing any personal information.

For the NP user group, participants were self-reported solus users of at least three Lyft NPs (currently marketed as Velo; British American Tobacco) per day and had used these NPs for a minimum of 6 months before screening. For the current smoker group, participants were self-reported solus smokers of at least 10 factory-made cigarettes (FMCs) per day and had smoked for at least one year before screening. For the former smoker group, participants were self-reported former smokers of FMCs who quit smoking at least six months before screening. For the never smoker group, participants had never smoked (<100 cigarettes in their life and none within the 6 months before screening). Compliance with long-term smoking abstinence in the NP and former smoker groups was verified by analysis of N-(2-cyanoethyl)valine (CEVal) in erythrocytes [67]. Urinary levels of anabasine (AB) and anabatine (AT) were also used to determine short-term abstinence from smokeless tobacco use.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Participants who are healthy men or women, aged 19 to 55 years
- Participants who have a BMI of 18.5 to 30.0 kg/m^2 (body weight exceeding 52 kg [men] or 45 kg [women])
- Participants who are in good health as judged by the principal investigator (PI) or the appropriately qualified designee based on medical history, physical examination, vital signs assessment, 12-lead electrocardiogram, clinical laboratory evaluations, and lung function spirometry test
- Participants who have given their written informed consent to participate in the study and have agreed to abide by the study restrictions
- Participants who can demonstrate the ability to comprehend the informed consent form, are able to communicate well with the PI or the appropriately qualified designee, can understand and comply with the requirements of the study, and can be judged suitable for the study in the opinion of the PI or the appropriately qualified designee
- Participants who will refrain from consuming alcohol within 24 hours before screening and admission
- Participants who will refrain from consuming cruciferous vegetables as well as grilled, fried, or barbequed food and avoid being in the presence of the cooking of cruciferous vegetables as well as grilled, fried, or barbequed food for 48 hours before screening and admission
- Arm A: exclusive nicotine pouch (NP) users
  - Participants who are regular (daily) users of at least three Lyft NPs (British American Tobacco) per day
  - Participants who have used Lyft for a minimum of 6 months before screening
  - Participants who have a urinary cotinine level ≥200 ng/mL and an exhaled carbon monoxide (eCO) level <7 ppm at screening and admission
- Arm B: current smokers
  - Participants who are regular solus smokers of commercially manufactured filter cigarettes
  - Participants who have smoked for at least one year before screening
  - Participants who typically smoke at least 10 cigarettes per day and have a urinary cotinine level ≥200ng/mL and an eCO level ≥7 ppm at screening and admission
- Arm C: former smokers
  - Participants who are former smokers of commercially manufactured filter cigarettes who quit smoking at least six months before screening
  - Participants who have a urinary cotinine level <200 ng/mL and an eCO level <7 ppm at screening and admission
- Arm D: never smokers
  - Participants who have never smoked (<100 cigarettes in their life and none within the 6 months before screening)
  - Participants who have a urinary cotinine level <200 ng/mL and an eCO level <7 ppm at screening and admission

Exclusion criteria

- Female participants who are pregnant or breastfeeding (confirmed at screening)
- Participants who have donated ≥400 mL of blood within 90 days before screening, plasma in the 7 days before screening, and platelets in the 6 weeks before screening
- Participants who have had an acute illness (eg, upper respiratory tract or viral infection) within 4 weeks before screening as judged by the PI
- Participants who have a significant history of alcoholism or drug or chemical abuse (apart from known smoking and vaping history) within 24 months before screening as determined by the PI or the appropriately qualified designee
- Participants who have a positive urine drugs of abuse panel or breath alcohol screen result (confirmed by repeat) at screening or admission
- Participants who have serum hepatitis or are carriers of the hepatitis B surface antigen or are carriers of the hepatitis C antibody; have a positive result for the test for HIV antibodies; have symptoms of a COVID-19 infection, have a positive result in the COVID-19 test at screening or admission indicating current, active infection (Sweden only), or not providing proof of a negative COVID-19 test taken within 48 hours of admission (Denmark only)
- Participants who have used prescription or over-the-counter bronchodilator medication (eg, inhaled or oral β-adrenergic agonists) to treat a chronic condition within the 12 months before screening
- Participants who have received any medications or substances (other than nicotine) that interfere with the cyclooxygenase pathway (eg, anti-inflammatory drugs, including aspirin and ibuprofen) within 14 days before screening or are known to be strong inducers or inhibitors of cytochrome P450 enzymes within 14 days or 5 half-lives of the drug (whichever is longer) before screening
- Participants who would need to take prescription medication not approved by the PI during the period beginning with screening and ending with discharge (for female participants, hormonal contraceptives are acceptable, and for all participants, painkillers [eg, paracetamol] are permitted)

- Participants who are unwilling or unable to comply with the study requirements
- Employees and immediate relatives of the tobacco industry or the clinical site
- Participants who have any clinically relevant abnormal findings on the physical examination, medical history, electrocardiogram, lung function tests, or clinical laboratory panel, unless deemed not clinically significant by the PI or the appropriately qualified designee
- Participants who have been diagnosed with a significant history of urticaria or asthma (childhood asthma is acceptable)
- Participants who have, or who have a history of, any clinically significant neurological, gastrointestinal, renal (including urinary tract infection or nephrolithiasis), hepatic, cardiovascular, psychiatric, respiratory, metabolic, endocrine, hematological, or other major disorder that, in the opinion of the PI or the appropriately qualified designee, would jeopardize the safety of the participant or have an impact on the validity of the study results
- Participants who have previously been diagnosed with any form of malignancy or carcinoma in situ
- Participants who are currently participating in another clinical trial (including follow-up)
- Participants who, in the opinion of the PI or the appropriately qualified designee, should not participate in this study
- Arm A: exclusive NP users
  - Participants who have used any form of tobacco or nicotine-containing product, other than the Lyft NP products, within 6 months before screening
- Arm B: current smokers
  - Participants who are self-reported noninhalers (smokers who draw smoke from the cigarette into the mouth and throat but who do not inhale)
- Arms C and D: former and never smokers
  - Participants who have used any form of tobacco or nicotine-containing product within the 6 months before screening

Investigational Products

No investigational products were provided; instead, participants were required to bring their own supply of NPs or cigarettes for use during the study confinement period. However, all participants recruited to the NP group were self-reported solus users of Lyft NPs; those recruited to the current smoker group could be smokers of any brand of FMCs.

Study Procedures

Potential participants were invited to attend the clinic to assess study eligibility. They received verbal and written information about the study and were asked to sign the informed consent form before undergoing any procedures. Screening consisted of physical, oral, and vital signs examinations, as well as routine laboratory testing. Tests for alcohol and drug consumption as well as pregnancy (women only) were also conducted, and extent of nicotine use and smoking status were determined through a questionnaire.

Individuals deemed eligible based on the screening assessments were invited back to the clinic for admission into the study within 7 days of screening. They were asked to bring with them a sufficient supply of their usual NPs (Lyft brand) or usual cigarettes to last the whole screening and confinement period. In addition, NP users were asked to bring excess pouches to enable the analysis of unused pouches for nicotine content. Those who successfully completed the admission assessments (Table 3) were enrolled in the study (day 1) and given a unique study number. Participant data were collected on a paper case report form (CRF) or entered directly on an electronic case report form (eCRF). After enrollment, participants began a period of 24-hour urine collection and were confined to the clinic during this time. The remaining study assessments, including blood sampling and physiological assessments, were performed during the remainder of the confinement period before discharge on day 2 (Table 3). During the confinement period, participants were requested to use their NPs or cigarettes as they would normally, except where product use might interfere with on-study assessments. This approach facilitated the measurement of short-term BoEs that reflected the participant's product use outside the clinic. In the case of NP users, pouches were collected after use for assessment of residual nicotine content. On 3 random occasions, participants in the NP group were asked to record the duration of pouch use to the nearest minute. They commenced timing upon placing the pouch under the lip and ended timing on removal of the pouch. Participants were discharged from the clinic on day 2 after completion of both the 24-hour urine collection period and study and discharge assessments. No later than 1 week after discharge, a poststudy follow-up was performed by telephone call to collect information on the status of any ongoing adverse events (AEs) at discharge and any new AEs experienced after discharge.

Table 3. Schedule of assessments.

Assessment	Screening	Admission (day 1)	On study (days 1-2)	Discharge (day 2)	Poststudy follow-up[a]
Participants are free to use NP[b] or smoke as usual[c]	✓	✓	✓	✓	✓
Participants collect used NPs[d]			✓		
Unused pouch collection			✓		
Informed consent	✓				
Inclusion and exclusion criteria	✓				
Sociodemographic data	✓				
Medical history	✓				
Prior and concomitant medications	✓	✓	✓	✓	✓
Tobacco and nicotine use history questionnaire	✓				
Pregnancy test (urine and serum)[e]	✓	✓			
COVID-19 test (Sweden only)	✓	✓			
Height, weight, BMI, and waist circumference	✓				
Vital signs[f]	✓	✓			
12-lead ECG[g]	✓				
Physical examination[h]	✓	✓		✓	
Urinary cotinine screen (dipstick)	✓	✓			
Urine drugs of abuse panel and alcohol screen[i]	✓	✓			
Serum biochemistry and hematology	✓				
Urinalysis	✓				
Virology (hepatitis B and C and HIV)	✓				
Exhaled carbon monoxide measurement[j]	✓	✓			
Spirometry (without bronchodilator)[k]	✓				
FeNO[l] measurement[m]			✓		
24-hour urine collection			✓		
Blood sampling for biomarker analysis[n]			✓		
Carotid intima-media thickness assessment			✓		
Quality-of-life questionnaire			✓		
Oral health assessment			✓		
Adverse event recording[o]	✓	✓	✓	✓	✓

[a]Within 7 days of discharge.

[b]NP: nicotine pouch.

[c]At any time, unless it would interfere with study assessments.

[d]All pouches used during confinement collected from participants in arm A commencing just before the start of 24-hour urine collection.

[e]Urine pregnancy test only at admission.

[f]Includes pulse rate, systolic and diastolic blood pressure, respiratory rate, and tympanic temperature.

[g]ECG: electrocardiogram.

[h]Full physical examination at screening; symptom-driven physical examination at admission and discharge, if deemed necessary.

[i]By breath test (alcometer).

[j]No food, smoking, or nicotine pouch use within 30 minutes before assessment.

[k]No food within 2 hours before assessment; no smoking or nicotine pouch use within 1 hour before assessment.

[l]FeNO: fractional exhaled nitric oxide.

[m]No food or drink within 1 hour before assessment; no smoking or nicotine pouch use within 30 minutes before assessment.

[n]Blood sampling for the following biomarker analysis: N-(2-cyanoethyl)valine, carboxyhemoglobin (drawn between 6 PM and 8 PM), lipid panel (for high-density lipoprotein analysis), soluble intercellular adhesion molecule-1, and white blood cell count.

[o]Reporting begins at provision of informed consent.

At any point, participants were able to withdraw from the study for any reason, or they may have been withdrawn at the discretion of the principal investigator (PI) or study sponsor (eg, for health reasons or protocol deviations). The reason for premature discontinuation would be clearly documented in the participant's eCRF. The PI could suspend or terminate the study for any reason after consultation with the sponsor; the sponsor could also suspend or terminate the study for any reason. If the study was terminated, the reasons would be fully documented.

Study Assessments

Overview

Routine clinical laboratory testing was conducted at screening to exclude individuals with significant medical conditions. Urine collection began on day 1, immediately after enrollment; all urine voided was pooled at the end of the 24-hour period and mixed before analyses. Blood samples were obtained on days 1 and 2 through direct venipuncture or a cannula inserted in a forearm vein. The blood sample for COHb analysis was drawn between 6 PM and 8 PM. A maximum of 100 mL was drawn and used for both laboratory tests and biomarker evaluations. Physiological assessments were performed on days 1 and 2 before discharge.

Compliance

For participants in the NP and former smoker groups, compliance with long-term abstinence from smoking before the study was assessed by measurement of CEVal in erythrocytes derived from 5 mL of whole blood [68]. In addition, short-term abstinence from smokeless tobacco use was assessed by measurement of urinary AB and AT. CEVal, AB, and AT were measured at Analytisch-Biologisches Forschungslabor (ABF) in Munich, Germany. AB and AT were analyzed by LC-MS/MS as follows. In brief, 60 µL deuterated internal standard (IS) solutions (AB-D4 and AT-D4, 12 ng each) and 900 µL formic acid were added to 0.6 mL urine and the mixture subjected to solid phase extraction on Oasis MCX cartridges (60 mg, 3 mL; Waters). After washing with 1.8 mL 0.5% formic acid, 3.2 mL water, 1.8 mL methanol, and 1.8 mL acetonitrile/methanol (6:4, volume:volume), and elution with 1.2 mL 2% aqueous ammonium hydroxide/59% acetonitrile/39% methanol, evaporation of the eluate, and reconstitution with 100 µL 10 mM aqueous ammonium acetate/acetonitrile (9:1, volume:volume), 10 µL was injected into an LC-MS/MS system (HP 1100 HPLC [Agilent Technologies] coupled to an API 4000 [Sciex]). Chromatography was conducted with a Gemini C18 (2) column (150×3 mm, 3 µm particle size; Phenomenex) by applying a gradient consisting of 10 mM aqueous ammonium acetate (A) and acetonitrile (B) under the following conditions: 0.5 mL/minute, 50 °C; 0 to 3 minutes: 10% to 75% B; 3 to 4 minutes: 75% B; 4 to 4.1 minutes: 75% to 10% B; and 4.1 to 9 minutes: 10% B. Mass spectrometric analysis was conducted in positive electrospray ionization mode using multiple reaction monitoring. Mass-to-charge ratios (m/z) for quantifier/qualifier transitions: AB: 163→80/163→92, AB-D4: 167→84/–, AT: 161→144/161→107, and AT-D4: 165→148/–. Limit of detection and lower limit of quantification for AB and AT in urine were 0.13/0.39 ng/mL and 0.08/0.24 ng/mL, respectively.

Measuring BoEs

Total NNAL [56], total nicotine equivalents [56], monohydroxybutenylmercapturic acid [56,58], HMPMA [56,58], 3-hydroxypropylmercapturic acid [56,58], total N-nitrosonornicotine [56], S-phenylmercapturic acid [58], and 3-hydroxybenzo[a]pyrene [59] in urine were analyzed by ABF using validated LC-MS/MS methods as previously described.

Measuring BoPHs

HDL was measured at Nordic Bioscience (Herlev, Denmark) and Clinical Chemistry and Pharmacology laboratory at Uppsala University Hospital in Uppsala, Sweden, using Advia Chemistry System–Direct HDL Cholesterol (Siemens Healthcare) and Cobas Pro (Roche Diagnostics International), in accordance with the manufacturer's protocol, respectively. Total WBC count was measured at Sanos Clinic (Herlev, Denmark) and Clinical Chemistry and Pharmacology laboratory (Uppsala University Hospital, Uppsala, Sweden) using the XN-550 and XN-20 systems (Sysmex), respectively.

Urinary 8-epi-PGF2α type III and 11-dTX B2 measurements were carried out at ABF as previously described [60]. Plasma sICAM-1 was measured at Celerion (Zurich, Switzerland) by an enzyme-linked immunosorbent assay kit (DuoSet; R&D Systems).

COHb analysis was carried out at ABF by headspace gas chromatography–mass spectrometry as previously described [61], with modifications. In brief, 100 µL of whole blood was spiked with 50 µL of IS solution (saturated whole blood containing 13COHb) and 1.4 mL of water. Carbon monoxide was released with the addition of 200 µL of potassium hexacyanoferrate solution 200 g/L at 55 °C for 30 minutes. Next, 1 mL of the head space was injected into a model 6890 gas chromatograph interfaced to a model 5973 mass selective detector (Agilent Technologies) using a multipurpose autosampler (Gerstel). Chromatographic separation was conducted on an Rt-Msieve 5A porous layer open tubular capillary column (30 m × 0.32 mm inner diameter, 30 µm film thickness; Restek). The injector temperature was set to 150 °C with a split of 9:1 and a constant helium flow of 1.9 mL/minute. An isothermal temperature program (45 °C) was applied for chromatographic separation. Mass spectrometry detection was performed in the selected ion monitoring mode with electron impact ionization. The transfer line temperature was set to 280 °C with a source temperature of 230 °C and a quadrupole temperature of 150 °C. The mass fragment m/z 28 (IS: 29) was used for quantification, with m/z 12 (IS: 13) as qualifier.

For CIMT, ultrasound assessment was performed on a 10-mm section of the distal portion of the common carotid artery, on both sides of the neck, at least 5 mm from the carotid bulb. The mean, SD, and maximum thickness of the intima-media were

recorded using the Acuson P500 Ultrasound System (Siemens Healthcare).

FEV_1%pred was measured by spirometry assessment (without a bronchodilator) using the EasyOne Pro (Sweden) or Easy on-PC (Denmark) spirometers (NDD Medical Technologies) in accordance with the procedures outlined by the American Thoracic Society and European Respiratory Society [65]; values were standardized to predictive values of the Global Lung Function Initiative [66]. Participants were not allowed to eat for 2 hours and 1 hour, or to use NPs or smoke for 1 hour and 30 minutes, before spirometry and FeNO assessments, respectively. FeNO was measured using the Vivatmo Pro device (Bosch Healthcare Solutions).

Other Assessments

Oral health was assessed with the Oral Health Assessment Tool [69,70]. Quality of life was assessed with the 36-Item Short Form Health Survey questionnaire (RAND Corporation) [71].

Nicotine Content in Used NPs

Unused NPs brought by the participants for nicotine content analysis were stored at 2 °C to 8 °C. NPs used during the confinement period were collected into a single container and stored at 2 °C to 8 °C until analysis. The NPs were analyzed for nicotine content by gas chromatography with flame ionization detector at Labstat International Inc in Kitchener, Ontario, Canada. In brief, 3 unused pouches (approximately 2 g) or all of the participants' used pouches were cut in half, and both the contents and the pouch material were added to an extraction vessel. Next, 5 mL of 2N sodium hydroxide was added to the extraction vessel, which was subsequently sealed and allowed to stand for 15 minutes. Subsequently, 50 mL of an extraction solution of 10 mL of quinoline primary stock (10 g of quinoline accurately weighed into a 250-mL volumetric flask and diluted to volume with methyl t-butyl ether) diluted to volume with methyl t-butyl ether was added to the extraction vessel, which was then sealed. The extraction vessel was shaken in a linear shaker in a horizontal position for 2 hours, after which it was placed in the dark in a vertical position to allow the phases to separate (maximum 2 hours). The organic phase (top layer) was then transferred to an amber autosampler vial.

Safety

Participant safety during the study was monitored by physical examination, vital signs, 12-lead electrocardiogram, and laboratory assessments, including hematology, virology, biochemistry, and urinalysis. Any AEs or serious AEs were monitored throughout the confinement period and by telephone follow-up up to 1 week after discharge. If the study was stopped because of an AE, it would not be restarted without consultation with the study ethics committee.

All AEs were recorded on the eCRF, coded in accordance with the latest version of the Medical Dictionary for Regulatory Activities, and tabulated by system organ class and preferred term. Severity was classified as mild (does not cause significant discomfort or change in activities of daily living; symptoms are easily tolerated), moderate (causes inconvenience or concern to the participant; interferes with activities of daily living but such activities may be continued), or severe (significantly interferes with activities of daily living to the point where they cannot be continued, or the participant is incapacitated). Numbers and percentages of participants reporting at least one AE, one serious AE, or an AE leading to withdrawal, as well as numbers and percentages of participants with AEs by severity were reported.

Participants who developed an AE at any time during the study, including the period between discharge and follow-up, were followed until assessments had returned to baseline, or the PI had determined that these events were no longer clinically significant. Provided there were no AEs that required further attention, the participant's involvement in the study was complete. The ethics committee was informed of study completion within 90 days of the last participant's final study procedures.

Statistical Analysis

In the absence of any NP biomarker data, the sample size was based on data from former and current smokers for sICAM-1, which shows the most variability in values in the literature. Assuming a ratio of mean values between NP users and smokers of 0.847 and a coefficient of variation of 27.1% to 32.8% based on data from Haswell et al [72], PROC POWER in SAS software (version 9.4; SAS Institute) was used to calculate that 84 to 120 participants would be the minimum needed to demonstrate a statistically significant difference with β=.2 and α=.05. The split between NP users and current smokers was not planned to be equal; therefore, a minimum sample size of 120 was fixed for the 2 groups combined. To allow for attrition and noncompliant NP users, 100 participants was the target to be recruited to the NP user group, 40 to the current smoker group (because the values are less variable and better described in the literature), and 40 to each of the former and never smoker groups to characterize biomarker levels in these groups. If withdrawal from the NP user group led to a substantial drop in sample size, new participants could be recruited to ensure that minimum values were met.

Data Analysis

The data were analyzed using SAS version 9.4. For continuous variables, the number of participants, mean, SD, median, minimum, and maximum were tabulated by study arm and overall. Categorical variable frequencies (number and percentages) were tabulated by study arm.

The group means of each of the primary end points were compared between participants who were solus users of Lyft NP products (arm A) and participants who were solus conventional cigarette smokers (arm B) in both the per-protocol population and the CEVal-, AB-, and AT-compliant populations. This was performed using a multiple linear regression model with the respective biomarker (Y_j) as the dependent variable and the arm (X_1) as the independent variable. The variables age (X_2), sex (X_3), and site (X_4) were added to the model in a stepwise manner and kept in the final model if they showed significance on an α level of .05. A final model for each biomarker (primary end point) was estimated; for example, the final model could differ among the end points because of the

stepwise approach. If the assumption of the model was not valid (normally distributed residual data), then the biomarker data were log-transformed, that is, log(Yj). If the data were log-transformed and the residuals remained not normally distributed, the Mann-Whitney *U* test was used to ensure an accurate testing method. To adjust for multiple testing for the primary end points, Bonferroni correction was applied. The α level was divided by 7 (7 primary end points): .05/7=.007143. Because of the adjustments, the 99.286% CIs for the estimated least square means were presented. The same approach was applied for the secondary end points as previously described for the primary end points but without Bonferroni adjustment.

Data Management

The protocol for data management is described in full in a data management plan, which was finalized before any data were collected. Completeness of the participants' records, accuracy of recording on the eCRFs, adherence to both the study protocol and good practice guidelines, and progress of enrollment were checked throughout the study by an independent clinical research associate. The eCRFs served as the source documents for reviewing data collection procedures.

Data that were initially collected on paper documents were entered in the electronic data capture system by staff at each clinical site. Data entry underwent quality control checks, and any discrepancies in the database were resolved. After all data validation steps, the PI or designee electronically signed the completed electronic data before database lock. All primary sources and copies of data generated by each study site (eg, data sheets, CRFs, electronic records, correspondence, laboratory records, and photographs) required for construction and evaluation of the study report will be retained in the archives of the 2 study sites for 25 years after study completion.

Results

The results of this study were received in mid-2022 and will be published in late 2022 to early 2023.

Discussion

Overview

NPs, a modern oral nicotine product, have been commercially available in a number of countries since the mid-2010s. Recent surveys of retail sales [17] and product use [16] show that NPs are gaining popularity in the United States, and some authors have suggested that they may form part of a THR approach [23]. To date, however, there are few data available on these relatively new products [14,15,21,22,73-78].

In terms of use and appearance, NPs are very similar to Swedish snus, an oral smokeless tobacco product that has been traditionally used in Scandinavia for more than 100 years. Although overall tobacco product use in Sweden is comparable with that in the rest of Europe, smoking-associated deaths are much lower because most tobacco consumers use snus [19]. This has been termed the "Swedish experience" [79], and the lower risks of harm from snus compared with combustible cigarettes have been recognized by the US Food and Drug Administration [20]. Of note, a recent analysis of the toxicant content of NPs compared with that of snus has demonstrated that most of the measured HPHCs (22 of 25) are unquantifiable in NPs, whereas only approximately half of the measured HPHCs (11 of 23) are unquantifiable in Swedish snus [15], raising the possibility that, similar to Swedish snus, NPs may have reduced health risks compared with cigarette smoking. To determine whether the low number and levels of HPHCs in NPs translate to a reduction in toxicant exposure and potential risk for users compared with cigarette smokers, this cross-sectional study compared BoEs and BoPHs between individuals who have been exclusively using NPs for 6 months and current smokers. The results from this study will provide an indication of the exposure of NP users to tobacco and tobacco smoke toxicants arising from NP use and relative levels compared with current, former, and never smokers. In addition, this study will give an indication of the real-world levels of BoPHs in regular NP users compared with current, former, and never smokers. Furthermore, the study will generally add to the scientific characterization of these relatively new nicotine products with additional subjective, physiological, and behavioral data.

Biomarker studies are frequently used to evaluate exposure to environmental and occupational toxicants and have recently been applied to assess the effects of switching from smoking combustible cigarettes to using alternative nicotine and tobacco products. Reductions in several BoEs and BoPHs have been documented when smokers switch to using e-cigarettes [27,80,81], tobacco heating products [25,26,28,56], and NRT [27], helping to establish the relative health risks of these products. This study will continue to build on data from these other tobacco and nicotine product categories. To the best of our knowledge, this is the first time that BoEs and BoPHs have been measured in NP users, providing information on 17 BoEs and BoPHs in NP users in comparison with current, former, and never smokers. The findings should add to our overall knowledge on NPs by providing the relative levels of exposure to tobacco toxicants as well as an insight into the potential risk from use of these modern tobacco-free NP products compared with cigarette smoking.

Strengths

This study includes some strengths. First, participants who self-reported as solus NP users and former smokers were confirmed as not having used combustible tobacco products through CEVal assessment [28,67]. Furthermore, as snus use is popular in Scandinavia, particularly in Sweden, an attempt was made to confirm that the NP users and former smokers did not use snus. Although snus is recognized as a reduced risk product [20], it has been shown to contain a higher number of toxicants than NPs [15]. Therefore, snus use could have potentially affected BoEs and BoPHs if participants in the NP group used snus but failed to report this, which was a possibility given the similarities between use and physical characteristics of NPs and snus. Hence, a further compliance assessment of AB and AT was included because CEVal, a biomarker for acrylonitrile exposure, cannot detect snus use. These alkaloids have been suggested as biomarkers to detect tobacco consumption during NRT use [82,83] and were suggested as potential compliance biomarker candidates to detect short-term

smokeless tobacco use during this study by experts from a bioanalytical laboratory, although an assessment of these alkaloids in NPs has not been made. A second strength of this study is that it measured BoEs and BoPHs in individuals who are regular users of NPs through their own choice, rather than in individuals who are asked to try the product for a few days [27,81], and should therefore provide information specific to this user group. Third, this cross-sectional approach recruited regular users of NPs, an approach which may better reflect real-world NP use compared with an approach that asks smokers to switch to NPs as part of a longitudinal design. Fourth, this cross-sectional approach limits the chance of participant withdrawals. Fifth, because of the cross-sectional study design, the sample size of 220 is considerably higher than that in some previous product-switching trials [80]. Finally, an additional strength of the study is that the confinement period allowed 24-hour urine samples to be collected (as opposed to spot urine collection) and blood samples to be collected at consistent times to help minimize variability in the biomarker data.

Limitations

The study also includes some limitations. First, the cross-sectional study design enables the study population to be assessed at a single point in time, but unlike in longitudinal studies, in which the same individuals are assessed multiple times over a longer study period (eg, up to 12 months [26,28]), information about changes over time will not be obtained. On the basis of the results from longitudinal studies, 6 months of NP use was deemed sufficient for changes in BoEs and particularly in BoPHs to have occurred in this study [28]. Second, the cross-sectional design approach means that no baseline assessments were made. Therefore, this may lead to greater variability in the biomarker results because comparisons were made between different populations as opposed to investigating biomarker-level changes within populations as per a longitudinal study approach. Third, some of the BoPHs assessed in this study (eg, WBCs, HDL, and sICAM-1) are not specific biomarkers of smoking-related disorders and may also be influenced by environmental exposure and lifestyle choices such as diet and exercise [84]. Finally, although compliance measures were implemented, these have limitations in terms of their sensitivity to detect tobacco cigarette and smokeless tobacco use, and they cannot detect use of other nicotine products such as e-cigarettes. In addition, participants self-reported product use (quantity and length of time that they have, or have not, been using the products), which cannot be corroborated fully with the current compliance and screening procedures (ie, eCO). Therefore, we cannot guarantee that current and past product use requirements will be fully met. This information is likely to be controlled better in a longitudinal study in which there is a defined switching period and regular contact with the participants.

Conclusions

With the rising consumer interest in NPs [16,17] and the potential role of these products in a THR approach [23], the results of this study are expected to provide timely information on BoE and BoPH levels among regular and relatively long-term (>6 months) users of NPs. These data will contribute to the growing body of evidence on NPs and their potential as a reduced-risk alternative nicotine source for smokers who fully switch from combustible cigarettes to using these tobacco-free NPs.

Data Availability

British American Tobacco is committed to the responsible sharing of data with the wider research community. Data access is administered for this study through an internal data-sharing committee on reasonable request after completion of a data-sharing request form and, if applicable, a data access agreement. Requests for data sharing in the first instance should be emailed to the corresponding author.

Authors' Contributions

DA, LEH, MM, NG, JT, and GH contributed to the design of the study. JT and FM provided statistical expertise, including the sample size calculation and statistical analysis plan review. DA led the study, supported by JF. DA wrote the first draft of the manuscript. All authors read, edited, and approved the final manuscript.

Conflicts of Interest

British American Tobacco (BAT) was the sponsor of this study and provided funding. All authors were employees of BAT at the point of manuscript submission, except for JT who was a BAT employee during the design of the study and throughout the clinical phase. BAT is a company that manufactures tobacco and nicotine products.

References

1. National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Atlanta, GA, USA: Centers for Disease Control and Prevention (US); 2014.
2. Hukkanen J, Jacob 3rd P, Benowitz NL. Metabolism and disposition kinetics of nicotine. Pharmacol Rev 2005 Mar;57(1):79-115. [doi: 10.1124/pr.57.1.3] [Medline: 15734728]
3. Benowitz N. Nicotine addiction. N Engl J Med 2010 Jun 17;362(24):2295-2303 [FREE Full text] [doi: 10.1056/NEJMra0809890] [Medline: 20554984]

4. Centers for Disease Control and Prevention (US), National Center for Chronic Disease Prevention and Health Promotion (US); Office on Smoking and Health (US). How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. Atlanta, GA, USA: Centers for Disease Control and Prevention (US); 2010.
5. Fearon IM, Phillips G, Carr T, Taylor M, Breheny D, Faux SP. The role of oxidative stress in smoking-related diseases. Mini Rev Org Chem 2011 Nov 01;8(4):360-371 [FREE Full text] [doi: 10.2174/157019311797440317]
6. Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observations on male British doctors. BMJ 1994 Oct 08;309(6959):901-911 [FREE Full text] [doi: 10.1136/bmj.309.6959.901] [Medline: 7755693]
7. Stratton K, Shetty P, Wallace R, Bondurant S. Clearing the smoke: the science base for tobacco harm reduction--executive summary. Tob Control 2001 Jun;10(2):189-195 [FREE Full text] [doi: 10.1136/tc.10.2.189] [Medline: 11387543]
8. McNeill A, Munafò MR. Reducing harm from tobacco use. J Psychopharmacol 2013 Jan;27(1):13-18. [doi: 10.1177/0269881112458731] [Medline: 23035032]
9. Nicotine without smoke: tobacco harm reduction. A Report by the Tobacco Advisory Group of the Royal College of Physicians. Royal College of Physicians. London, UK: Royal College of Physicians; 2016 Apr. URL: https://www.rcplondon.ac.uk/projects/outputs/nicotine-without-smoke-tobacco-harm-reduction [accessed 2022-08-13]
10. Gottlieb S. Protecting American Families: Comprehensive Approach to Nicotine and Tobacco. U.S. Food & Drug Administration. White Oak, MD, USA: U.S. Food & Drug Administration; 2017 Jun 27. URL: https://www.fda.gov/news-events/speeches-fda-officials/protecting-american-families-comprehensive-approach-nicotine-and-tobacco-06282017 [accessed 2022-08-13]
11. Health matters: stopping smoking – what works? Public Health England. London, UK: Public Health England; 2019 Dec 17. URL: https://www.gov.uk/government/publications/health-matters-stopping-smoking-what-works/health-matters-stopping-smoking-what-works [accessed 2022-08-13]
12. Cox S, Dawkins L. Global and local perspectives on tobacco harm reduction: what are the issues and where do we go from here? Harm Reduct J 2018 Jun 22;15(1):32 [FREE Full text] [doi: 10.1186/s12954-018-0239-5] [Medline: 29933744]
13. O'Leary R, Polosa R. Tobacco harm reduction in the 21st century. Drugs Alcohol Today 2020 Jul 13;20(3):219-234 [FREE Full text] [doi: 10.1108/dat-02-2020-0007]
14. Plurphanswat N, Hughes JR, Fagerström K, Rodu B. Initial information on a novel nicotine product. Am J Addict 2020 Jul;29(4):279-286. [doi: 10.1111/ajad.13020] [Medline: 32176374]
15. Azzopardi D, Liu C, Murphy J. Chemical characterization of tobacco-free "modern" oral nicotine pouches and their position on the toxicant and risk continuums. Drug Chem Toxicol 2022 Sep;45(5):2246-2254. [doi: 10.1080/01480545.2021.1925691] [Medline: 34034614]
16. Delnevo CD, Hrywna M, Miller Lo EJ, Wackowski OA. Examining market trends in smokeless tobacco sales in the United States: 2011-2019. Nicotine Tob Res 2021 Aug 04;23(8):1420-1424 [FREE Full text] [doi: 10.1093/ntr/ntaa239] [Medline: 33241271]
17. Marynak KL, Wang X, Borowiecki M, Kim Y, Tynan MA, Emery S, et al. Nicotine pouch unit sales in the US, 2016-2020. JAMA 2021 Aug 10;326(6):566-568 [FREE Full text] [doi: 10.1001/jama.2021.10366] [Medline: 34374729]
18. Tattan-Birch H, Jackson SE, Dockrell M, Brown J. Tobacco-free nicotine pouch use in Great Britain: a representative population survey 2020-2021. Nicotine Tob Res 2022 Aug 06;24(9):1509-1512 [FREE Full text] [doi: 10.1093/ntr/ntac099] [Medline: 35417551]
19. Clarke E, Thompson K, Weaver S, Thompson J, O'Connell G. Snus: a compelling harm reduction alternative to cigarettes. Harm Reduct J 2019 Nov 27;16(1):62 [FREE Full text] [doi: 10.1186/s12954-019-0335-1] [Medline: 31775744]
20. FDA grants first-ever modified risk orders to eight smokeless tobacco products. U.S. Food & Drug Administration. 2019 Oct 22. URL: https://www.fda.gov/news-events/press-announcements/fda-grants-first-ever-modified-risk-orders-eight-smokeless-tobacco-products [accessed 2022-08-13]
21. Bishop E, East N, Bozhilova S, Santopietro S, Smart D, Taylor M, et al. An approach for the extract generation and toxicological assessment of tobacco-free 'modern' oral nicotine pouches. Food Chem Toxicol 2020 Nov;145:111713 [FREE Full text] [doi: 10.1016/j.fct.2020.111713]
22. Yu F, Rudd K, Pour SJ, Trelles Sticken E, Dethloff O, Wieczorek R, et al. Preclinical assessment of tobacco-free nicotine pouches demonstrates reduced in vitro toxicity compared with tobacco snus and combustible cigarette smoke. Appl In Vitro Toxicol 2022 Mar 17;8(1):24-35 [FREE Full text] [doi: 10.1089/aivt.2021.0020]
23. Palmer AM, Toll BA, Carpenter MJ, Donny EC, Hatsukami DK, Rojewski AM, et al. Reappraising choice in addiction: novel conceptualizations and treatments for tobacco use disorder. Nicotine Tob Res 2022 Jan 01;24(1):3-9 [FREE Full text] [doi: 10.1093/ntr/ntab148] [Medline: 34270729]
24. Institute of Medicine (US) Committee to Assess the Science Base for Tobacco Harm Reduction, Stratton K, Shetty P, Wallace R, Bondurant S. Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction. Washington, DC, USA: National Academies Press (US); 2001.
25. Gale N, McEwan M, Eldridge AC, Fearon IM, Sherwood N, Bowen E, et al. Changes in biomarkers of exposure on switching from a conventional cigarette to tobacco heating products: a randomized, controlled study in healthy Japanese subjects. Nicotine Tob Res 2019 Aug 19;21(9):1220-1227 [FREE Full text] [doi: 10.1093/ntr/nty104] [Medline: 29912406]

26. Lüdicke F, Ansari SM, Lama N, Blanc N, Bosilkovska M, Donelli A, et al. Effects of switching to a heat-not-burn tobacco product on biologically relevant biomarkers to assess a candidate modified risk tobacco product: a randomized trial. Cancer Epidemiol Biomarkers Prev 2019 Nov;28(11):1934-1943. [doi: 10.1158/1055-9965.EPI-18-0915] [Medline: 31270101]
27. Round EK, Chen P, Taylor AK, Schmidt E. Biomarkers of tobacco exposure decrease after smokers switch to an e-cigarette or nicotine gum. Nicotine Tob Res 2019 Aug 19;21(9):1239-1247 [FREE Full text] [doi: 10.1093/ntr/nty140] [Medline: 30202883]
28. Gale N, McEwan M, Camacho OM, Hardie G, Proctor CJ, Murphy J. Changes in biomarkers after 180 days of tobacco heating product use: a randomised trial. Intern Emerg Med 2021 Nov;16(8):2201-2212 [FREE Full text] [doi: 10.1007/s11739-021-02798-6] [Medline: 34196886]
29. McEwan M, Gale N, Ebajemito JK, Camacho OM, Hardie G, Proctor CJ, et al. A randomized controlled study in healthy participants to explore the exposure continuum when smokers switch to a tobacco heating product or an E-cigarette relative to cessation. Toxicol Rep 2021 May 8;8:994-1001 [FREE Full text] [doi: 10.1016/j.toxrep.2021.05.003] [Medline: 34026564]
30. WHO study group on tobacco product regulation: report on the scientific basis of tobacco product regulation: fifth report of a WHO study group. World Health Organization. Geneva, Switzerland: World Health Organization; 2015. URL: https://apps.who.int/iris/handle/10665/161512 [accessed 2022-08-13]
31. Calapai G, Caputi AP, Mannucci C, Russo GA, Gregg E, Puntoni R, et al. Cardiovascular biomarkers in groups of established smokers after a decade of smoking. Basic Clin Pharmacol Toxicol 2009 Apr;104(4):322-328 [FREE Full text] [doi: 10.1111/j.1742-7843.2008.00361.x] [Medline: 19175368]
32. Félétou M, Vanhoutte PM, Verbeuren TJ. The thromboxane/endoperoxide receptor (TP): the common villain. J Cardiovasc Pharmacol 2010 Apr;55(4):317-332. [doi: 10.1097/fjc.0b013e3181d8bc8a] [Medline: 20422736]
33. Lopez LR, Guyer KE, Torre IG, Pitts KR, Matsuura E, Ames PR. Platelet thromboxane (11-dehydro-Thromboxane B2) and aspirin response in patients with diabetes and coronary artery disease. World J Diabetes 2014 Apr 15;5(2):115-127 [FREE Full text] [doi: 10.4239/wjd.v5.i2.115] [Medline: 24748925]
34. Milne GL, Musiek ES, Morrow JD. F2-isoprostanes as markers of oxidative stress in vivo: an overview. Biomarkers 2005 Nov;10 Suppl 1:S10-S23. [doi: 10.1080/13547500500216546] [Medline: 16298907]
35. Scherer G. Suitability of biomarkers of biological effects (BOBEs) for assessing the likelihood of reducing the tobacco related disease risk by new and innovative tobacco products: a literature review. Regul Toxicol Pharmacol 2018 Apr;94:203-233. [doi: 10.1016/j.yrtph.2018.02.002] [Medline: 29428304]
36. Hisamatsu T, Miura K, Arima H, Kadota A, Kadowaki S, Torii S, Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA) Research Group. Smoking, smoking cessation, and measures of subclinical atherosclerosis in multiple vascular beds in Japanese men. J Am Heart Assoc 2016 Aug 29;5(9):e003738 [FREE Full text] [doi: 10.1161/JAHA.116.003738] [Medline: 27572823]
37. Kianoush S, Yakoob MY, Al-Rifai M, DeFilippis AP, Bittencourt MS, Duncan BB, et al. Associations of cigarette smoking with subclinical inflammation and atherosclerosis: ELSA-Brasil (The Brazilian Longitudinal Study of Adult Health). J Am Heart Assoc 2017 Jun 24;6(6):e005088 [FREE Full text] [doi: 10.1161/JAHA.116.005088] [Medline: 28647689]
38. Conklin DJ, Schick S, Blaha MJ, Carll A, DeFilippis A, Ganz P, et al. Cardiovascular injury induced by tobacco products: assessment of risk factors and biomarkers of harm. A Tobacco Centers of Regulatory Science compilation. Am J Physiol Heart Circ Physiol 2019 Apr 01;316(4):H801-H827 [FREE Full text] [doi: 10.1152/ajpheart.00591.2018] [Medline: 30707616]
39. Lind P, Engström G, Stavenow L, Janzon L, Lindgärde F, Hedblad B. Risk of myocardial infarction and stroke in smokers is related to plasma levels of inflammation-sensitive proteins. Arterioscler Thromb Vasc Biol 2004 Mar;24(3):577-582. [doi: 10.1161/01.ATV.0000116863.37311.82] [Medline: 14726408]
40. Hedblad B, Ogren M, Engström G, Wollmer P, Janzon L. Heterogeneity of cardiovascular risk among smokers is related to degree of carbon monoxide exposure. Atherosclerosis 2005 Mar;179(1):177-183. [doi: 10.1016/j.atherosclerosis.2004.10.005] [Medline: 15721025]
41. Hedblad B, Engström G, Janzon E, Berglund G, Janzon L. COHb% as a marker of cardiovascular risk in never smokers: results from a population-based cohort study. Scand J Public Health 2006;34(6):609-615. [doi: 10.1080/14034940600590523] [Medline: 17132594]
42. Barnes PJ, Dweik RA, Gelb AF, Gibson PG, George SC, Grasemann H, et al. Exhaled nitric oxide in pulmonary diseases: a comprehensive review. Chest 2010 Sep;138(3):682-692. [doi: 10.1378/chest.09-2090] [Medline: 20822990]
43. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2013 Mar 15;187(4):347-365. [doi: 10.1164/rccm.201204-0596PP] [Medline: 22878278]
44. Emerging Risk Factors Collaboration, Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, et al. Major lipids, apolipoproteins, and risk of vascular disease. JAMA 2009 Nov 11;302(18):1993-2000 [FREE Full text] [doi: 10.1001/jama.2009.1619] [Medline: 19903920]
45. Charland SL, Malone DC. Prediction of cardiovascular event risk reduction from lipid changes associated with high potency dyslipidemia therapy. Curr Med Res Opin 2010 Mar;26(2):365-375. [doi: 10.1185/03007990903484802] [Medline: 19995326]

46. Soria-Florido M, Schröder H, Grau M, Fitó M, Lassale C. High density lipoprotein functionality and cardiovascular events and mortality: a systematic review and meta-analysis. Atherosclerosis 2020 Jun;302:36-42. [doi: 10.1016/j.atherosclerosis.2020.04.015] [Medline: 32438197]
47. Ridker PM, Hennekens CH, Roitman-Johnson B, Stampfer MJ, Allen J. Plasma concentration of soluble intercellular adhesion molecule 1 and risks of future myocardial infarction in apparently healthy men. Lancet 1998 Jan 10;351(9096):88-92. [doi: 10.1016/S0140-6736(97)09032-6] [Medline: 9439492]
48. Malik I, Danesh J, Whincup P, Bhatia V, Papacosta O, Walker M, et al. Soluble adhesion molecules and prediction of coronary heart disease: a prospective study and meta-analysis. Lancet 2001 Sep 22;358(9286):971-976. [doi: 10.1016/S0140-6736(01)06104-9] [Medline: 11583751]
49. Wu KK, Aleksic N, Ballantyne CM, Ahn C, Juneja H, Boerwinkle E. Interaction between soluble thrombomodulin and intercellular adhesion molecule-1 in predicting risk of coronary heart disease. Circulation 2003 Apr 08;107(13):1729-1732. [doi: 10.1161/01.CIR.0000064894.97094.4F] [Medline: 12668515]
50. Zalokar JB, Richard JL, Claude JR. Leukocyte count, smoking, and myocardial infarction. N Engl J Med 1981 Mar 19;304(8):465-468. [doi: 10.1056/NEJM198102193040806] [Medline: 7453772]
51. Mänttäri M, Manninen V, Koskinen P, Huttunen JK, Oksanen E, Tenkanen L, et al. Leukocytes as a coronary risk factor in a dyslipidemic male population. Am Heart J 1992 Apr;123(4 Pt 1):873-877. [doi: 10.1016/0002-8703(92)90690-w] [Medline: 1549995]
52. Brown DW, Giles WH, Croft JB. White blood cell count: an independent predictor of coronary heart disease mortality among a national cohort. J Clin Epidemiol 2001 Mar;54(3):316-322. [doi: 10.1016/s0895-4356(00)00296-1] [Medline: 11223329]
53. Madjid M, Fatemi O. Components of the complete blood count as risk predictors for coronary heart disease: in-depth review and update. Tex Heart Inst J 2013;40(1):17-29 [FREE Full text] [Medline: 23467296]
54. Hecht SS, Murphy SE, Stepanov I, Nelson HH, Yuan JM. Tobacco smoke biomarkers and cancer risk among male smokers in the Shanghai cohort study. Cancer Lett 2013 Jun 28;334(1):34-38 [FREE Full text] [doi: 10.1016/j.canlet.2012.07.016] [Medline: 22824243]
55. Xue J, Yang S, Seng S. Mechanisms of cancer induction by tobacco-specific NNK and NNN. Cancers (Basel) 2014 May 14;6(2):1138-1156 [FREE Full text] [doi: 10.3390/cancers6021138] [Medline: 24830349]
56. Gale N, McEwan M, Eldridge AC, Sherwood N, Bowen E, McDermott S, et al. A randomised, controlled, two-centre open-label study in healthy Japanese subjects to evaluate the effect on biomarkers of exposure of switching from a conventional cigarette to a tobacco heating product. BMC Public Health 2017 Aug 22;17(1):673 [FREE Full text] [doi: 10.1186/s12889-017-4678-9] [Medline: 28830420]
57. Yuan JM, Butler LM, Stepanov I, Hecht SS. Urinary tobacco smoke-constituent biomarkers for assessing risk of lung cancer. Cancer Res 2014 Jan 15;74(2):401-411 [FREE Full text] [doi: 10.1158/0008-5472.CAN-13-3178] [Medline: 24408916]
58. Pluym N, Gilch G, Scherer G, Scherer M. Analysis of 18 urinary mercapturic acids by two high-throughput multiplex-LC-MS/MS methods. Anal Bioanal Chem 2015 Jul;407(18):5463-5476. [doi: 10.1007/s00216-015-8719-x] [Medline: 25935678]
59. Rögner N, Hagedorn HW, Scherer G, Scherer M, Pluym N. A sensitive LC–MS/MS method for the quantification of 3-hydroxybenzo[a]pyrene in urine-exposure assessment in smokers and users of potentially reduced-risk products. Separations 2021 Oct 05;8(10):171 [FREE Full text] [doi: 10.3390/separations8100171]
60. Sterz K, Scherer G, Ecker J. A simple and robust UPLC-SRM/MS method to quantify urinary eicosanoids. J Lipid Res 2012 May;53(5):1026-1036 [FREE Full text] [doi: 10.1194/jlr.D023739] [Medline: 22338011]
61. Angerer J. Carboxyhemoglobin [Biomonitoring Methods, 1985]. In: Parlar H, Brock TH, editors. The MAK-Collection for Occupational Health and Safety. Hoboken, NJ, USA: Wiley Online Library; 1985.
62. Molino A, Fuschillo S, Mosella M, Accardo M, Guida P, Motta A, et al. Comparison of three different exhaled nitric oxide analyzers in chronic respiratory disorders. J Breath Res 2019 Mar 06;13(2):021002. [doi: 10.1088/1752-7163/ab0167] [Medline: 30673653]
63. Tailor H, Mackie I, Mellick A, Machin S. Evaluation of the Sysmex XN-550, a Novel Compact Haematology analyser from the XN-L series, compared to the XN-20 system. Int J Lab Hematol 2017 Dec;39(6):585-589. [doi: 10.1111/ijlh.12701] [Medline: 28649771]
64. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr 2008 Mar;21(2):93-190. [doi: 10.1016/j.echo.2007.11.011] [Medline: 18261694]
65. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of spirometry 2019 update. An official American thoracic society and European respiratory society technical statement. Am J Respir Crit Care Med 2019 Oct 15;200(8):e70-e88 [FREE Full text] [doi: 10.1164/rccm.201908-1590ST] [Medline: 31613151]

66. Cooper BG, Stocks J, Hall GL, Culver B, Steenbruggen I, Carter KW, et al. The Global Lung Function Initiative (GLI) Network: bringing the world's respiratory reference values together. Breathe (Sheff) 2017 Sep;13(3):e56-e64 [FREE Full text] [doi: 10.1183/20734735.012717] [Medline: 28955406]
67. Camacho OM, Hedge A, Lowe F, Newland N, Gale N, McEwan M, et al. Statistical analysis plan for "A randomised, controlled study to evaluate the effects of switching from cigarette smoking to using a tobacco heating product on health effect indicators in healthy subjects". Contemp Clin Trials Commun 2020 Mar;17:100535 [FREE Full text] [doi: 10.1016/j.conctc.2020.100535] [Medline: 32072070]
68. Scherer G, Newland K, Papadopoulou E, Minet E. A correlation study applied to biomarkers of internal and effective dose for acrylonitrile and 4-aminobiphenyl in smokers. Biomarkers 2014 Jun;19(4):291-301 [FREE Full text] [doi: 10.3109/1354750X.2014.910271] [Medline: 24754403]
69. Chalmers J, Johnson V, Tang JH, Titler MG. Evidence-based protocol: oral hygiene care for functionally dependent and cognitively impaired older adults. J Gerontol Nurs 2004 Nov;30(11):5-12. [doi: 10.3928/0098-9134-20041101-06] [Medline: 15575186]
70. Oral health Assessment Tool. National Institute for Health and Care Excellence. 2016. URL: https://www.nice.org.uk/guidance/ng48/resources/oral-health-assessment-tool-pdf-2543183533 [accessed 2022-02-18]
71. 36-Item Short Form Survey Instrument (SF-36). RAND Corporation. Santa Monica, CA, USA: RAND Corporation; 2021. URL: https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form/survey-instrument.html [accessed 2022-02-18]
72. Haswell LE, Papadopoulou E, Newland N, Shepperd CJ, Lowe FJ. A cross-sectional analysis of candidate biomarkers of biological effect in smokers, never-smokers and ex-smokers. Biomarkers 2014 Aug;19(5):356-367. [doi: 10.3109/1354750X.2014.912354] [Medline: 24854418]
73. Lunell E, Fagerström K, Hughes J, Pendrill R. Pharmacokinetic comparison of a novel non-tobacco-based nicotine pouch (ZYN) with conventional, tobacco-based Swedish snus and American moist snuff. Nicotine Tob Res 2020 Oct 08;22(10):1757-1763. [doi: 10.1093/ntr/ntaa068] [Medline: 32319528]
74. East N, Bishop E, Breheny D, Gaca M, Thorne D. A screening approach for the evaluation of tobacco-free 'modern oral' nicotine products using Real Time Cell Analysis. Toxicol Rep 2021 Feb 25;8:481-488 [FREE Full text] [doi: 10.1016/j.toxrep.2021.02.014] [Medline: 33718000]
75. McEwan M, Azzopardi D, Gale N, Camacho OM, Hardie G, Fearon IM, et al. A randomised study to investigate the nicotine pharmacokinetics of oral nicotine pouches and a combustible cigarette. Eur J Drug Metab Pharmacokinet 2022 Mar;47(2):211-221 [FREE Full text] [doi: 10.1007/s13318-021-00742-9] [Medline: 34923602]
76. Rensch J, Liu J, Wang J, Vansickel A, Edmiston J, Sarkar M. Nicotine pharmacokinetics and subjective response among adult smokers using different flavors of on!® nicotine pouches compared to combustible cigarettes. Psychopharmacology (Berl) 2021 Nov;238(11):3325-3334. [doi: 10.1007/s00213-021-05948-y] [Medline: 34432106]
77. Stanfill S, Tran H, Tyx R, Fernandez C, Zhu W, Marynak K, et al. Characterization of total and unprotonated (free) nicotine content of nicotine pouch products. Nicotine Tob Res 2021 Aug 18;23(9):1590-1596. [doi: 10.1093/ntr/ntab030] [Medline: 34233354]
78. Azzopardi D, Ebajemito J, McEwan M, Camacho OM, Thissen J, Hardie G, et al. A randomised study to assess the nicotine pharmacokinetics of an oral nicotine pouch and two nicotine replacement therapy products. Sci Rep 2022 Apr 28;12(1):6949 [FREE Full text] [doi: 10.1038/s41598-022-10544-x] [Medline: 35484309]
79. Ramboll. Systematic review and update of the literature on the health effects of Swedish snus. Ramboll. 2019 May 13. URL: https://www.swedishmatch.com/globalassets/documents/other/ramboll-health-effects-update-report_20190513.pdf [accessed 2022-02-17]
80. Lorkiewicz P, Riggs DW, Keith RJ, Conklin DJ, Xie Z, Sutaria S, et al. Comparison of urinary biomarkers of exposure in humans using electronic cigarettes, combustible cigarettes, and smokeless tobacco. Nicotine Tob Res 2019 Aug 19;21(9):1228-1238 [FREE Full text] [doi: 10.1093/ntr/nty089] [Medline: 29868926]
81. Cohen G, Goldenson NI, Bailey PC, Chan S, Shiffman S. Changes in biomarkers of cigarette smoke exposure after 6 days of switching exclusively or partially to use of the JUUL System with two nicotine concentrations: a randomized controlled confinement study in adult smokers. Nicotine Tob Res 2021 Nov 05;23(12):2153-2161 [FREE Full text] [doi: 10.1093/ntr/ntab134] [Medline: 34161586]
82. Jacob 3rd P, Yu L, Shulgin AT, Benowitz NL. Minor tobacco alkaloids as biomarkers for tobacco use: comparison of users of cigarettes, smokeless tobacco, cigars, and pipes. Am J Public Health 1999 May;89(5):731-736. [doi: 10.2105/ajph.89.5.731] [Medline: 10224986]
83. Jacob 3rd P, Hatsukami D, Severson H, Hall S, Yu L, Benowitz NL. Anabasine and anatabine as biomarkers for tobacco use during nicotine replacement therapy. Cancer Epidemiol Biomarkers Prev 2002 Dec;11(12):1668-1673. [Medline: 12496059]
84. Chang CM, Cheng YC, Cho TM, Mishina EV, Del Valle-Pinero AY, van Bemmel DM, et al. Biomarkers of potential harm: summary of an FDA-sponsored public workshop. Nicotine Tob Res 2019 Jan 01;21(1):3-13. [doi: 10.1093/ntr/ntx273] [Medline: 29253243]

Abbreviations

11-dTX B2: 11-dehydrothromboxane B2
8-Epi-PGF2α type III: 8-Epi-prostaglandin F2α type III
AB: anabasine
ABF: Analytisch-Biologisches Forschungslabor
AE: adverse event
AT: anatabine
BAT: British American Tobacco
BoE: biomarker of exposure
BoPH: biomarker of potential harm
CEVal: N-(2-cyanoethyl)valine
COHb: carboxyhemoglobin
CRF: case report form
eCO: exhaled carbon monoxide
eCRF: electronic case report form
FeNO: fractional exhaled nitric oxide
FEV_1%pred: forced expiratory volume in 1 second as percentage of predicted
FMC: factory-made cigarette
HDL: high-density lipoprotein
HMPMA: 3-hydroxy-1-methylpropylmercapuric acid
HPHC: harmful and potentially harmful constituent
IS: internal standard
LC-MS/MS: liquid chromatography with tandem mass spectrometry
m/z: mass-to-charge ratio
NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NP: nicotine pouch
NRT: nicotine replacement therapy
PI: principal investigator
sICAM-1: soluble intercellular adhesion molecule-1
THR: tobacco harm reduction
WBC: white blood cell

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Protocol

Associations Between the Severity of Obsessive-Compulsive Disorder and Vocal Features in Children and Adolescents: Protocol for a Statistical and Machine Learning Analysis

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Abstract

Background: Artificial intelligence tools have the potential to objectively identify youth in need of mental health care. Speech signals have shown promise as a source for predicting various psychiatric conditions and transdiagnostic symptoms.

Objective: We designed a study testing the association between obsessive-compulsive disorder (OCD) diagnosis and symptom severity on vocal features in children and adolescents. Here, we present an analysis plan and statistical report for the study to document our a priori hypotheses and increase the robustness of the findings of our planned study.

Methods: Audio recordings of clinical interviews of 47 children and adolescents with OCD and 17 children and adolescents without a psychiatric diagnosis will be analyzed. Youths were between 8 and 17 years old. We will test the effect of OCD diagnosis on computationally derived scores of vocal activation using ANOVA. To test the effect of OCD severity classifications on the same computationally derived vocal scores, we will perform a logistic regression. Finally, we will attempt to create an improved indicator of OCD severity by refining the model with more relevant labels. Models will be adjusted for age and gender. Model validation strategies are outlined.

Results: Simulated results are presented. The actual results using real data will be presented in future publications.

Conclusions: A major strength of this study is that we will include age and gender in our models to increase classification accuracy. A major challenge is the suboptimal quality of the audio recordings, which are representative of in-the-wild data and a large body of recordings collected during other clinical trials. This preregistered analysis plan and statistical report will increase the validity of the interpretations of the upcoming results.

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KEYWORDS

machine learning; obsessive-compulsive disorder; vocal features; speech signals; children; teens; adolescents; OCD; AI; artificial intelligence; tool; mental health; care; speech; data; clinical trial; validity; results

Introduction

Obsessive-compulsive disorder (OCD) is a chronic, debilitating disorder, which can lower self-esteem, shorten life-expectancy, strain the family, and make it difficult to maintain friendships and attend school [1,2]. First-line treatment for moderate to severe OCD in youth (defined as individuals under age 18 years of age) is cognitive behavioral therapy (CBT) with exposure and response prevention (ERP) [3,4]. During exposure practice, the child tracks the level of distress caused by symptom-provoking stimuli across and within sessions. Here, distress refers to fear, disgust, discomfort, shame, embarrassment, and feelings of incompleteness or emptiness. Monitoring distress provides useful information to clinicians, who use it to plan exposures and help the patient remain mentally present with the exposure [5]. Distress levels also comprise one dimension of the gold-standard measure of symptom severity in OCD. When collected over time, distress can provide information about disease progression and improvement [6]. Frequent measures of distress are essential for understanding mechanisms of change in exposure-based therapies [5]. Self-rated distress may not be frequent enough to discover the processes responsible for therapeutic change, which has led some researchers to code videos of exposure sessions [7]. Behavioral coding is a time-consuming, costly process that is prone to inconsistency and not entirely immune to bias. Ideally, distress would be assessed objectively and affordably in a noninvasive manner.

Objective and automatic psychiatric assessments can be achieved by feeding vocal features into machine learning models. Speech patterns, tempo, volume, and intonation comprise an important part of the overall clinical impression that has been used to diagnose psychiatric disorders for at least 100 years [8]. Speech reflects changes in cognition, affect, motor characteristics, and physiology seen in psychiatric disorders [9]. Voice quality features capture information relating to voice creakiness, harshness, and breathiness [9]. Decreased formant frequencies observed in depressed and anxious speech may reflect dry mouth, decreased articulation, or motor coordination [9].

Vocal features have demonstrated promising results in machine learning for predicting the severity of psychiatric disorders and clinical improvement. A recent review summarized 127 studies that have used automatically extracted speech features to detect the presence or severity of psychiatric disorders [10]. The vocal fold features, jitter, and shimmer were found to be significantly elevated in adults with depression, anxiety, and OCD. Only one study has investigated vocal fold features in OCD. Results from 35 adults suggest that individuals with OCD have voices with more jitter, breathiness, hoarseness and speak at a lower rate than individuals without a psychiatric diagnosis [11]. Increased percent jitter and hoarseness have also been found in children (6-15 years old) with attention-deficit/hyperactivity disorder compared with healthy controls [12].

One major conclusion of the systematic review is that future studies should focus on linking vocal features to specific transdiagnostic problems, such as distress [10]. One study found that self-reported distress and electrodermal activity corresponded with vocal indicators of distress [13]. High levels of cortisol have also been linked to vocal indicators of distress [14]. Another study used audio recordings of 3- to 8-year-old children giving a speech under stressful conditions. The machine learning model classified children with and those without internalizing disorders using vocal features as input with 80% accuracy [15].

The aim of this paper is to increase the robustness of a planned study by documenting our analysis plan of a study with the following objectives: (1) to investigate the correspondence between activation-specific features and OCD diagnosis and severity [16] and (2) to adapt models trained on adult English speech to better align with the target population (Danish speech from children), thus obtaining improved indicators of OCD. In this paper, we also weigh our methodological decisions.

Methods

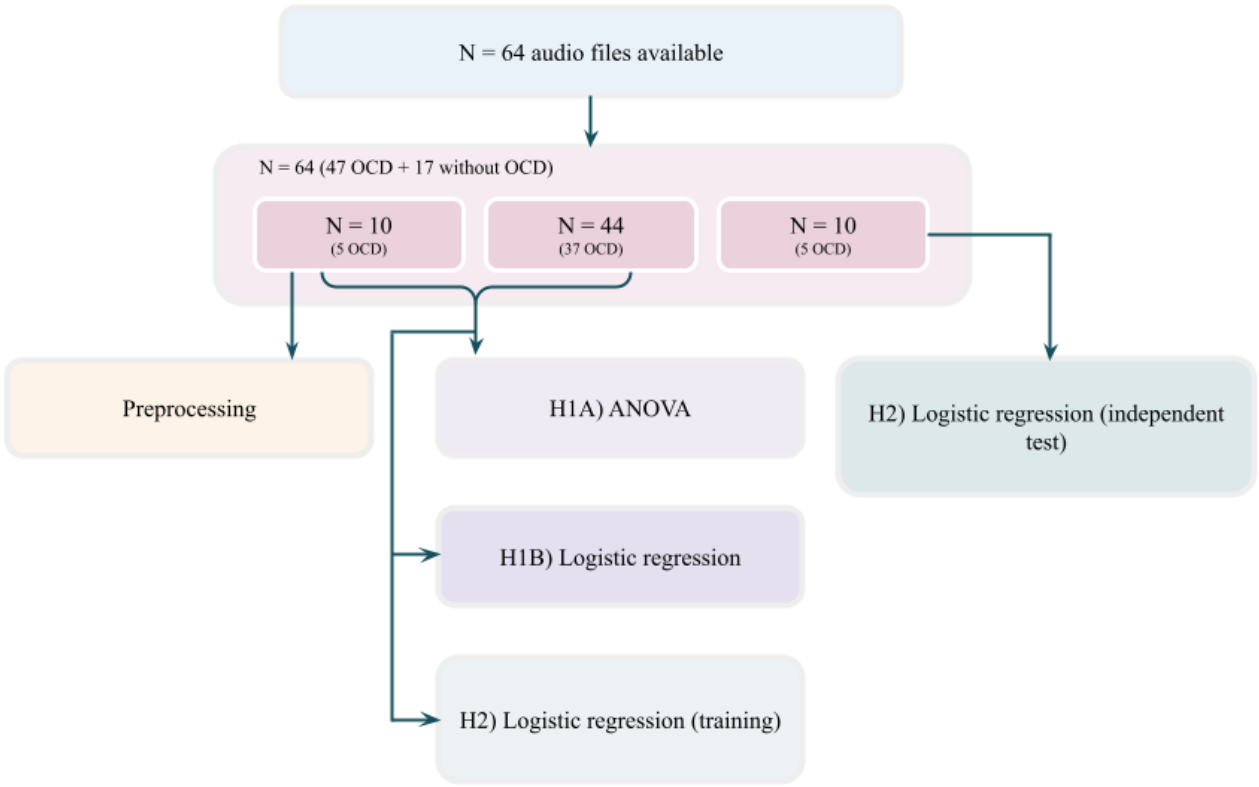
Participants and Setting

We will include audio recordings from a total of 64 youths aged 8 to 17 years (47 with OCD and 17 healthy controls). The audio recordings of diagnostic interviews stem from a large randomized clinical trial and case-control study of OCD, called TECTO [17]—TECTO runs at a public hospital in Denmark.

Ethics Approval

TECTO and the planned analyses have been approved by the ethics committee of the Capital Region of Denmark (H-18010607). The selection of participants in the current study is depicted in Figure 1.

Figure 1. Flow diagram of audio data selection. OCD: obsessive-compulsive disorder.



Measures

Trained mental health professionals conducted clinical interviews before inclusion in TECTO to establish diagnoses and OCD severity in patients and rule out psychiatric diagnoses in controls.

Diagnostic Status

Trained mental health professionals used a semistructured clinical interview—the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS)—to screen for and establish diagnoses in participants [18]. The K-SADS is designed to establish psychiatric diagnoses in youth between the ages of 6 and 18 years.

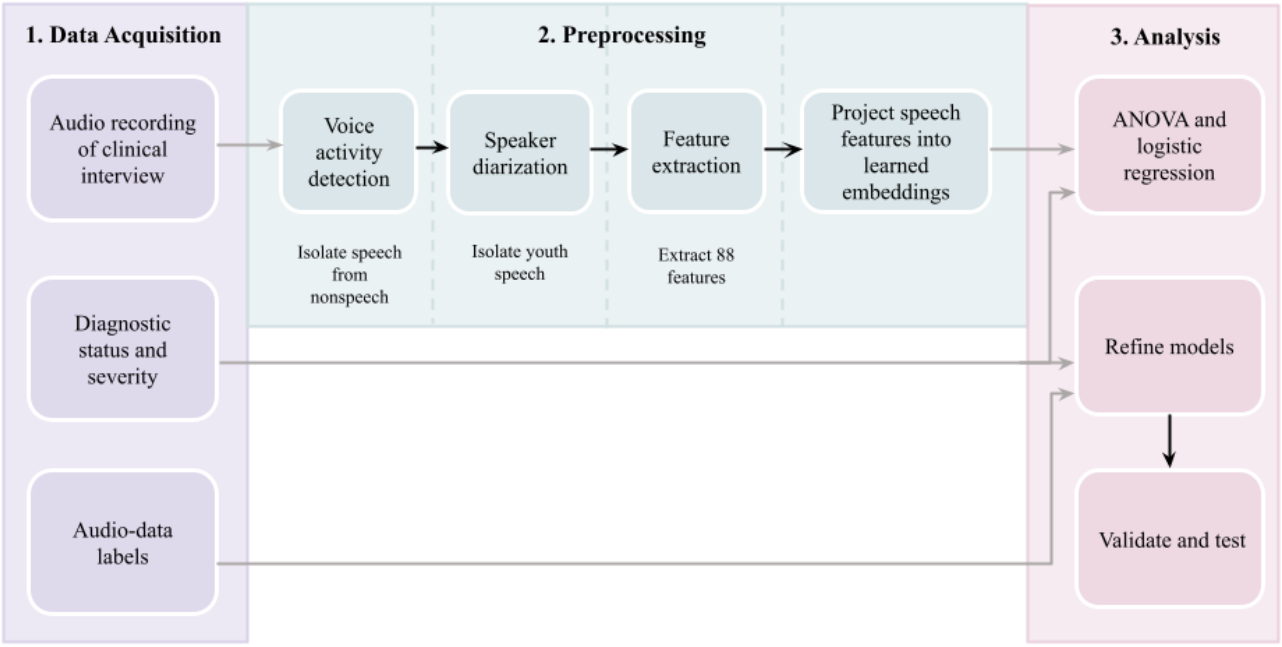
OCD Severity

Trained mental health professionals assessed the clinical severity of OCD using the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) [19]. The CY-BOCS interview begins with a checklist of obsessions and compulsions to establish which symptoms have been present over the past week. On a scale from 0 to 4, clinicians rate 5 items on the severity of obsessions and 5 items on the severity of compulsions. Severity is rated on 5 dimensions: level of distress caused by the symptoms, functional interference, time consumed by symptoms, and resistance to and degree of control over symptoms. A total severity score is calculated by summing all 10 items on a scale from 0 to 40. Although CY-BOCS scores are continuous, a previous study of 815 youth between the ages of 4 and 18 years found the following cutoff scores to be consistent with global clinical severity ratings: 0-7, subclinical; 8-15, mild; 16-24, moderate; and 25-40, moderate-severe to severe [20]. A CY-BOCS score of ≥16 was required to be included in the study.

Audio Data Source

Samples of child speech will be taken from the K-SADS interviews. Owing to limited labeled data, we will use the first 10 minutes of the 30- to 90-minute interviews. Audio recordings were obtained using an on-camera microphone of a Sony video camera placed in various positions and in different rooms across observations. Data analysis is outlined in Figure 2.

Figure 2. Overview of the data analysis process.



Statistical Analysis Plan

The planned study has two main objectives:

1. Test the usefulness of a previously learned latent model, composed of 2 dimensions representing a compressed vocal feature space guided by activation labels [16], as a marker for OCD diagnosis and severity.
2. Learn a new latent model, which we will propose as an improved candidate indicator of OCD severity.

Our first objective will be achieved through 2 statistical analyses, with the following hypotheses:

1. Objective 1 (H1): an ANOVA will be conducted to test the first research hypothesis (objective H1A) that there is an effect of diagnosis (OCD vs no psychiatric diagnosis) on the vocal feature latent model. With logistic regression (H1B), we will test hypothesis H1, which states that there is an effect of the vocal feature latent model on OCD severity classifications in moderate to extreme OCD cases, with the vocal feature latent model corrected for age and gender. This analysis will only include patients with OCD, and we will examine the classification accuracy of this model.
2. Objective 2 (H2): the second objective will be achieved through data labeling and machine learning modeling. Here, outcomes will include diagnostic status (OCD vs no psychiatric diagnosis) and OCD severity (CY-BOCS severity scores). We will validate the modeling using a leave-two-individuals-out cross-validation and prediction accuracies. Subsequently, we will assess the obtained results using an independent test. We will extract data from 10 of the youths' audio samples post machine learning modeling for this purpose.

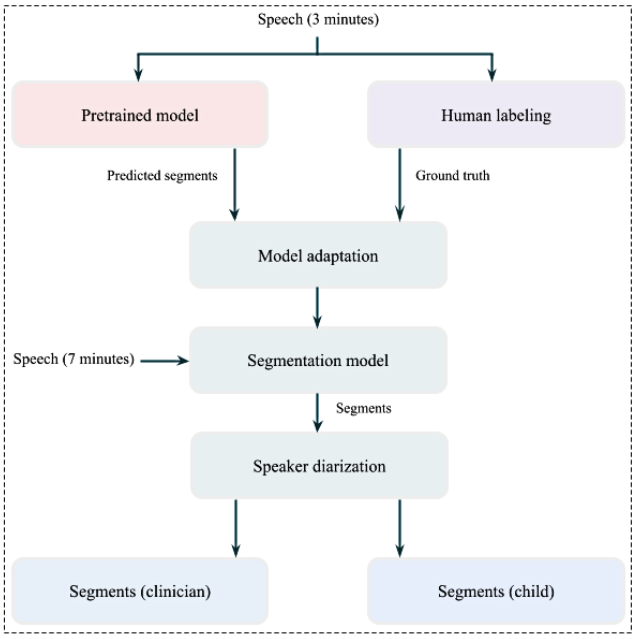
Processing Pipeline

Preprocessing Audio and Annotations

The audio preprocessing system is illustrated in Figure 3. To effectively use the audio signals, the audio recordings must be segmented into shorter segments. Next, speech and nonspeech regions must be differentiated. To obtain speaker segments, the conversations will first be segmented into speech and nonspeech regions.

We will use pretrained voice activation and diarization models that will be fine-tuned with a few manually annotated ground-truth labels of speech and nonspeech samples from our data set [21]. We follow this approach to ensure a balance between resources spent in training a model while maintaining high accuracy in the obtained speaker segments. Following speaker segmentation of the audio recordings, only the audio segments corresponding to the youth are retained.

Figure 3. Flow diagram of the preprocessing pipeline.



Pretrained Segmentation and Diarization Model

We used the vad-crdnn-libriparty pretrained model from SpeechBrain for speech detection [22] owing to its flexibility and modular structure, which is a favorable quality when applying models to clinical data owing to the tractability of errors. The pretrained model is based on a combination of convolutional and recurrent neural networks and a fully connected network. The model accepts audio segments as input and yields a posterior probability frame-level or segment-level posterior probability as output. Finally, a threshold is applied on the output posterior probability to classify the segments as speech and nonspeech.

We define a speaker segment to be an utterance of 2-4 seconds from a youth. The interviews will have a varying number of utterances. For a balanced analysis, we will randomly select 10 speaker segments per youth. Since the random selection of speaker segments may result in a high variance within the observations, we will also explore the feasibility of analyzing specific audio segments consistently over all speakers. These audio segments will be selected on the basis of insightful segments in the interview; for instance, questions in the interview associated with depression. In total, 10 interviews—5 with youth with OCD and 5 with those with no psychiatric diagnosis—have already been used to develop an appropriate method for speaker segmentation [21]. We will add the remaining 54 observations once we commence the described analysis.

Audio Features

From each speaker segment, we will extract the extended Geneva minimalistic acoustic parameter set [23], consisting of functionals of lower-level features. We will use the OpenSmile toolkit to extract these features and the resulting feature vector has a length of 88 [24].

The derived feature vector will be used as input to a neural network autoencoder model to obtain a latent model. The latent model is pretrained on English speech using the Interactive Emotional Dyadic Motion Capture data set and a semisupervised loss as previously described [16]. The latent model is a 2D latent space ($v1$ and $v2$) in a semisupervised denoising autoencoder with a reconstruction loss plus a loss based on the linear association between the activation labels and the latent space (the aim is a high association). Thus, to obtain $v1$ and $v2$, the 88 vocal features are projected into the latent space through the pretrained network. Previous analyses indicate that this latent space represents 2 dimensions of speech activation or intensity [16]. Sad and bored speech is characterized by low activation whereas elated and angry speech is characterized by high activation [25]. Thus, we assume that this latent space represents emotional intensity. We do not have an objective metric to evaluate this quantitatively using the current data and labels. Therefore, we will test this assumption in future work when more data labels are available.

For the machine learning analyses, we will use the raw speech signals to learn new features.

Statistical Models

Let $v1$ and $v2$ describe the vocal feature latent model adjusted for age and gender effects.

Statistical Models for Objective H1A

We will perform an ANOVA using a mixed effects regression model with the vocal features $v1$ and $v2$ as the outcome. We code the diagnosis, $Diagnosis$={0, 1} for no-OCD or OCD, respectively. The model for the jth vocal feature is as follows:

$$v_{ij} = \mu_j + \alpha_j(age_i) + \gamma_j(gender_{ii}) + v_j(age \times gender)_i + \delta_j(Diagnosis_i) + y_j(youth_i) + \varepsilon_{ij} \quad (1)$$

where μ_j is a constant offset for the jth endpoint, i = 1, ..., 200, y_j $(youth_i) \sim N$ $(0, \sigma^2_{yj})$, $\varepsilon_i \sim N$ $(0, \sigma^2_j)$, and the effects are mutually independent. Age, gender, and an interaction between age and gender are included as fixed effects to remove confounding effects from these variables. Diagnosis is included

as a fixed effect and is our primary interest. The individual youth, denoted *youth*, is included as a random effect. *Diagnosis* is included as a fixed effect. In total, 10 repeated measures are available for each of the 64 youths included in this model.

With this analysis, we shall test the hypothesis that there is no effect of diagnosis; that is, $H_0 : \delta_j = 0$, or equivalently that the means of the vocal features are equal for the OCD and no-OCD groups (when effects of age and gender are removed), at a 1.25% level of significance.

Statistical Models for Objective H1B

We will use a logistic regression with OCD severity categories moderate and severe-extreme as the outcomes. We denote the severity $s = 0, 1$. We will fit the following logistic regression model to the scores:

$$\text{logit}(si) = \theta + b1 \square i + b2 \square i + \varepsilon i \quad (2)$$

where $\varepsilon_i \sim N(0, \sigma_{2j})$ and v_j is the jth latent vocal feature adjusted for age and gender and averaged over the 10 repetitions for each youth, as described in the following.

This analysis aims to test the effects from vocal features on the severity scores through the null hypotheses that $b_1 = 0$ and $b_2 = 0$, which we will test at a 1.25% level of significance.

Adjusting for Confounding and Calculating Average Features

We expect age and gender to have an influence on the vocal features and would like to remove these confounding effects from the signals. We will exclude effects from age, gender, and age and gender interactions from the vocal features through a linear regression, as follows.

First, we will find the confounding effects using a linear regression model, which estimates age and gender contributions to vocal features as follows:

where, for the ith observations and jth vocal feature, $j = 1, 2$. The vocal features adjusted for age and gender are then as follows:

Finally, we will use the average vocal features over the 10 repetitions for the kth youth to obtain $\square_{jk} = \Sigma i \varepsilon youth_k \, v_{ji} / 10$.

Adjusting for Multiple Testing

We are interested in the null hypotheses associated with the effect of a diagnosis on the two dimensions in the latent model as well as the effects from the two adjusted latent dimensions on the severity scores. We will adjust our 4 P values using the Bonferroni method, and thus test each null hypothesis at a 5%/4=1.25% level of significance resulting in a family-wise error rate for the four tests of 5%.

Machine Learning Models for Objective 2

To improve the vocal features for possible use as biomarkers of OCD severity, we shall use the following methodology. First, 2 authors (SD and NLL) will annotate samples for activation and valence on a 5-point Likert scale with 1 indicating low activation and 5 indicating high activation. We shall only provide the annotators with one speech segment at a time in a blinded manner and in random order.

For the planned analyses, we will not use the valence labels, but the activation labels as these labels have shown promise in previous investigations [16]. We will use these labels as in our previous work [16]. The major advantages of labeling speech signals with activation scores include making labels for Danish speech and for children's speech, and labeling speech of patients and controls. Thus, the labels provide added information as no open source data exist, thus supporting transfer learning wherever feasible.

Subsequently, we shall train the following machine learning models using the following annotations: variational and denoising autoencoders with semisupervised losses based on activation labels and a reconstruction error, plus a logistic regression or logistic regression loss in a neural network to obtain a classification model.

Model Validation Strategies

We will use a leave-two-youth-out cross-validation, leaving 1 control plus 1 patient out for validation in each fold to tune the hyperparameters in our machine learning models and to choose between a simple logistic regression or a neural network with a logistic regression loss. To validate the results, we will use an independent test set of 10 interviews (5 with the patients and 5 with the controls) to evaluate the performance of these methods. These interviews will be transferred at the time of the independent test.

Software

Data will be processed and analyzed using the most current and reliable version of Praat [26], Audacity [27], Python [28], R (R Core Team) [29,30], and OpenSmile [24].

Results

Statistical Report Model 1A

The statistical analysis in this section was performed with simulated data, simulated with the same structure as described above; that is, repeated measures from 10 individuals and with age and gender effects on the vocal feature latent model. The model 1A residuals are illustrated in Figure 4.

No strong effects were found, indicating that the assumptions have been violated. Thus, in this case, we will analyze the results from the model. A summary of the fixed effects is provided in Table 1 and one for the random effects is given in Table 2.

Finally, the CIs for all the parameter estimates are summarized in Table 3. We shall repeat this analysis for $v1$ and $v2$. We shall compare the P value [$Pr(> |t|)$] from the diagnosis to the 1.25% level of significance to asses if we can reject our null hypothesis of no effect from diagnosis. In the simulation, 2.92×10^{-06} is less than .0125; thus, we would reject the null hypothesis.

Figure 4. Quantile-quantile plot of residuals from model 1A with end point v_j. Data are simulated and placeholders for results.

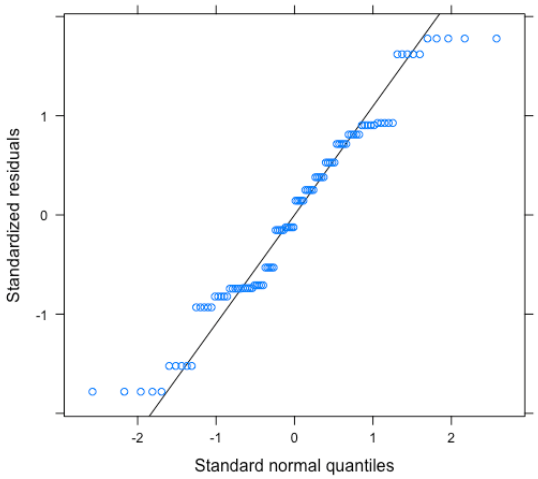


Table 1. Summary of fixed effects for v_j. Data are simulated and placeholder for results.

Effect	Estimate	SE	*t* test	*df*	*P* [r(>|*t*|)] value
Intercept (μ)	1.16	0.12	9.54	4.99	2.15×10^{-4}
Age (α)	0.49	0.01	51.23	4.99	5.36×10^{-8}
Gender (γ)	0.83	0.13	6.16	4.99	1.64×10^{-3}
Diagnosis (δ)	0.94	0.04	22.95	4.99	2.92×10^{-6}
Age:gender (ν)	0.02	0.01	1.19	4.99	2.87×10^{-1}

Table 2. Summary of simulated random effects v_j with 100 observations and 10 groups (youth).

Groups	Variance	SD
Youth (σ_y)	2.29×10^{-3}	4.79×10^{-2}
Residual (σ_e)	2.33×10^{-3}	4.83×10^{-2}

Table 3. Simulated CIs for effects on v_j.

Effect	Effects (%), CI	
	2.5%	97.5%
σ_y	1.87×10^{-2}	5.73×10^{-2}
σ_e	4.2×10^{-2}	5.63×10^{-2}
Intercept	9.71×10^{-1}	1.34
Age	4.76×10^{-1}	5.05×10^{-1}
Gender	6.23×10^{-1}	1.04
Diagnosis	8.74×10^{-1}	9.99×10^{-1}
Age:gender	-4.16×10^{-3}	3.34×10^{-2}

Statistical Report Model 1B

We shall first assess the assumptions of our model by examining the surrogate residuals in a quantile-quantile (q-q) plot (see Figure 5). In this case, the assumptions are violated as the residuals are not normally distributed. In case the assumptions are violated, we will not report on parameter estimates and their confidence intervals, as these will not be meaningful. However, we can still use the model for predictions.

Figure 6 illustrates the receiver operating characteristic (ROC) curve for the training data, and the estimated classification accuracy is 80%. Additionally, we will report sensitivity,

specificity, area under the curve, and a confusion matrix, similar to the next section.

If the surrogate residuals show an approximated normal distribution in the q-q plot, we will report parameter estimates, etc, as we have for model 1A.

Figure 5. Quantile-quantile plot of surrogate residuals from model 1B with endpoint v_j. Data are simulated and placeholders for results.

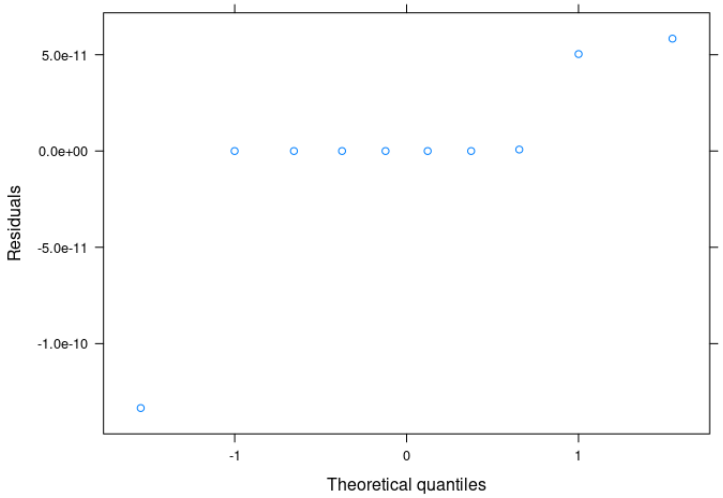
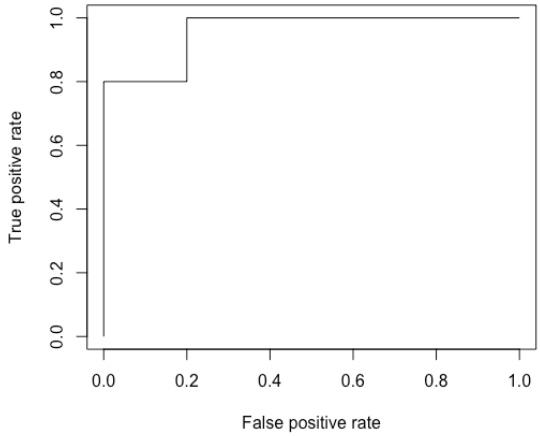


Figure 6. Receiver operating characteristic curve for the training data.



Statistical Report Model 2

The evaluation results of the machine learning model on simulated results are reported using the classification metrics in Table 4, the ROC curve in Figure 7 and the confusion matrix in Figure 8. The results will be presented for the validation data (the left-out youth) over the cross-validation to select hyperparameters and a model. We will also compare to the same measures for the training data to assess the amount of possible overfitting. Final results will be provided for the independent test data consisting of 10 youths.

Table 4. Simulated classification performance.

Evaluation metric	Value (normalized)
Accuracy	0.82
Sensitivity	0.78
Specificity	0.86
Area under the curve	0.89

Figure 7. Receiver operating characteristic curve for the classification model. AUC: area under the curve; OCD: obsessive-compulsive disorder.

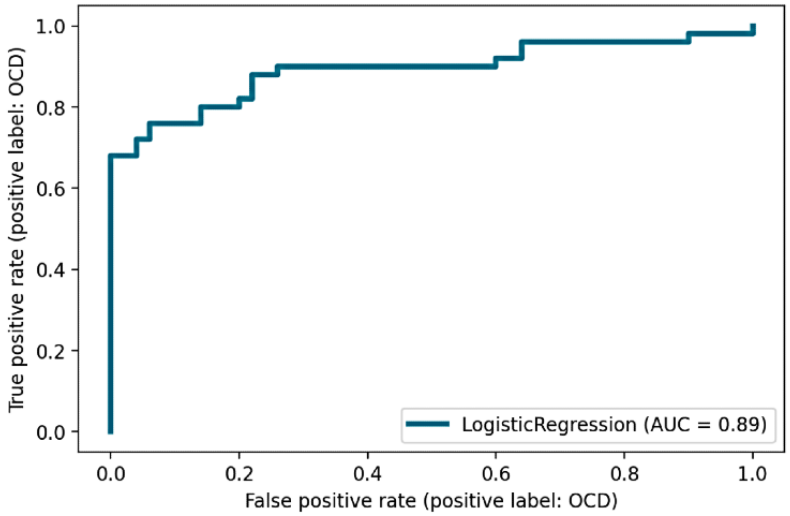
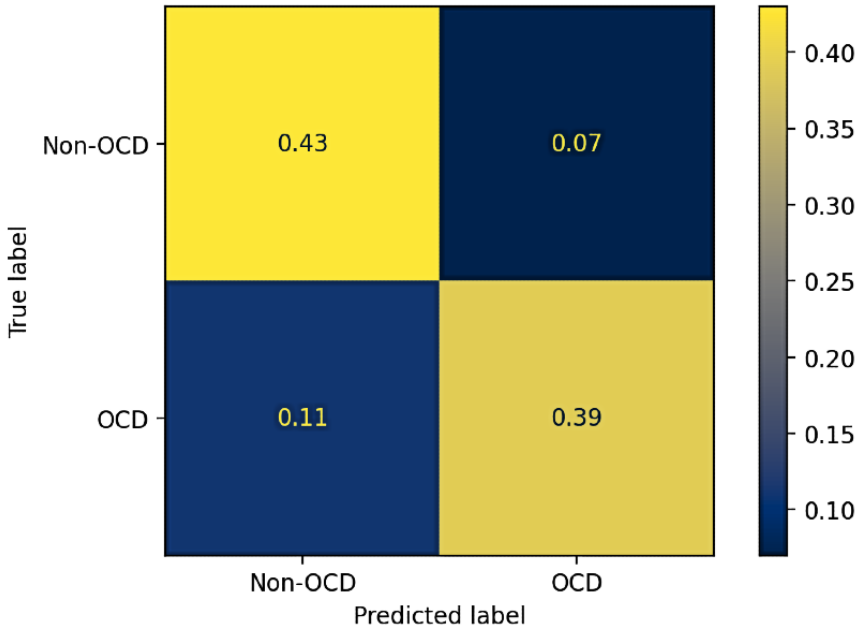


Figure 8. Confusion matrix for the classification model. OCD: obsessive-compulsive disorder.



Discussion

Expected Findings

In this paper, we describe the methods and analysis plan for testing the effects of OCD diagnosis and symptom severity on vocal features in the youth. We anticipate that we can improve the methods that model these putative associations. Through this work, we aim to obtain reliable transdiagnostic indicators of clinical severity from voice that would serve as valuable monitoring tools in psychiatry [31]. Additionally, the vocal indicators obtained from this work, in tandem with additional data modalities including video and semantics of the speech conversation, will be employed in multi-sensor modeling of OCD behavior in future work [32]. The results described in this analysis plan will be published in relevant scientific journals.

Strengths

A major strength of the planned study is this documentation of the analysis plan prior to performing analyses. Documented a priori hypotheses prevent unscientific practices such as selectively reporting significant results [33]. Furthermore, diagnostic status and OCD severity levels were established by trained mental health professionals using gold-standard clinical interviews. Another strength of the planned study is that we will include gender in the models. Compared with male speech, female speech is marked by a higher pitch. A study found that gender-specific models were more accurate in detecting sadness and positive and negative affect than gender-independent models [34]. Depressed speech is marked by reduced pitch, whereas anxious speech is marked by increased pitch [10].

Another study found that pitch appears more important for detecting stress in men while Root Mean Square Energy appears more influential in detecting stress in women [35]. Thus, if training data sets are overrepresented by one gender, an automatic depression or anxiety severity rating algorithm may misclassify speech by other genders. We also attempted to strengthen our analyses by adding age to the models. The available latent model that we will use in our study of youth of

a wide age range were trained on adult speech. With age, pitch and formant frequencies tend to decrease [36]. From childhood to adolescence, speech rate increases, and conveying emotions with prosodic cues, including pitch and timing, is a development feat [37].

Limitations

The planned analyses have some foreseeable challenges. First, we plan to recruit a small sample. Preprocessing and data labeling, required for the planned analyses, are time-consuming tasks. Our small sample size increases the risk of type II errors. Machine learning techniques are more robust as we can improve models by adding more labeled data and testing on a new independent data set. Second, the audio samples that will be analyzed were collected for clinical purposes and not under optimal conditions for audio feature extraction and analysis (ie, using high quality microphones in a quiet environment). Thus, methods developed on these data will likely translate well to other naturalistic settings [38-41]. Finally, this study focuses on the associations among OCD diagnosis, severity, and vocal features in the child. In future work, we will study the effect of OCD diagnosis on vocal features while accounting for secondary diagnoses and investigate the influence of clinician's vocal characteristics on the vocal features of the child.

Conclusions

This predefined plan will limit bias in the interpretations and conclusions of the reported results of the future publication. If the results in the planned study are promising, this will be a step toward using vocal sensing to automate objective assessments and monitoring of severity of psychiatric disorders such as OCD.

Acknowledgments

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Data Availability

We are not permitted to share voice samples or other personal identifying information. We will investigate the possibility of making an anonymized data set with extracted voice features available. If possible, we shall indicate where to obtain the data set with the published results.

Conflicts of Interest

None declared.

References

1. Meier SM, Mattheisen M, Mors O, Schendel DE, Mortensen PB, Plessen KJ. Mortality among persons with obsessive-compulsive disorder in Denmark. JAMA Psychiatry 2016 Mar;73(3):268-274 [FREE Full text] [doi: 10.1001/jamapsychiatry.2015.3105] [Medline: 26818216]
2. Piacentini J, Bergman RL, Keller M, McCracken J. Functional impairment in children and adolescents with obsessive-compulsive disorder. J Child Adolesc Psychopharmacol 2003;13 Suppl 1:S61-S69. [doi: 10.1089/104454603322126359] [Medline: 12880501]
3. OCD Clinical Practice Review Task Force. Clinical Practice Review for OCD: Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Anxiety & Depression Association of America. 2015 Jun 15. URL: https://adaa.org/resources-professionals/practice-guidelines-ocd [accessed 2022-09-12]
4. Obsessive-compulsive disorder and body dysmorphic disorder: treatment. National Institute for Health and Care Excellence. 2005 Nov 29. URL: https://www.nice.org.uk/guidance/cg31 [accessed 2022-09-12]
5. Benito KG, Walther M. Therapeutic process during exposure: habituation model. J Obsessive Compuls Relat Disord 2015 Jul 01;6:147-157 [FREE Full text] [doi: 10.1016/j.jocrd.2015.01.006] [Medline: 26258012]
6. Skarphedinsson G, De Nadai AS, Storch EA, Lewin AB, Ivarsson T. Defining cognitive-behavior therapy response and remission in pediatric OCD: a signal detection analysis of the Children's Yale-Brown Obsessive Compulsive Scale. Eur Child Adolesc Psychiatry 2017 Jan;26(1):47-55 [FREE Full text] [doi: 10.1007/s00787-016-0863-0] [Medline: 27209422]
7. Benito KG, Machan J, Freeman JB, Garcia AM, Walther M, Frank H, et al. Measuring fear change within exposures: functionally-defined habituation predicts outcome in three randomized controlled trials for pediatric OCD. J Consult Clin Psychol 2018 Jul;86(7):615-630 [FREE Full text] [doi: 10.1037/ccp0000315] [Medline: 29939055]
8. Kraepelin E. Manic depressive insanity and paranoia. J Nerv Ment Dis 1921;53(4):350. [doi: 10.1097/00005053-192104000-00057]
9. Cummins N, Scherer S, Krajewski J, Schnieder S, Epps J, Quatieri TF. A review of depression and suicide risk assessment using speech analysis. Speech Communication 2015 Jul;71:10-49. [doi: 10.1016/j.specom.2015.03.004]
10. Low DM, Bentley KH, Ghosh SS. Automated assessment of psychiatric disorders using speech: a systematic review. Laryngoscope Investig Otolaryngol 2020 Feb;5(1):96-116 [FREE Full text] [doi: 10.1002/lio2.354] [Medline: 32128436]

11. Cassol M, Reppold CT, Ferrão Y, Gurgel LG, Almada CP. Análise de características vocais e de aspectos psicológicos em indivíduos com transtorno obsessivo-compulsivo. Rev soc bras fonoaudiol 2010 Dec;15(4):491-496. [doi: 10.1590/s1516-80342010000400004]
12. Garcia-Real T, Diaz-Roman TM, Garcia-Martinez V, Vieiro-Iglesias P. Clinical and acoustic vocal profile in children with attention deficit hyperactivity disorder. J Voice 2013 Nov;27(6):787.e11-787.e18. [doi: 10.1016/j.jvoice.2013.06.013] [Medline: 24246332]
13. Adams P, Rabbi M, Rahman T, Matthews M, Voida A, Gay G, et al. Towards Personal Stress Informatics: Comparing Minimally Invasive Techniques for Measuring Daily Stress in the Wild. 2014 Presented at: 8th International Conference on Pervasive Computing Technologies for Healthcare; May 20-23, 2014; Oldenburg. [doi: 10.4108/icst.pervasivehealth.2014.254959]
14. Holmqvist-Jämsén S, Johansson A, Santtila P, Westberg L, von der Pahlen B, Simberg S. Investigating the role of salivary cortisol on vocal symptoms. J Speech Lang Hear Res 2017 Oct 17;60(10):2781-2791. [doi: 10.1044/2017_JSLHR-S-16-0058] [Medline: 28915296]
15. McGinnis EW, Anderau SP, Hruschak J, Gurchiek RD, Lopez-Duran NL, Fitzgerald K, et al. Giving voice to vulnerable children: machine learning analysis of speech detects anxiety and depression in early childhood. IEEE J Biomed Health Inform 2019 Nov;23(6):2294-2301 [FREE Full text] [doi: 10.1109/JBHI.2019.2913590] [Medline: 31034426]
16. Das S, Lund NL, Lønfeldt NN, Pagsberg AK, Clemmensen LH. Continuous metric learning for transferable speech emotion recognition and embedding across low-resource languages. In: Proceedings of the Northern Lights Deep Learning Workshop 2022. Tromsø: Septentrio Academic Publishing; Apr 06, 2022.
17. Pagsberg AK, Uhre C, Uhre V, Pretzmann L, Christensen SH, Thoustrup C, et al. Family-based cognitive behavioural therapy versus family-based relaxation therapy for obsessive-compulsive disorder in children and adolescents: protocol for a randomised clinical trial (the TECTO trial). BMC Psychiatry 2022 Mar 19;22(1):204 [FREE Full text] [doi: 10.1186/s12888-021-03669-2] [Medline: 35305587]
18. Puig-Antich J, Ryan N. Kiddie schedule for affective disorders and schizophrenia. Pittsburgh, PA: Western Psychiatric Institute; 1986.
19. Scahill L, Riddle MA, McSwiggin-Hardin M, Ort SI, King RA, Goodman WK, et al. Children's Yale-Brown Obsessive Compulsive Scale: reliability and validity. J Am Acad Child Adolesc Psychiatry 1997 Jun;36(6):844-852 [FREE Full text] [doi: 10.1097/00004583-199706000-00023] [Medline: 9183141]
20. Lewin AB, Piacentini J, De Nadai AS, Jones AM, Peris TS, Geffken GR, et al. Defining clinical severity in pediatric obsessive-compulsive disorder. Psychol Assess 2014 Jun;26(2):679-684. [doi: 10.1037/a0035174] [Medline: 24320764]
21. Das S, Lønfeldt N, Pagsberg A, Clemmensen L. Speech detection for child-clinician conversations in Danish for low-resource in-the-wild conditions: a case study. arXiv Preprint posted online April 25, 2022. [doi: 10.48550/arXiv.2204.11550]
22. Ravanelli M, Parcollet T, Plantinga P, Rouhe A, Cornell S, Lugosch L, et al. SpeechBrain: a general-purpose speech toolkit. arXiv Preprint posted online June 8, 2021. [doi: 10.48550/arXiv.2106.04624]
23. Eyben F, Scherer KR, Schuller BW, Sundberg J, Andre E, Busso C, et al. The Geneva Minimalistic Acoustic Parameter Set (GeMAPS) for voice research and affective computing. IEEE Trans Affective Comput 2016 Apr 1;7(2):190-202. [doi: 10.1109/taffc.2015.2457417]
24. Eyben F, Wöllmer M, Schuller B. Opensmile: the munich versatile and fast open-source audio feature extractor. 2010 Presented at: MM '10: ACM Multimedia Conference; October 25-29, 2010; Firenze. [doi: 10.1145/1873951.1874246]
25. Alonso JB, Cabrera J, Medina M, Travieso CM. New approach in quantification of emotional intensity from the speech signal: emotional temperature. Expert Syst Appl 2015 Dec;42(24):9554-9564. [doi: 10.1016/j.eswa.2015.07.062]
26. Boersma P, Weenink D. Praat: doing phonetics by computer. URL: https://www.fon.hum.uva.nl/praat/ [accessed 2022-09-12]
27. Audacity. URL: https://audacityteam.org/ [accessed 2022-09-12]
28. Van Rossum G, Drake Jr JF. Python tutorial. Centrum voor Wiskunde en Informatica Amsterdam. 1995. URL: https://www.google.com/ [accessed 2022-09-12]
29. The R Project for Statistical Computing. URL: https://www.r-project.org/ [accessed 2022-09-12]
30. Liu Q, Shepherd B, Li C. PResiduals: an R Package for residual analysis using probability-scale residuals. J Stat Soft 2020;94(12):1-27. [doi: 10.18637/jss.v094.i12]
31. Kapur S, Phillips AG, Insel TR. Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? Mol Psychiatry 2012 Dec;17(12):1174-1179. [doi: 10.1038/mp.2012.105] [Medline: 22869033]
32. Lønfeldt N, Frumosu F, Lund N, Das S, Pagsberg A, Clemmensen L. Computational behavior recognition in child and adolescent psychiatry: a statistical and machine learning analysis plan. arXiv Preprint posted online May 11, 2022.
33. Forstmeier W, Wagenmakers E, Parker TH. Detecting and avoiding likely false-positive findings - a practical guide. Biol Rev Camb Philos Soc 2017 Nov;92(4):1941-1968. [doi: 10.1111/brv.12315] [Medline: 27879038]
34. Black MP, Katsamanis A, Baucom BR, Lee C, Lammert AC, Christensen A, et al. Toward automating a human behavioral coding system for married couples' interactions using speech acoustic features. Speech Communication 2013 Jan;55(1):1-21. [doi: 10.1016/j.specom.2011.12.003]
35. Zuo X, Fung PN. A cross gender and cross lingual study on acoustic features for stress recognition in speech. 2011 Presented at: 17th International Congress of Phonetic Sciences; August 17-21, 2011; Hong Kong.

36. Gautam S, Singh L. The development of spectral features in the speech of Indian children. Sādhanā 2019 Jan 2;44(1). [doi: 10.1007/s12046-018-1028-2]
37. Dilley LC, Wieland EA, Gamache JL, McAuley JD, Redford MA. Age-related changes to spectral voice characteristics affect judgments of prosodic, segmental, and talker attributes for child and adult speech. J Speech Lang Hear Res 2013 Feb;56(1):159-177 [FREE Full text] [doi: 10.1044/1092-4388(2012/11-0199)] [Medline: 23275414]
38. Cummins N, Sethu V, Epps J, Schnieder S, Krajewski J. Analysis of acoustic space variability in speech affected by depression. Speech Communication 2015 Dec;75:27-49. [doi: 10.1016/j.specom.2015.09.003]
39. Alghowinem S, Goecke R, Epps J, Wagner M, Cohn J. Cross-cultural depression recognition from vocal biomarkers. Proc. Interspeech 2016:1943-1947. [doi: 10.21437/Interspeech.2016-1339]
40. Das S, Lønfeldt N, Pagsberg A, Clemmensen L. Towards transferable speech emotion representation: on loss functions for cross-lingual latent representations. 2022 Presented at: ICASSP 2022 - 2022 IEEE International Conference on Acoustics, Speech and Signal Processing (ICASSP); May 23-27, 2022; Singapore. [doi: 10.1109/icassp43922.2022.9746450]
41. Das S, Lund N, Lønfeldt N, Pagsberg A, Clemmensen L. Zero-shot Cross-lingual Speech Emotion Recognition: A Study of Loss Functions and Feature Importance. 2022 Presented at: ISCA Symposium on Security and Privacy in Speech Communication 2022 (forthcoming); 2022; Incheon, Korea.

Abbreviations

CBT: cognitive behavioral therapy
CY-BOCS: Children's Yale-Brown Obsessive Compulsive Scale
ERP: exposure and response prevention
K-SADS: Kiddie Schedule for Affective Disorders and Schizophrenia
OCD: obsessive-compulsive disorder
q-q: quantile-quantile
ROC: receiver operating characteristic

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Protocol

Objective Assessment of the Nature and Extent of Children's Internet-Based World: Protocol for the Kids Online Aotearoa Study

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Abstract

Background: Children under 18 years of age account for approximately 1 in 3 internet users worldwide. Largely unregulated, the internet-based world is evolving rapidly and becoming increasingly intrusive. There is a dearth of objective research globally on children's real-time experiences of the internet-based world.

Objective: This paper reports an objective methodology to study the nature and extent of children's internet-based world, their engagement with it, and how this impacts their health and well-being.

Methods: A total of 180 year 8 students from 12 schools will be recruited into the study within the Wellington region of Aotearoa, New Zealand. Children use Zoom video teleconferencing software to record real-time, screen-shared internet-based content, for 4 consecutive days. Data on demographics, health and well-being, and attitudes and perceived behaviors in relation to the internet-based world are collected. Phone screen-time balances are retrieved. Data collection commenced in June 2021 and is anticipated to be completed in 2023.

Results: Recordings show children exploring diverse web-based settings and content, including personalized content curated by algorithms on platforms such as TikTok, YouTube, and Instagram. Preliminary analysis shows that the data can be used to study a wide range of topics. Behavioral Observation Research Interaction Software is being used to manually code recordings. Artificial Intelligence techniques are also being applied, including hashtag extraction, optical character recognition, as well as object, pattern, speech, and lyric recognition.

Conclusions: This novel methodology reveals the unique internet-based experiences of children. It is underpinned by a commitment to ensuring that their rights are protected. It seeks to provide concrete evidence on internet usage in this group and to facilitate appropriate political and societal action to effectively regulate the internet-based world to prevent harm to children.

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KEYWORDS

public health; child health; internet; policy; methods; child; youth; methodology; student; human-computer interaction; digital health; eHealth; technology use; computer use; user experience; perception; attitude; internet use; screen time; perceived behavior; phone use; social media

Introduction

Children and adolescents aged under 18 years account for approximately 1 in 3 internet users worldwide and access the internet at increasingly younger ages [1]. The largely unregulated internet-based world is evolving rapidly and becoming increasingly intrusive owing to constant connectivity to "always on" gaming, social media, and other applications [2,3]. Children primarily use smartphones to navigate the internet-based world [2]. Smartphones fuel a "bedroom culture" of childhood, characterized by low levels of supervision and a highly personalized, private experience [1]. The internet-based world affords children access to reliable information and connectivity with friends and family. Simultaneously, it increases their likelihood of encountering harmful or distressing web-based content and behavior, such as marketing for harmful products, violent or discriminatory material, cyberbullying, or sexual solicitation [2].

There is unequivocal evidence linking children's high screen-time with adiposity, depressive symptoms, and an unhealthy diet [4-6], alongside emerging literature about a range of other harms from internet-based interaction, such as exposure to marketing for unhealthy products; bullying; racist, discriminatory, or hate speech material; sexual and violent content; and websites advocating unhealthy or dangerous behaviors such as self-harm, suicide, and anorexia [1,2]. Nonetheless, there is a dearth of objective research globally on children's real-time experiences of the internet-based world [2].

To the best of our knowledge, existing evidence in this area has relied predominantly on self-report data or observations made in controlled experimental conditions, owing in part to the difficulty of capturing engagement with personalized internet-based content [7]. Existing research typically considers the internet's effect on children in terms of the time spent on the internet, as opposed to the nature of the content encountered [2]. Evidence remains especially scarce for preteens [2]. A method capable of capturing internet-based experiences in real time is urgently needed. This paper reports an objective methodology to study the nature and extent of children's internet-based world, their engagement with it, and how this may impact their health and well-being.

Methods

Study Design

Kids Online Aotearoa (Kids Online) is a cross-sectional observational study of children's real-time experiences of the internet-based world; it is currently in the field and due for completion in 2023. Kids Online aims to recruit 180 year 8 students (aged 11-13 years) from 12 schools in the Wellington region of Aotearoa, New Zealand, using a stratified sample design (see below). Participants use Zoom video teleconferencing software [8] to record real-time, internet-based, screen-shared content for 4 consecutive days (Thursday to Sunday, inclusive). Data on demographics; health and well-being; attitudes and behaviors in relation to the internet-based world; and daily phone use (screen-time) data balances are also collected.

Ethical Approval

Ethical approval was obtained from the University of Otago Human Ethics Committee (Health; 20/006) to study the nature and extent of children's internet-based world, their engagement with it, and how it may impact their health and well-being.

Pilot Study

In 2019, a feasibility study was undertaken with medical student participants, which demonstrated that Zoom recordings enabled the study of adults' internet-based world [9]. Building on this, a pilot study was conducted with 5 preteens from one school in late 2020. A focus group with the children revealed that the study was well explained, easy to undertake, and enjoyable. Children were familiar with Zoom, or similar applications, from internet-based learning and communication during the COVID-19 pandemic. Termination of Zoom recordings when locking phones and an overcomplicated instruction booklet were the key issues that the children highlighted. Consequently, during the full study, children were asked to disable their phone locking function, an additional briefing was added, and a simplified, generic instruction sheet was developed. The study protocol was updated and is available on the internet [10].

Sampling and Recruitment

Sampling and recruitment are being undertaken in 2 stages. All 93 schools in the Wellington region with year 8 students are eligible for selection. Sampling is stratified to provide equal explanatory power [11] by school decile (socioeconomic measures: low=1-5, high=6-10) and student ethnicity (Māori, Pacific, non-Māori, and non-Pacific), using nationwide enrollment data from the Ministry of Education.

In total, 12 schools were randomly selected from the resulting 6 strata, using probability-proportional-to-size sampling methods (such that schools with a larger proportion of year 8 students in a stratum have a higher probability of invitation). The sampling method allows for a school to be selected for multiple ethnicities. Year 8 children are then randomly selected from the class list.

The total sample size is limited by feasibility and budget. Data analysis for projects using these data will account for the complex sampling design using sampling weights, appropriate management of stratification variables, and clustering of children within schools [12]. As of July 2022, a total of 22 students from 3 schools have participated.

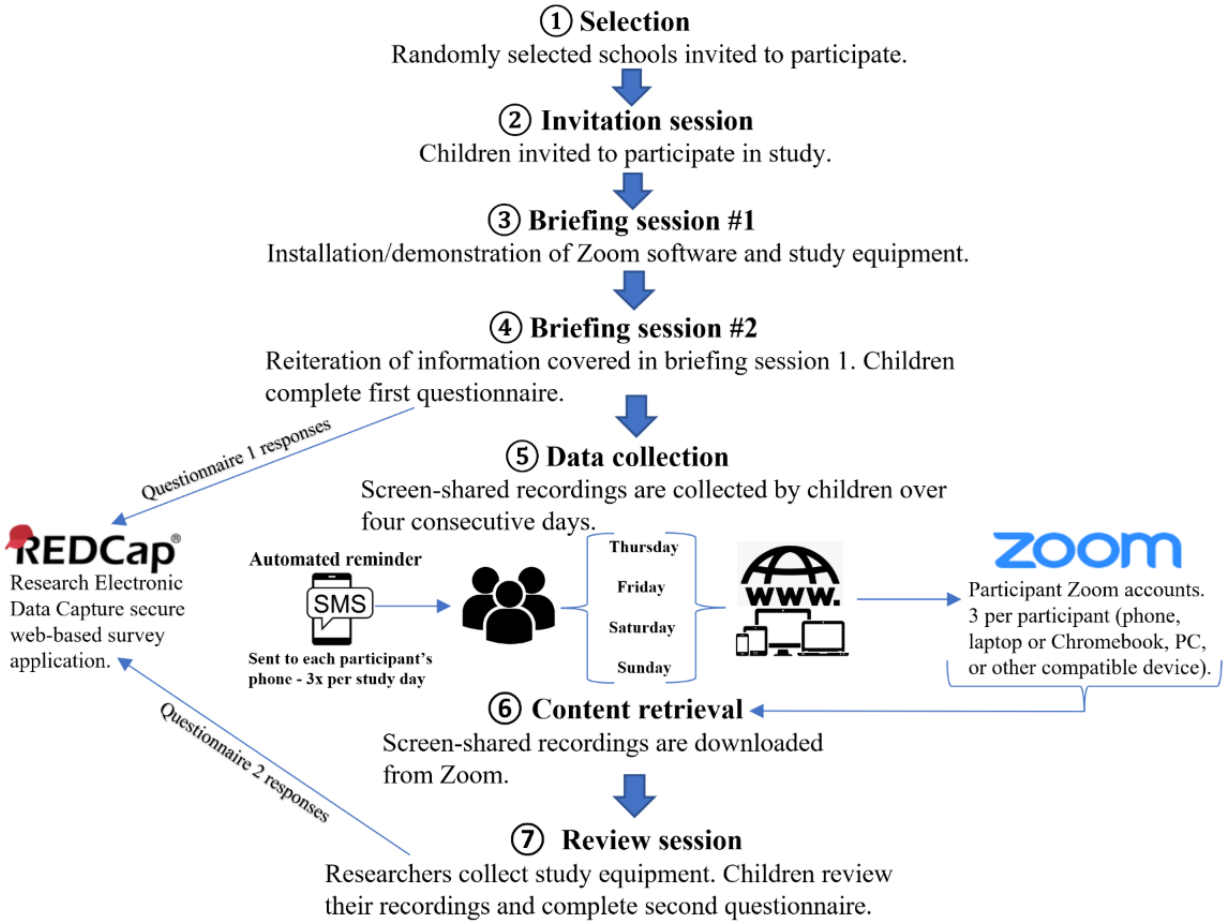
Data Collection

Selection

Selected schools are invited to participate (Figure 1). School principals inform their school community about the study, and it proceeds if no objections are raised. Participating schools provide a list of eligible children by ethnicity. Children unable to undertake the study, owing to health or family circumstances, are excluded on the advice of senior staff. Eligible children for each ethnicity strata selected for that school are randomized using Excel (Microsoft Inc). They are invited to participate in a half-hour invitation session at their school. The number of invitees exceeds the number of required participants to reduce the burden on schools from multiple rounds of invitation.

Written consent is obtained from participating schools, children's parents or guardians, and children. Children are informed that their anonymity and that of third parties will be protected, and if any data are used in publications, all personally identifiable information will be obscured. The first 10 children on the list for each ethnic group who return signed consent forms are selected.

Figure 1. Participant recruitment and data collection.



Briefings

Selected children are briefed twice about the study at school over 2 days, fitting around their timetables. Children are asked to bring their portable electronic devices. Researchers work with each child to ensure that Zoom is installed on their devices and teach them how to install it on other devices they use. Children are given 3 university-operated Zoom accounts to record up to 3 screen devices (mobile phones, laptops or Chromebooks, and PCs). Researchers text children their Zoom account log-in and password details. They are asked to log in to Zoom on each of their devices and to select the "stay signed in" button. Children are instructed to use Zoom to share their screen, internal device audio, and ambient sound captured via the device microphone any time they access the internet over the 4 days of the study. They are asked to use the internet as they normally would and to make a trial Zoom recording following the first briefing. The installation of Zoom and their ability to use it is confirmed at the second briefing.

Children are given the instruction sheet and a statement explaining the study to communicate to third parties if asked. An Alcatel LINKZONE wireless internet device is provided to participants. This enables internet access when other trusted networks are unavailable and prevents costs to participants through use of personal mobile data. Zoom recordings cause device batteries to discharge rapidly. To ensure that the children can charge devices without connecting to an electrical outlet, a Fast Charge power bank coupled with charging cables is also provided. Children are instructed to keep devices charged. An automated web-based SMS text messaging service (Vodafone multiTXT) is used to send 3 texts on each of the study days, reminding children to share their screen and to charge all devices. Researchers and children communicate via text as needed.

Children complete the first questionnaire on their attitudes toward and perceived behavior in relation to the internet-based world. The questionnaire is based on the Global Kids Online qualitative methodology for researchers [13]. A validated measure of self-reported general well-being is also included (the 5-item World Health Organization Well-Being Index) [14].

Content Retrieval

Children's screen-shared recordings are downloaded from Zoom cloud storage on the Monday following data collection to a secure university server. The recorded content is subsequently

deleted from Zoom. The researchers do not view the data at this stage.

Review

In the days following content retrieval, researchers conduct a review session with the children. They are reminded of the project's commitment to maintain anonymity. Children are asked whether they recorded anything they did not wish the researchers to see. If so, that content is deleted by the researchers without being viewed. A second questionnaire is completed, which includes validated measures assessing anxiety (the 7-item Generalized Anxiety Disorder scale) [15], depression (the 9-item Patient Health Questionnaire) [16], and adolescent self-esteem (the Adolescent Self-esteem Questionnaire) [17]. Additional questions on sleep quality and habits, and device use prior to sleep are also included (see Multimedia Appendices 1 and 2 for the questionnaires). Participants' height and weight are measured, and their feedback on the study is recorded. Wherever possible, children's daily phone use (screen-time) balances are recorded for the week preceding and during the week of the study. This enables comparison of phone use prior to and during the study period.

Quality Control

Researchers are trained in the study protocol. Data are collected by pairs of researchers, initially MG and LS. Other researchers assisted and took over once proficient. All wireless devices, charging cables, and battery packs are tested for functionality. Calibrated scales (Wedderburn HD-316) and stadiometers are used to calculate children's weight and height to derive their BMI.

Data Management

Data are downloaded to a secure university server and backed up to a password-protected external hard drive. Data access is restricted to members of the research team who sign a data release form, which includes strict data access protocols. Demographic information is anonymized using participant numbers.

Data Analysis

Manual coding of recordings is conducted using the Behavioral Observation Research Interaction Software (version 7.11.1) [18], which permits events of interest to be coded using user-generated coding ethograms: "a catalogue or table of all the different kinds of behavior or activity observed" [19]. Artificial Intelligence (AI) pattern recognition techniques will also be used for data analysis. First, various OpenCV [20] and Scikit-Image [21] utilities will be used to detect specific topics of interest—for example, TikTok or YouTube video scenes—using global and local template matching. Second, object detection will be carried out; for example, identifying fast food logos. It may be possible to detect multiple objects with one scan, further improving efficiency [22]. Third, Google Tesseract [23] will be used to analyze video frames and extract hashtags and other displayed words within a scene, allowing for lexicographic analysis and sentiment analysis. Further, machine learning techniques will be used to analyze the audio data, including speech and lyric recognition, and musical mood classification [24].

Results

The Kids Online methodology enables objective investigation of the nature and extent of children's internet-based world. The retrieved recordings depict children exploring diverse internet-based settings and content, including personalized content curated by algorithms on social media platforms such as TikTok, YouTube, and Instagram, the use of which is commonplace.

The method permits observation of; the complexity of the internet-based world, the speed at which transitions occur between settings, how children use technology to access and navigate the internet, and how this differs between home and school.

Characteristics of internet-based settings are clearly discernible, as are children's interactions occurring within them, such as scrolling or browsing, clicking, posting, and communicating. On-screen events, such as pop-up advertisements, notifications, messaging, and alerts, are obvious and occur frequently.

As of July 2022, a total of 197 hours of real-time, screen-shared Zoom recordings have been uploaded by 22 children. This indicates that a substantial amount of data is likely to be retrieved. Participants reported that they recorded most of their internet use and had used the internet normally. Children cited forgetting to record as the main reason for data loss. Daily phone use (screen-time) balances were retrievable from most children's phones. These permit comparisons of participant phone use (daily screen-time durations) preceding and during the study, approximating any effect due to the study itself. Additionally, the balances indicate data loss when compared to total duration for daily Zoom phone recordings.

The method permits a large sample size as participants collect data themselves, significantly reducing time and resources. To date, 1 in 4 children who were invited had participated, with no participant dropout or any expression of concern by third parties. No child has requested that any data be deleted. All children have reported that Zoom is easy to use. Zoom allows consistent uploading and archiving of intact recordings, unlike previous methods [25]. Conducting 2 briefing sessions ensures that participants can undertake the study correctly. Provision of mobile data enables consistent Zoom data collection, which is data-intensive and expensive, particularly in Aotearoa New Zealand.

Initial analysis suggests the data can be used to study a wide range of content (Figures 2-4), such as exposures to harmful advertising (Figure 3). Initial coding of data for gambling and gaming indicates that manual coding is possible, despite the complexity of the image data (Figures 2 and 4). Initial AI video analysis demonstrates that, for example, TikTok viewing sessions can be detected and extracted with 98% reliability.

Figure 2. Examples of internet-based content encountered by children (left to right): a screenshot from TikTok on November 18, 2020, from video data captured by participant 4, depicting referencing to recreational drug use; a screenshot from TikTok on November 18, 2020, from video data captured by participant 4, depicting referencing to recreational drug use, profanity, and "bad girl" or risk-taking imagery; a screenshot from TikTok on September 25, 2021, from video data captured by participant 10, depicting in-game reward purchasing (requires real money to be used) or gambling-like content; and a screenshot from TikTok on September 25, 2021, from video data captured by participant 10, depicting gaming content. We received consent from all participants and their parents, caregivers, or other legal guardians to use their video data to generate screenshot images for use here. We created the images and have permission to use them.

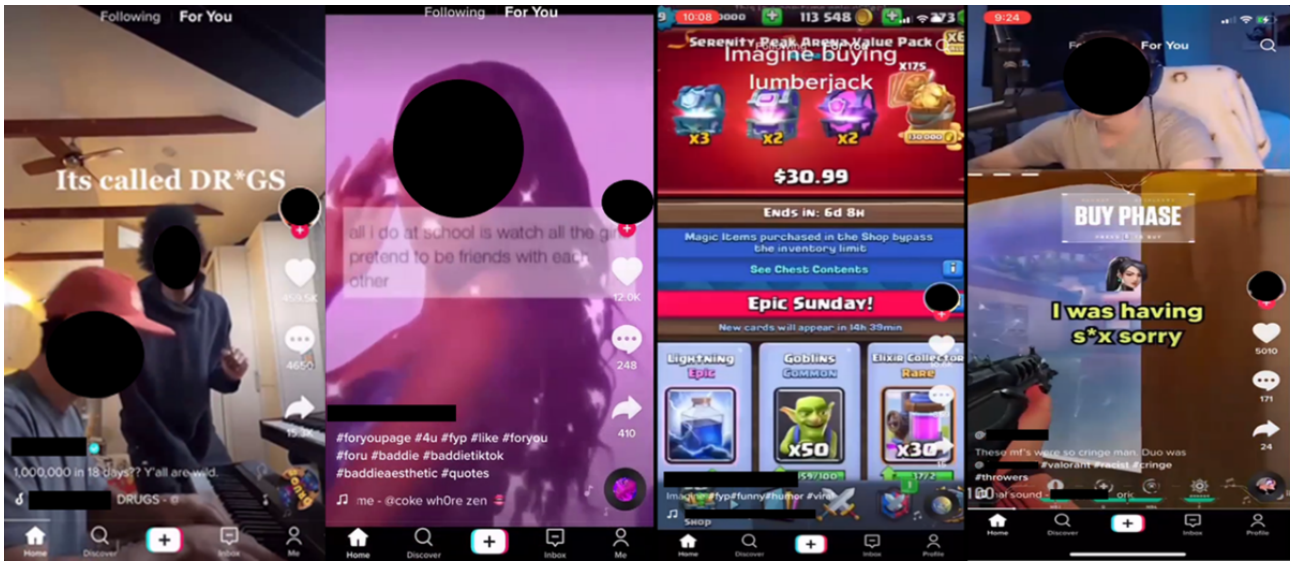


Figure 3. Screenshot taken from video data captured by participant 13 on September 23, 2021, depicting an in-game (mobile app) advertisement for Woodford Reserve Kentucky Straight Bourbon whiskey from Brown-Forman Corp. We received consent from all participants and their parents, caregivers, or other legal guardians to use their video data to generate screenshot images for use in publications. We created the images and have permission to use them.

Figure 4. A screenshot recorded by participant 14 on September 23, 2021, depicting the complexity and type of internet-based content that may be seen by participants. This image shows a MacOS laptop being used in conjunction with the Mozilla Firefox web browser, depicting gaming-related content on the SkyCrypt website [26]. SkyCrypt is a free open-source stats viewer for Hypixel SkyBlock. The open tab text has been obscured because it contains potentially identifiable information. Multiple browser tabs are open and visible. Numerous applications are open as evidenced in the taskbar (icons at the bottom of the screen), owned by Apple, Dropbox, Mozilla, Spotify, Meta, Microsoft, Google, and others. We received consent from all participants and their parents, caregivers, or other legal guardians to use their video data to generate screenshot images for use in publications. We created the images and have permission to use them.

Discussion

Expected Findings

The internet-based world affords children many benefits, such as connectivity, and access to educational and cultural content. Simultaneously, it increases their likelihood to encounter harm. Harms include marketing for unhealthy products; bullying; racist, discriminatory, or hate speech material; sexual and violent content; and websites advocating unhealthy or dangerous behaviors, such as self-harm, suicide, and anorexia.

The Kids Online methodology allows researchers to study the unique internet-based experiences of children and how these may impact their health and well-being. It enables children to document their internet-based world in real time via objective screen-share recordings. Retrieved recordings are highly personalized, their content is diverse, and they depict numerous web-based settings - providing researchers with individualized contexts and perspectives on internet usage among preteens, a demographic for which very little evidence currently exists. This insight cannot be garnered using researcher observation or survey research.

While only one-quarter of invited students have participated so far, this should still represent the broader experience of students in this age group. Researchers need to be technologically savvy given that children use a range of devices of different generations. It is also necessary to brief the children well, although they are often very technology literate. Manual coding of recordings is feasible, albeit time intensive. AI techniques will assist in reducing coding time.

Given that the wireless devices provided internet access that did not include restrictions that may be imposed by schools or parents, it is possible that participants used the internet more, or differently than normal. It is also possible that children selectively exclude or include certain internet-based content or behaviors while recording. However, children were instructed to use the internet as they normally would and largely reported doing so - comparison with phone use (screen-time) balances will provide some insight. Nevertheless, the data captured are a true record of the children's internet-based experiences.

Collectively, the retrieved recordings and demographic, attitude, and behavioral insights, and the health and well-being data provide a rich basis for future analyses of the nature and extent of all aspects of children’s internet-based world, their engagement with it, and the impact on their health and well-being. The method is legal, ethical, and acceptable to child participants, the adults in their lives, and those whom they interact with.

Conclusions

The Kids Online Aotearoa methodology is a novel, objective approach to investigate children’s internet-based world. It aims to inform appropriate political and societal action to effectively

regulate the internet-based world to ensure that the rights of children are upheld [27], thereby preventing web-based harm and enabling them to flourish.

Acknowledgments

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Data Availability

The data analyzed during the current study will not be made publicly available, in accordance with our ethical agreement.

Authors' Contributions

LS and MS conceived the study and developed the study design with assistance from AH-B, RG, JS, and MG. XW, TL, MG, and LS collected the data. JDD and SZ developed the AI methodology and undertook the initial analysis. LS provided overall leadership in the study. All authors contributed to this manuscript and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Questionnaire 1 used in study.
[PDF File (Adobe PDF File), 75 KB - resprot_v11i10e39017_app1.pdf]

Multimedia Appendix 2
Questionnaire 2 used in study.
[PDF File (Adobe PDF File), 60 KB - resprot_v11i10e39017_app2.pdf]

References

1. The State of the World's Children 2017. UNICEF. 2017. URL: https://www.unicef.org/reports/state-worlds-children-2017
2. Stoilova M, Livingstone S, Khazbak R. Investigating risks and opportunities for children in a digital world: a rapid review of the evidence on children's internet use and outcomes Mariya. UNICEF. 2021. URL: https://www.unicef-irc.org/publications/pdf/Investigating-Risks-and-Opportunities-for-Children-in-a-Digital-World.pdf [accessed 2022-09-23]
3. LeBourgeois MK, Hale L, Chang A, Akacem LD, Montgomery-Downs HE, Buxton OM. Digital media and sleep in childhood and adolescence. Pediatrics 2017 Nov;140(Suppl 2):S92-S96 [FREE Full text] [doi: 10.1542/peds.2016-1758J] [Medline: 29093040]
4. Stiglic N, Viner RM. Effects of screentime on the health and well-being of children and adolescents: a systematic review of reviews. BMJ Open 2019 Jan 03;9(1):e023191 [FREE Full text] [doi: 10.1136/bmjopen-2018-023191] [Medline: 30606703]
5. Fang K, Mu M, Liu K, He Y. Screen time and childhood overweight/obesity: a systematic review and meta-analysis. Child Care Health Dev 2019 Sep;45(5):744-753. [doi: 10.1111/cch.12701] [Medline: 31270831]
6. Tang S, Werner-Seidler A, Torok M, Mackinnon AJ, Christensen H. The relationship between screen time and mental health in young people: a systematic review of longitudinal studies. Clin Psychol Rev 2021 Jun;86:102021 [FREE Full text] [doi: 10.1016/j.cpr.2021.102021] [Medline: 33798997]
7. A governance framework for algorithmic accountability and transparency. European Parliamentary Research Service. 2019. URL: https://www.europarl.europa.eu/thinktank/en/document/EPRS_STU(2019)624262
8. Zoom. URL: https://zoom.us/ [accessed 2022-09-23]
9. Vaipuna T, Allison L, Bhasin A, Choi K, Chu A, Grice K, et al. An objective methodology capturing online commodity marketing and other harms. Health Promot Int 2020 Dec 01;35(6):1312-1319. [doi: 10.1093/heapro/daz131] [Medline: 31986195]
10. Kids Online Aotearoa 2021-2023: data collection protocol. Health Promotion and Policy Research Unit, University of Otago. 2021. URL: https://www.otago.ac.nz/heppru/research/otago837246.pdf
11. Mana Whakamärama - Equal Explanatory Power: Mäori and non-Mäori sample size in national health surveys. Te Röpü Rangahau Hauora a Eru Pömare - Wellington School of Medicine and Health Sciences, University of Otago. URL: https://www.fmhs.auckland.ac.nz/assets/fmhs/Te%20Kupenga%20Hauora%20M%C4%81ori/docs/Equal_explanatory_power.pdf
12. Lumley T. Complex Surveys: A Guide to Analysis Using R. New York, NY: John Wiley & Sons; 2011.

13. Quantitative tools. Global Kids Online. URL: http://globalkidsonline.net/tools/survey/ [accessed 2022-09-23]
14. Topp CW, Østergaard SD, Søndergaard S, Bech P. The WHO-5 Well-Being Index: a systematic review of the literature. Psychother Psychosom 2015;84(3):167-176 [FREE Full text] [doi: 10.1159/000376585] [Medline: 25831962]
15. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006 May 22;166(10):1092-1097. [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
16. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001 Sep;16(9):606-613 [FREE Full text] [doi: 10.1046/j.1525-1497.2001.016009606.x] [Medline: 11556941]
17. Hafekost J, Lawrence D, Boterhoven de Haan K, Johnson SE, Saw S, Buckingham WJ, et al. Methodology of young minds matter: the second Australian child and adolescent survey of mental health and wellbeing. Aust N Z J Psychiatry 2016 Sep;50(9):866-875. [doi: 10.1177/0004867415622270] [Medline: 26698821]
18. Friard O, Gamba M. BORIS: a free, versatile open-source event-logging software for video/audio coding and live observations. Methods Ecol Evol 2016 May 28;7(11):1325-1330. [doi: 10.1111/2041-210x.12584]
19. Oxford Languages and Google. Oxford Languages. URL: https://languages.oup.com/google-dictionary-en/ [accessed 2022-09-23]
20. OpenCV AI Competition 2022!. OpenCV. URL: https://opencv.org/ [accessed 2022-09-23]
21. van der Walt S, Schönberger JL, Nunez-Iglesias J, Boulogne F, Warner JD, Yager N, scikit-image contributors. scikit-image: image processing in Python. PeerJ 2014;2:e453 [FREE Full text] [doi: 10.7717/peerj.453] [Medline: 25024921]
22. Lin H, Deng JD, Albers D, Siebert FW. Helmet use detection of tracked motorcycles using CNN-based multi-task learning. IEEE Access 2020;8:162073-162084. [doi: 10.1109/access.2020.3021357]
23. Tesseract Open Source OCR Engine (main repository). GitHub. URL: https://github.com/tesseract-ocr/tesseract [accessed 2022-09-23]
24. Deng JD, Simmermacher C, Cranefield S. A study on feature analysis for musical instrument classification. IEEE Trans Syst Man Cybern B Cybern 2008 Apr;38(2):429-438. [doi: 10.1109/TSMCB.2007.913394] [Medline: 18348925]
25. Kelly B, Bosward R, Freeman B. Australian children's exposure to, and engagement with, web-based marketing of food and drink brands: cross-sectional observational study. J Med Internet Res 2021 Jul 12;23(7):e28144 [FREE Full text] [doi: 10.2196/28144] [Medline: 34255675]
26. SkyCrypt. URL: https://sky.shiiyu.moe [accessed 2022-09-23]
27. Convention on the rights of the child text. UNICEF. URL: https://www.unicef.org/child-rights-convention/convention-text [accessed 2022-09-23]

Abbreviations

AI: artificial intelligence
Kids Online: Kids Online Aotearoa

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Corrigenda and Addenda

Correction: Culturally Safe eHealth Interventions With Aboriginal and Torres Strait Islander People: Protocol for a Best Practice Framework

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Related Article:

Correction of: https://www.researchprotocols.org/2022/6/e34904

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In "Culturally Safe eHealth Interventions With Aboriginal and Torres Strait Islander People: Protocol for a Best Practice Framework" (JMIR Res Protoc 2022;11(6):e34904), the authors noted one error.

In the originally published article, Reference 23 incorrectly appeared as follows:

> *Mitchell-Box K, Braun KL. Fathers' thoughts on breastfeeding and implications for a theory-based intervention. J Obstet Gynecol Neonatal Nurs 2012 Nov;41(6):E41-E50. [doi: 10.1111/j.1552-6909.2012.01399.x] [Medline: 22861175]*

In the corrected version, the correct Reference [23] has been updated as follows:

> *Couch D, Doherty Z, Panozzo L, Naren T, Burzacott J, Ward B, et al. The impact of telehealth on patient attendance and revenue within an Aboriginal Community Controlled Health Organisation during COVID-19. Australian Journal for General Practitioners 2021 Nov;50(11):851-855. [doi: 10.31128/AJGP-07-21-6060] [Medline: 34713288]*

The correction will appear in the online version of the paper on the JMIR Publications website on October 14, 2022, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

Reference

23. Couch D, Doherty Z, Panozzo L, Naren T, Burzacott J, Ward B, et al. The impact of telehealth on patient attendance and revenue within an Aboriginal Community Controlled Health Organisation during COVID-19. Australian Journal for General Practitioners 2021 Nov;50(11):851-855. [doi: 10.31128/AJGP-07-21-6060] [Medline: 34713288]

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Protocol

Rationale and Design of an Ecological Momentary Assessment Study Examining Predictors of Binge Eating Among Sexual Minority and Heterosexual Young Women: Protocol for the Health and Experiences in Real Life (HER Life) Study

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Abstract

Background: Previous research has identified health disparities between sexual minority and heterosexual women, including increased rates of obesity and binge eating in sexual minority women. Established predictors of binge eating behavior include negative emotions and sociocultural processes; however, these studies are generally conducted in samples of young women where sexual identity is not known or reported. There is a dearth of research evaluating how sexual minority–specific factors (eg, minority stress and connectedness to the lesbian, gay, bisexual, transgender, and queer community) may affect binge eating in sexual minority women. In addition, no studies have examined these processes in racially diverse samples or considered how intersecting minority identities (eg, Black and sexual minority) may affect eating behaviors.

Objective: The Health and Experiences in Real Life (HER Life) Project aims to clarify real-world predictors of binge eating in young heterosexual and sexual minority women using ecological momentary assessment. The role of affective, social, and health behavior factors in binge eating will be examined for all women (aim 1), and sexual minority–specific predictors will also be considered for sexual minority women participants (aim 2). Person-level moderators of race, body- and eating-related factors, and sexual minority–specific factors will also be examined to better understand how real-world binge eating predictors may differ for various demographic groups (aim 3).

Methods: Researchers aim to recruit 150 sexual minority and 150 heterosexual women from across the United States, including at least 50 Black women for each group, using web-based recruitment methods. The eligibility criteria include identifying as a woman, being aged between 18 and 30 years, and having had at least two binge eating episodes in the last 2 weeks. Participants must endorse being only or mostly attracted to men (considered heterosexual) or only or mostly attracted to women or having a current or most recent female partner (considered sexual minority). Eligible participants complete an initial web-based baseline survey and then 14 days of ecological momentary assessment involving the completion of a morning and before-bed survey and 5 prompted surveys per day as well as a user-initiated survey after binge eating episodes. The data will be analyzed using a series of multilevel models.

Results: Data collection started in February 2021. We have currently enrolled 129 sexual minority women and 146 heterosexual women. Data collection is expected to conclude in fall 2022.

Conclusions: The Health and Experiences in Real Life Project aims to elucidate potential differences between sexual minority and heterosexual women in within-person factors predicting binge eating and inform eating disorder interventions for sexual minority women. The challenges in recruiting sexual minority women, including the determination of eligibility criteria and considerations for remote data collection, are discussed.

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KEYWORDS

sexual minority women; ecological momentary assessment; binge eating; sexual minority stress; negative affective states; mobile phone

Introduction

Background

Obesity and obesity-related conditions are the leading causes of death in the United States [1], making them a significant public health concern. On the basis of several recent national reports [2,3], there are disparities in the health and well-being of sexual minority individuals (eg, gay, lesbian, and bisexual) as compared with their heterosexual peers in a range of health conditions and health behaviors. In particular, large-scale studies suggest that sexual minority women are at least twice as likely to be obese as heterosexual women [4,5], and studies of young women have similarly found higher rates of being overweight or obese in young lesbian women (35.2%) than in young heterosexual women (22.8%) [6]. There is also evidence that rates of binge eating, defined as overeating with loss of control of eating, are similarly higher in sexual minority individuals. For example, in a study of nearly 14,000 people, young adult lesbian women were twice as likely to binge eat as heterosexual women [7]. Despite these documented disparities, relatively little is known about the contributing factors, which is a critical first step in developing interventions to address these health concerns among sexual minority women.

In working toward increased understanding of factors that contribute to higher obesity and binge eating rates in sexual minority women, the goal of this study is to use ecological momentary assessment (EMA) to identify general and minority-specific real-world predictors of binge eating. EMA involves the use of repeated assessments of people's current behaviors, states, and experiences as they are going about their lives [8]. EMA approaches provide unique advantages over other research methods (eg, cross-sectional and traditional longitudinal methods), including greater real-world generalizability and reduced concerns regarding memory biases associated with retrospective recall that are generally present in traditional measures. In addition, as EMA uses repeated assessments (typically multiple times throughout the day), researchers can examine dynamic within-person processes and answer research questions that cannot be addressed using other methods [8,9]. For example, most previous research on binge eating among sexual minority women has used cross-sectional designs, which can address questions regarding between-person processes (eg, do women who are more depressed also binge eat more?). EMA approaches provide an opportunity to answer questions regarding *within-person* processes (eg, when women experience a more depressed mood, are they more likely to binge eat?). This study—called the Health and Experiences in Real Life (HER Life) Project—will examine within-person associations between a range of general predictors of binge eating (ie, affect, body dissatisfaction, social processes, and health behaviors) in young heterosexual and sexual minority women as well as sexual minority–specific factors (eg, minority stress and discrimination) among young sexual minority women. The existing empirical evidence and theoretical framework supporting this study are described in the following sections.

General Factors Associated With Binge Eating in Daily Life (Aim 1)

The factors influencing disordered eating are complex, and researchers have highlighted the potential utility of EMA to study disordered eating, including binge eating, in natural settings [10]. EMA research shows that disordered eating, including binge eating, is associated with affective states (eg, negative mood, stress, and body dissatisfaction) [11,12], social experiences (eg, interactions and media use), and health behaviors (eg, alcohol use and physical activity) in studies of young women where sexual orientation was not assessed or reported (hereafter referred to as general samples). However, with few exceptions [13], EMA studies have yet to consider how affective states, social processes, and health behaviors in daily life are associated with sexual minority women's binge eating, which is a primary aim of this study.

The role of negative emotions (eg, negative affect and stress) in binge eating is often examined as a way of evaluating the affect regulation model of eating disorders [14]. A meta-analysis of EMA studies evaluating the affect regulation model of binge eating found that negative emotions increased leading up to a binge eating episode, with more mixed findings regarding negative affect after binge eating episodes [12]. Negative feelings about one's body, or body dissatisfaction, have also been examined via EMA in general samples of young women but, with few exceptions [15], studies have generally focused on associations between body dissatisfaction and social processes, not disordered eating behaviors [16-18]. Although these studies show that negative mood and body dissatisfaction may be associated with binge eating in daily life, this work is largely based on general samples of young women, and whether and how these processes operate in sexual minority women is less clear. There is some preliminary evidence demonstrating that negative affect is associated with binge eating at the day level in a daily diary study of 30 lesbian women [13], but there are no EMA studies of body dissatisfaction in sexual minority women. Cross-sectional studies designed to answer between-person research questions have produced mixed findings, with some suggesting that body dissatisfaction is similar in sexual minority and heterosexual women [19] and others finding that larger body sizes are more acceptable among sexual minority social groups and, thus, body dissatisfaction may be lower [5]. However, as described previously, this study will fill gaps in the literature by assessing negative affect, stress, and body dissatisfaction in daily life to examine how they are

associated with binge eating among both young sexual minority and heterosexual women.

There is a long history of research demonstrating the contribution of sociocultural processes to disordered eating behaviors [20,21]. In fact, the sociocultural model of disordered eating suggests that there are social pressures to be thin (and, increasingly, to be fit or toned) in Western countries, which are communicated directly and indirectly through the media, peers, and family and can become internalized (ie, thin ideal internalization) [22]. In recent years, several EMA studies have examined how social experiences are associated with body dissatisfaction and eating behaviors in daily life. For example, in a general sample of 121 women aged 18 to 40 years, women reported greater body dissatisfaction in social situations (ie, when they had had an interaction in the previous 30 minutes) than when alone and particularly when they perceived that the interaction quality was lower [18]. To our knowledge, studies on the effect of social processes in daily life on eating behaviors have been conducted only among general samples of young women and, thus, it remains unclear whether sexual minority women experience the same sociocultural influences as heterosexual women in daily life. Cross-sectional research suggests that larger body sizes may be more acceptable in sexual minority women's social groups and relationships [5,23] and, thus, they may be less susceptible to thin ideals that they are exposed to in social interactions and the media. However, as described by the dual identity framework, there may also be commonalities between sexual minority and heterosexual women [24]. According to this framework, sexual minority women are influenced, as women, by the mainstream (heterosexual) community and, as sexual minority individuals, by the sexual minority community. Thus, sexual minority women's eating behaviors will likely be influenced by general social processes but potentially to a lesser extent than heterosexual women. The HER Life Project will explore social influences on both sexual minority and heterosexual women in daily life, thus allowing for a better understanding of how these dual influences may operate for young sexual minority women.

In addition to the demonstrated importance of sociocultural considerations for understanding disordered eating, cross-sectional and meta-analytic studies have shown that hazardous alcohol use is associated with disordered eating in general samples of young adults [25] and among lesbian women. For instance, a cross-sectional survey found that lesbian women with obesity were more likely to report heavy drinking compared with lesbian women who were not overweight or obese [26]. Research on the associations between binge eating and physical activity are more equivocal [27], but 1 study with a general sample of young women found that those with binge eating disorder reported less physical activity compared with weight-matched women who did not have binge eating disorder [28]. Even less is known about physical activity and binge eating in sexual minority women, but 1 study of lesbian and bisexual women found that being overweight or obese was associated with less frequent exercise [29]. It is clear that there is a dearth of research on the associations among alcohol use, physical activity, and binge eating, especially in sexual minority women. This is particularly notable because of the documented disparities in alcohol use and physical activity, with sexual minority women engaging in more hazardous drinking [30-32] and less physical activity [33,34] than heterosexual women. This study will assess alcohol use and physical activity in daily life, which will allow for a real-world examination of how these health behaviors may operate among sexual minority and heterosexual young women, and explore potential associations with binge eating.

Sexual Minority–Specific Factors Associated With Binge Eating in Daily Life (Aim 2)

In addition to the aforementioned general factors that may influence binge eating, sexual minority women face unique experiences and stressors because of their marginalized and stigmatized status in society. This phenomenon has been described in minority stress theories by Meyer [35] and Hatzenbuehler [36]. These theories complement each other in describing how general and minority-specific stressors can affect mental health and well-being. For example, the minority stress theory by Meyer argues that sexual minority individuals experience stressors related to their minority status. These stressors include chronic and acute external events (discrimination, harassment, invalidations, and vicarious experiences through other sexual minority individuals) and internal stressors (concealment of sexual identity, expected rejection, and internalization of negative societal messages about sexual minorities [internalized heterosexism]) that can negatively affect mental health. The psychological mediation framework by Hatzenbuehler extended these ideas to suggest that general (eg, coping, emotion regulation, and social support) and minority-specific (eg, distal and proximal minority stressors) experiences operate together to influence sexual minority individuals' well-being. These theories have been extended from their initial focus on understanding mental health to also consider the impact of minority stressors on physical health and health behaviors.

In recent years, minority stress theories have been used to identify potential mechanisms to explain health disparities between sexual minority and heterosexual individuals, including disordered eating. Cross-sectional studies of sexual minority women have found between-person associations between heterosexist experiences (eg, harassment, rejection, and sexual orientation discrimination) and disordered eating [37-39]. More recently, there have been several daily diary and EMA studies that have assessed within-person associations between minority stressors and disordered eating behaviors at the day or moment level. For example, in a sample of 30 young lesbian women who reported binge eating, researchers found that, on days when the women reported more discrimination, they also reported more binge eating (and this effect occurred in part through negative affect) [13]. In an EMA study of 55 sexual minority women who were overweight or obese, Panza et al [40] similarly found that those with higher baseline levels of internalized homophobia and sexual orientation concealment reported more binge eating and overeating during a 5-day EMA period. Taken together, sexual minority stress theories and empirical research suggest that sexual minority stress is associated with poor mental health, with substantially fewer studies considering the effects on binge eating. The goal of this study is to examine the

within-person direct and indirect (through negative affect) effects of sexual minority stressors on binge eating in a subsample of sexual minority women. In other words, this study allows us to consider whether, at times when sexual minority women experience a minority stressor, that experience is either concurrently or subsequently associated with binge eating in daily life. Such information may improve the understanding of the potential mechanisms whereby sexual minority women experience more disordered eating behaviors as compared with heterosexual women.

Risk and Protective Factors for Binge Eating (Aim 3)

Given that theories on binge eating and sexual minority health and health disparities are complex, with factors influencing these behaviors at various *levels*, an additional aim of this study is to consider how *between-person* factors may strengthen or weaken the aforementioned *within-person* associations. Three broad groups of moderators will be considered in this study: race, body- and eating-related factors, and sexual minority–specific factors. Considering these cross-level moderators can be useful for clarifying previous conflicting findings and provide a more complete picture of both *when* and *for whom* various real-world binge eating predictors operate.

Although cross-sectional research shows that sexual minority women are more likely to report binge eating compared with heterosexual women [7,41,42], many of these studies were conducted in samples that were not racially diverse. There is some conflicting research regarding potential racial differences in binge eating between Black and White women in the United States. Some studies in general samples of young women have found no differences in disordered eating (including binge eating) between Black and White women [43,44] but, in a general sample of women with binge eating disorder, Black women reported 1.5 times as many binge eating episodes per week compared with White women [45]. However, taken together, these studies fail to consider how multiple minority identities (ie, being a Black sexual minority woman) might interact to exacerbate health behavior risks, and there is scant research examining the effect of the intersection of sexual and racial identities on binge eating. In fact, we found only 1 study that assessed binge eating in a small, racially diverse sample of lesbian and bisexual women. This cross-sectional study found that 1.6% of White heterosexual women (n=63) reported binge eating at least twice per week compared with rates of 4.5% for White lesbian and bisexual women (n=67) and 3.1% for Black lesbian and bisexual women (n=64) [46]. Importantly, this study was cross-sectional and had a small sample. Therefore, to extend these past findings, in the HER Life Project, we powered to test for Black-White race moderator effects of the within-person associations between the general and minority-specific predictors of binge eating outlined in the first 2 study aims, allowing us to examine how intersecting minority statuses (ie, being Black and of a sexual minority) may uniquely shape eating behavior in daily life.

In addition to considering how women's racial identity may moderate within-person associations, this study will consider 4 body- and eating-related variables: BMI, person-level (baseline) body dissatisfaction, disordered eating, and thin norm internalization. These variables were selected based on past research demonstrating that individuals higher or lower in these constructs may exhibit different associations between our predictors of interest and binge eating [17].

In addition, this study considers sexual minority–specific moderators of EMA associations, which will be considered among the subsample of sexual minority women. In particular, we will evaluate 3 protective factors (positive sexual minority identity; lesbian, gay, bisexual, transgender, and queer [LGBTQ+] community connection; and identification with the LGBTQ+ community) and one risk factor (lifetime sexual minority discrimination). Previous cross-sectional research suggests that connection to and identification with the sexual minority community may buffer against the deleterious effects of sexual minority stress [47], including perceived stigma and depressive symptoms [48]. Furthermore, in a cross-sectional study of lesbian, gay, and bisexual young adults, social support (eg, from the sexual minority community) attenuated the associations between minority stress and emotional distress [49]. Conversely, lifetime discrimination may be a risk factor for maladaptive health behaviors. In a daily diary study of Black college students, perceived lifetime racial discrimination moderated the associations between negative mood and alcohol use [50], providing evidence that (person-level) lifetime racial discrimination influences daily health behaviors. Taken together, the third aim of this study is to consider a variety of person-level moderators of the within-person associations explored in the first 2 study aims.

Overview of Study Aims

The broad objective of the HER Life Project is to enhance the understanding of the real-world predictors of binge eating among young sexual minority and heterosexual women. To address this objective, this study is organized around 3 aims.

Aim 1: To Examine the Role of Affective, Social, and Health Behavior Factors in Binge Eating

We hypothesize that, when sexual minority and heterosexual women experience higher levels of negative emotion variables (negative affect, general stress, and body dissatisfaction), they engage in more binge eating (hypothesis 1a). We also expect that social experiences (eg, social interactions and media use) will be associated with more binge eating for both groups (hypothesis 1b), but the associations will be stronger for heterosexual women than for sexual minority women (hypothesis 1c). A priori hypotheses for binge eating, alcohol use, and physical activity associations are not made because of limited previous EMA research.

Aim 2: To Examine the Associations Between Sexual Minority Stress and Binge Eating Among Sexual Minority Women

Direct within-person associations are hypothesized such that, when sexual minority women experience more sexual minority stress, they will engage in more binge eating (hypothesis 2a). Consistent with theory, we also expect that negative affect will mediate the association between sexual minority stress and binge eating (hypothesis 2b). These aims will be tested within the subsample of sexual minority women recruited for this study.

Aim 3: To Explore Race and Other Person-Level Moderators of Associations in Aims 1 and 2

Race, body- and eating-related factors (BMI, body dissatisfaction, disordered eating, and thin norm internalization), and sexual minority–specific factors (lifetime discrimination, positive sexual minority identity, and community identification and connection) will be explored as moderators of EMA associations in aims 1 and 2. Given the scant previous research, no a priori hypotheses are specified, but the study is powered to test for Black-White group differences for aims 1 and 2 to explore the intersection of multiple minority identities.

Methods

Project Overview

The HER Life Project is an ongoing EMA study of young sexual minority and heterosexual women who binge eat. Young women aged 18 to 30 years are the focus of this study given that they report high levels of binge eating [4,5] and, thus, represent an at-risk group. We selected women aged 18 to 30 years as, although "young adulthood" has no clear definition, there is evidence that sexual identity continues to develop during this period, and data suggest associations among sexual identity, negative affect, and disordered eating up to the age of approximately 30 years [51]. Participants are being recruited from across the United States, and data collection is occurring entirely remotely as we are using web-based surveys and a smartphone app to deploy EMA surveys. Participants receive and review the written and video study procedure descriptions before beginning the study. They complete a web-based screening and baseline survey before beginning the 2-week EMA data collection period and conclude their participation with an end-of-study survey. During the EMA period, participants complete daily morning and before-bed surveys, 5 prompted surveys each day, and a user-initiated binge eating survey after binge eating episodes.

Ethics Approval

The Old Dominion University Institutional Review Board approved all the study procedures (project 1362990).

Power Analysis

A 3-step power analysis was conducted to determine sample size. First, a regression power analysis using G*Power (version 3.1.9) [52] was conducted, powering the hardest-to-detect effects (aim 1 hypothesis 1c: sexual identity moderation; aim 3: race moderation) and the examinations using only sample subsets (aim 2: direct effects, sexual minority women only). To achieve a power of 0.80 using an α of .05, 227 independent observations are required for a small to medium effect (f^2=0.035) for moderation examinations with 5 predictors (to allow for relevant covariates). Specifying the same power level, α, and effect size with 3 predictors for aim 2 main effects (to allow for relevant covariates), 227 independent observations among sexual minority women only would be necessary. Second, we applied a formula to account for the multiple correlated observations for each person and identify the number of actual participants needed [53]. This equation accounts for level-1 (assessments or moments) and level-2 (participants) sample sizes and the intraclass correlation coefficient (ICC; within-person relatedness). On the basis of past EMA studies of similar constructs among young women [54,55], a conservative estimate of the average number of assessments per person (n_{L1}) is 25, reflecting constructs only asked once or twice per day (as opposed to all prompts), approximately 70% compliance, and the reporting of approximately 6 binge eating episodes. If 100 sexual minority and 100 heterosexual women are recruited, this would result in approximately 5000 total observations (2500 from sexual minority women). We expect ICC values from 0.33 to 0.43 for binge eating. Using the West et al [53] formula and past studies, n_{L2} of 100 sexual minority and 100 heterosexual women would result in an N-effective of 280 within sexual identity if the ICC is 0.33 and an N-effective of 221 within sexual identity if the ICC is 0.43. This means that, although there are 2500 assessments from sexual minority women, because of the degree of relatedness of observations within each individual, these are equivalent to 221 independent pieces of information. Thus, recruiting 200 women should provide sufficient power for these aims. In addition, to detect small to medium mediation effects (aim 2) using empirical bias-corrected bootstrap CIs, 148 independent observations should be sufficient [56]. Finally, to power for aim 3, half of the 100 participants in each sexual identity group (n=50) will need to identify as Black to optimize power. However, given the demographic representation in previous work examining eating behaviors in young women using EMA [54,55], it is expected that we will need to enroll >100 women of each identity to have 50 Black women in each group even if deliberately oversampling. To ensure that we are sufficiently powered to test all aims and have similar numbers in both groups, we aim to enroll 150 sexual minority women (50 Black) and 150 heterosexual women (50 Black).

Participant Selection

Participants are being recruited using various web-based sources, including from web-based research panels, social media, and lists of people who participated in past studies and expressed an interest in future research opportunities. We are working with several market research firms who have access to web-based panels of people who are interested in participating in web-based research. Community Marketing & Insights is an LGBTQ+ market research firm that manages a proprietary panel of individuals who identify within the LGBTQ+ community and are interested in participating in web-based studies. Marketing Systems Group and Qualtrics International Inc are also assisting with accessing existing panels of individuals who regularly participate in web-based studies, primarily to recruit heterosexual women. We have also placed advertisements on social media (eg, Facebook and Instagram) using the Meta advertising platform and through advertisements on our laboratory social media page.

To be eligible to take part in the study, participants must (1) identify as women (from a multi-select question, selecting woman or woman *and* some combination of genderqueer, nonconforming, or nonbinary and also indicating that they were assigned female at birth), (2) be aged between 18 and 30 years (inclusive), (3) report binge eating (ie, overeating with a feeling

of loss of control of eating) at least two times in the past 2 weeks, (4) not be currently receiving treatment for an eating disorder, and (5) have a schedule that allows for answering surveys during daytime hours. In addition, the participants must also meet either the sexual minority or heterosexual criteria. Women are included in the sexual minority sample if they report that they are (1) only or mostly attracted to women or (2) equally attracted to men and women or attracted to people regardless of their gender identity *and* also have a current or most recent romantic partner who identifies as a woman. Women are included in the heterosexual sample if they report that they are only or mostly attracted to men.

Study Procedures

Recruitment

For participants being recruited through the marketing research firms, the firm makes initial contact with potential participants and administers an initial web-based screening survey. Contact information for the eligible participants is then provided to the research team. At this time, participants are contacted via email and screened directly by the research team using a brief web-based screening survey. For participants being recruited through social media and lists of past research participants interested in research studies, potential participants are provided directly with a web-based screening survey and screened by our team.

Informed Consent Process and Baseline Survey

Eligible participants are provided with additional information about the study during the informed consent process. First, a 3-minute video providing a general overview of the study's purpose, procedures, and participation requirements (eg, downloading a smartphone app) and compensation is emailed to potentially eligible participants. Second, participants are provided with information about how to download the smartphone app needed to complete the EMA surveys. Participants confirm their interest in participating by downloading the smartphone app and notifying the research team that they have done so. The LifeData (LifeData, LLC) survey software and RealLife Exp (LifeData, LLC) app are being used for this study. This software allows for custom EMA surveys and alarm schedules to be created, and the surveys can be deployed on any Android or Apple smartphone using the RealLife Exp app. Plans are in place to provide a phone to participants if they do not have an Android or Apple phone that they are willing or able to use for the study (none have requested this option to date). Participants who do not respond to these emails are sent up to 3 reminders to review the video and download the smartphone app. Additional details regarding the email reminder system used throughout the study process are provided in the following sections. Once participants confirm their interest in proceeding with the study (as evidenced by downloading the app to their phone), they are sent a web-based link to complete an electronic informed consent form, which is immediately followed by the baseline survey, which takes approximately 45 minutes to complete.

EMA Surveys

After completing the baseline survey, participants receive an email from our team with instructions on how to download the study-specific EMA smartphone surveys (within the app they previously downloaded) and a document with frequently asked questions and answers about study procedures. Once participants download the study-specific surveys, they complete an initial "startup" session where they enter their study-specific identification number and watch 2 additional brief training videos created by the research team. The first video provides additional information about when and how to complete each type of EMA survey and is approximately 3 minutes long. The second video provides a definition and examples of a binge eating episode to help participants in identifying their binge eating and improve understanding of when to initiate a binge eating survey; this video is approximately 2 minutes long. These informational videos and the document with frequently asked questions and answers are accessible to participants within the smartphone app throughout the entirety of the EMA portion of the study.

The day after the study-specific EMA surveys are downloaded, participants begin to receive 5 prompted surveys per day for the next 14 days at semirandom times between 9 AM and 9 PM each day. In addition to the prompted surveys, participants complete 3 different user-initiated surveys: an after binge eating survey, a morning survey, and a before-bed survey. They are instructed to complete the post–binge eating survey after a binge eating episode; as described previously, participants receive written and video instructions defining, describing, and providing examples of a binge eating episode. They are instructed to self-initiate the morning survey immediately after waking up and the before-bed survey just before going to sleep at night, but the app also provides a reminder notification for each (at 10 AM for the morning survey and 9 PM for the before-bed survey).

End-of-Study Survey

After day 14 of the EMA surveys, participants receive an email including a link to complete a survey regarding their experience as research participants in this study. Additional information on this measure can be found in the Measures section.

Compensation

Participants can earn up to US $150 for taking part in this study. They receive US $20 for completing the baseline survey and US $10 for completing the end-of-study survey. Each week of the EMA, they receive US $40 (a total of US $80). To incentivize compliance, they can also receive a US $20 bonus each week if they complete 80% of the daily surveys (averaging a morning survey, 4 prompted surveys, and a before-bed survey per day). Within a week of completing the end-of-study survey, participants receive an email thanking them for taking part and notifying them of their compensation amount. Participants receive an electronic gift card (selected from several options) via email at the conclusion of their participation.

Email Reminder and Check-in Systems

Given that this study is being conducted entirely remotely and participants need to move through various steps to enroll in and

complete the study, we developed a system for reminding participants who do not respond to initial emails or complete tasks as expected. Throughout each stage of the process—screening, completing the baseline survey, beginning the EMA surveys, and completing the end-of-study survey—project staff send participants up to 2 reminders, approximately 2 to 3 days apart, to encourage participation. If participants do not respond to these reminders, a final email is sent by the study principal investigator (PI; KH) to inquire about questions and encourage their continued participation.

In addition to monitoring the overall flow throughout the study, we carefully track compliance with the EMA surveys. Participants' completion of the daily surveys is tracked and recorded each day using a daily tracking spreadsheet. Participants are sent a general check-in email on day 2 or 3, day 7 or 8, and day 13 or 14 of the EMA portion of the study to thank participants for their completion thus far, offer the opportunity to ask questions, and encourage continued compliance. Participants demonstrating a pattern of noncompliance (eg, no prompted surveys completed in a day, no morning or before-bed surveys completed in a day, or many prompted surveys not completed) receive a noncompliance email. Noncompliance emails are sent to participants to advise them as to which surveys they are not completing on a regular basis, check whether they are experiencing difficulty completing the daily surveys, and encourage participation.

Measures

The measures in the baseline survey are described in Table 1 and are grouped together by construct. Participants generally complete the same baseline survey, with 2 exceptions. First, there are several specific questionnaires for sexual minority women regarding minority stressors (eg, discrimination and rejection), identity, and LGBT community connection. To balance survey length and content, heterosexual women complete questionnaires regarding their identity as women and their general social support. Second, as we are interested in assessing alcohol use but did not require participants to drink alcohol to participate in this study, we ask about alcohol use only of those women who drank in the past 30 days and administer a series of questionnaires regarding reasons for not drinking and general coping to nondrinkers to similarly balance for time.

The measures in the 4 different EMA surveys (morning, before bed, after binge eating, and prompted) are described in Table 2. Items were either drawn directly from existing EMA scales or past studies or were adapted from non-EMA measures and developed for the purposes of this study in instances where no EMA measure of a construct existed.

The end-of-study survey collects information about participants' experiences in the study, interest in and willingness to be involved in future mobile health interventions regarding physical and mental health, and COVID-19–related questions. Table 3 provides a description of the constructs included in the end-of-study survey.

Table 1. Baseline measures.

Construct and description	Measure name
Demographics—age, sexual orientation (identity, attraction, and behavior), height, weight, address, geographic location, relationship status and length, employment status, education level, average individual income, and finances	N/A[a]
Sexual identity—self-identity, identity disclosure, and "coming out" (for sexual minority women only)	N/A
Eating and body image	
Eating pathology (body dissatisfaction, binge eating, cognitive restraint, purging, restricting, and excessive exercise)	Eating Pathology Symptoms Inventory [57]
Diagnostic criteria for eating disorder behaviors	Eating Disorder Examination Questionnaire 6.0—selected items [58]
Trait-level body dissatisfaction	Body Shape Questionnaire [59]
Societal and interpersonal norms and pressures regarding appearance and norm internalization	Sociocultural Attitudes Toward Appearance Questionnaire-4-Revised [60]
Trait-level ability to eat intuitively following their physical hunger and satiety cues	Intuitive Eating Scale-2 [61]
Fat talk engagement and negative body-related conversations	Fat Talk Questionnaire [62]
Extent to which individuals who engage in disordered eating lie about such behaviors	Deliberate Denial of Disordered Eating Behaviors Scale [63]
Gender experiences and identity	
Experiences of unfair treatment	Everyday Discrimination Scale [64]
Degree to which an individual identifies with and has interest in their own race or ethnicity	Multigroup Ethnic Identity Measure [65]
Degree to which people apply weight-based stereotypes to themselves and base their self-evaluations on weight	Modified Weight Bias Internalization Scale [66]
Sexual minority women's experiences, identity, and support (for sexual minority women only)	
Sexual minority discrimination	Heterosexist Harassment Rejection, and Discrimination Scale [67]
Sexual minority identity and psychosocial functioning	Lesbian, Gay, and Bisexual Identity Scale [68]
Connectedness to the LGBT[b] community	Connectedness to the LGBT Community Scale [69,70]
Feelings about being part of the sexual minority community and the extent to which their status is important to their identity	Sexual Minority Community Identification [71,72]
Women's identity and support (for heterosexual women only)	
Feminist identity development	Feminist Identity Composite [73-75]
Individuals' appraisals of perceived social support	Social Support Appraisals Scale [76]
Mood, stress, and other general life experiences	
Depressive symptoms	Center for Epidemiological Studies Depression 10-item Scale [77]
Anxiety symptoms	Generalized Anxiety Disorder 7-item Scale [78]
Perceived life stress	Perceived Stress Scale [79]
Self-harm and suicidal ideation, plans, and attempts within the past 12 months	Self-Harm Questions-Adapted [80,81]
Ability to bounce back or recover from stress	Brief Resilience Scale [82]
Engagement in comparison behaviors	Iowa-Netherlands Comparison Orientation Measure [83]
Early traumatic experiences and adverse life events	Childhood Traumatic Events Scale [84]
Past 30-day alcohol use—any alcohol use in the last 30 days	N/A
Alcohol use (for women who drank in the last 30 days)	
Quantity, volume, and frequency during a typical week	Daily Drinking Questionnaire [85]

Construct and description	Measure name
Motives for drinking	Drinking Motives Questionnaire [86]
Alcohol consequences experienced by young adult drinkers	Brief Young Adult Alcohol Consequences Questionnaire [87]
Eating-related behaviors related to alcohol consumption	Compensatory Eating and Behaviors in Response to Alcohol Consumption Scale [88,89]
General coping with stress (for women who did not drink in the last 30 days)	
Importance of various reasons for not drinking	Reasons for Not Drinking scale [90]
Strategies for effective and ineffective coping	Brief Coping Orientation to Problems Experienced [91,92]
Other health and health behaviors	
Health-related quality of life	Medical Outcomes Study Short Form-36 [93]
Typical marijuana quantity used each day	General Marijuana Use [85,94]
Typical cigarette quantity used each day	General Cigarette Use [85]
Perceived drinking norms for heterosexual and sexual minority women	Alcohol Descriptive Norms [95]
Reasons why people do not engage in as much physical activity as they think they should	Barriers to Being Active Quiz [96]
Expected outcomes of engaging in physical activity	Exercise Motivation Scale [97]

[a]N/A: not applicable (no named measure).

[b]LGBT: lesbian, gay, bisexual, and transgender.

Table 2. Ecological momentary assessment surveys.

Survey, construct, and description	Measure name and reference
Morning survey	
Sleep—time in bed, time to fall asleep, wake-up time, length of time asleep, and quality of sleep	Items adapted from the Pittsburgh Sleep Quality Index [98]
Alcohol use—quantity, time drinking, type, location, and interactions (for drinking days only)	Items adapted from various sources, including the study by Heron et al [99]
Compensatory behaviors for drinking (for drinking days only)	Items adapted from the Compensatory Eating and Behaviors in Response to Alcohol Consumption Scale [88]
Nondrinking questions (for nondrinking days only)	Items adapted from various sources, including the study by Heron et al [99]
Mood—anticipated mood for the upcoming day: happy, bored, relaxed, sad, excited, content, worried or anxious, angry, frustrated, or energetic	Items adapted from the Positive and Negative Affect Schedule-Expanded Form [100,101]
Anticipated upcoming stressful and pleasant experiences	Items developed for this study
Before-bed survey	
Mood—overall mood for the day: happy, bored, relaxed, sad, excited, content, worried or anxious, angry, frustrated, or energetic	Items adapted from the Positive and Negative Affect Schedule-Expanded Form [100,101]
Social comparison—nature of social comparison, number of times, type of comparison, person compared with, and feelings about comparison (for social comparison days only)	Items were adapted from sources including the study by Arigo et al [102]
General social experiences—types of people interacted with, pleasantness of interactions, and importance of interactions and topics (for non–social comparison days only)	Items developed for this study
Tobacco—tobacco use	Items developed for this study
Physical activity—length, type, amount, thoughts about activity, estimated amount of physical activity, and exercise the following day	Items adapted from multiple sources [102,103]
Post–binge eating survey	
Date, time, and location of binge eating	Items developed for this study
Eating speed, fullness, with others, and emotions after eating	Items adapted from the Eating Disorder Diagnostic Scale [104] and the DSM-5[a] binge eating description [105]
Purging and intended purging	Items adapted from the Eating Disorder Diagnostic Scale [104]
Mood before, during, and after binge eating	Items developed for this study based on pilot study participant feedback
Perceived factors contributing to the binge eating episode	Items developed for this study based on pilot study participant feedback
Prompted survey	
Location activity—location of survey notification and activity upon notification	Items developed for this study
Mood—current mood ratings for happy, bored, relaxed, sad, excited, content, worried or anxious, angry, frustrated, or energetic	Affect words selected from the Positive and Negative Affect Schedule-Expanded Form [100,101]
Body image—satisfaction with physical appearance, body shape, weight, physical attractiveness, and looks	Items from the Body Image States Scale [106] adapted from a 9-point scale to a 7-point scale [103]
Self-objectification—thinking about appearance to other people	Item adapted from the study by Holland et al [107]
General stress—stressful or unpleasant experiences	Items adapted from the Daily Inventory of Stressful Events [108] and used in the study by Heron et al [109]
Identity stress—discrimination based on aspect of identity and aspect of identity responsible for discrimination	Items adapted from the study by Panza et al [110]

Survey, construct, and description	Measure name and reference
Disordered eating behaviors—overeating, loss of control of eating, guilt after eating, emotional eating, concerns about eating with others, restriction, avoiding foods	Items from the Eating Disorder Examination Questionnaire 6.0 [111], items adapted using language from the DSM-5 [105], and items from the Emotional Eater Questionnaire [112]
Intuitive eating behaviors—eating for physical hunger, trusting body to eat, body-food choice congruence, permission to eat desirable foods	Items adapted from the Intuitive Eating Scale [61,113]
Physical activity—intensity level of physical activity, type of exercise, length of exercise, and typical amount of exercise	Items adapted from the International Physical Activity Questionnaires [114]
Media use—social media use, type, and activity	Items developed for this study
Appearance-related pressures and source of pressures	Items adapted from the Sociocultural Attitudes Toward Appearance Questionnaire-4 [115]
Negative body-related talk and source of talk	Items adapted from the Fat Talk Questionnaire [62]
Social interactions—type, pleasantness, and importance of people and topic of interaction	Items adapted from the studies by Bernstein et al [116] and Zhaoyan et al [117]

[a]DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

Table 3. End-of-study survey.

Construct and description	Measure name
Accessibility of EMA[a] surveys—questions measuring the burden and accessibility of the EMA surveys	Items developed for this study
Experiences with post–binge eating surveys—measured participants' accurate identification of binge eating episodes and feedback on the survey	Items developed for this study
Identity inclusivity feedback—assessed whether survey items were inclusive of participant identities and captured their experiences	Items developed for this study
Desire to improve health—measured desire and interest in improving physical and mental health	Items developed for this study
Help seeking—assessed resources in social circle that could help the participant address health problems (assessed physical health and mental health problems separately)	Adapted from the General Help-Seeking Questionnaire [118]
Willingness to use mobile health technology—assessed willingness to use mobile health technology to improve physical and mental health or implement health behavior changes	Adapted from the study by Cramer et al [119]
COVID-19 situation—current and previous state of shelter-in-place orders, social distancing practices, and experience of illness with COVID-19	Items developed for this study
COVID-19 health impacts—impact of the COVID-19 pandemic on physical and mental health symptoms as well as change in health behaviors since the start of the pandemic	Items developed for this study [120]
COVID-19 general impacts—changes in responsibilities, finances, and work or school roles since the start of the COVID-19 pandemic	Items selected from the Epidemic-Pandemic Impacts Inventory [121]
COVID-19 minority impacts—impact of the COVID-19 pandemic on minority experiences	Open-ended questions developed for this study

[a]EMA: ecological momentary assessment.

Data Analysis Plan

EMA data are inherently hierarchical, with surveys (*level 1*) nested within a person (*level 2*). As such, we will use multilevel modeling to account for similarities between responses for each person. Before hypothesis testing, the data will be examined for normality, outliers, and nonlinear relationships between continuous variables. Model comparison procedures will be used to determine the fixed versus random effects for each model.

Multilevel modeling is robust to missing data (eg, skipped EMA surveys). For variables skipped within a completed assessment, expectation maximization imputation will be used to replace missing values, an approach demonstrated to minimize bias [122]. Participants with complete data will be compared with those with missing data to identify potential attrition biases, and significant predictors will be included as covariates in all analyses.

To test our main hypotheses, level-1 associations between relevant predictors (negative emotions, social factors, and health behaviors) and outcomes (binge eating and loss of control of eating) will be examined using a series of multilevel models: isolated models with each predictor modeled separately first

and then a final model examining all predictors simultaneously to explore unique effects (hypotheses 1a-b). Sexual identity will then be included as a level-2 predictor, and cross-level interactions between sexual orientation (*level 2*) and general factors (*level 1*) will indicate whether momentary associations are different across groups (hypothesis 1c). Aim 2 analyses will use only sexual minority women's data. Level-1 associations between sexual minority stress and eating outcomes will be examined using the same approach as in aim 1: a series of isolated then simultaneous multilevel models (hypothesis 2a). To assess hypothesis 2b, a multilevel structural equation model will be used to examine if negative affect mediates these relationships (1-1-1 model) [123] using Monte Carlo CIs to assess the significance of indirect effects [124]. For aims 1 and 2, we will conduct the aforementioned analyses for momentary associations (random surveys) and event-lagged associations (event and random surveys), allowing for the examination of time-lagged associations (eg, negative affect *before* the event). Aim 3 analyses will examine race- and person-level body- and eating-related factors (BMI, body dissatisfaction, disordered eating, and thin norm internalization), and sexual minority–specific factors (lifetime discrimination, positive sexual minority identity, and community identification and connection) will be included as level-2 predictors in a series of models. Cross-level interactions will indicate whether person-level factors moderate level-1 associations between general factors and binge eating (moderation of aim 1) or between minority-specific factors and binge eating (moderation of aim 2). Three-way interactions among level-1, level-2 sexual orientation, and other level-2 moderators will indicate whether the differential associations detected in the second component of aim 1 (ie, whether associations are stronger or weaker across sexual identity) are moderated by other person-level factors.

Results

Recruitment began in February 2021 and is expected to continue until fall 2022. We have currently consented 129 sexual minority women and 146 heterosexual women into the study. Data cleaning and analysis will begin after data collection is complete.

Discussion

Overview

The goal of the HER Life Project is to examine general and sexual minority–specific predictors of disordered eating, in particular binge eating, among sexual minority and heterosexual young women in their daily lives. This study uses an EMA approach to assess participants at fixed times (morning and before bed), at semirandom times throughout the day, and following self-reported binge eating episodes, thus providing rich information regarding the affective, social, behavioral, and minority-specific experiences of these women. Although there is a growing body of literature considering real-world associations among affective processes (eg, negative affect, stress, and body dissatisfaction), social processes (eg, interactions and social comparisons), and binge eating in general samples of young women where sexual identity is not known or reported, it remains unclear whether and how these processes operate for sexual minority women and if there are minority-specific predictors (eg, sexual minority stressors) for these women as well. This study includes samples of both sexual minority and heterosexual young women in an effort to explore potential similarities and differences in binge eating experiences and predictors. We expect that there will be many similar affective, social, and health behavior predictors of binge eating across sexual minority and heterosexual women but that there may also be some differences, particularly with regard to body dissatisfaction and unique sexual minority stressors. The findings from this study can help improve our understanding of potential processes that may contribute to health disparities between sexual minority and heterosexual young women's disordered eating behaviors and can be used to inform culturally tailored interventions for binge eating for young sexual minority women. In the following sections, we discuss some of the questions we considered and the challenges we have experienced when designing and carrying out the HER Life Project.

Methodological Challenges

Defining Sexual Identity and Gender Identity

One of the ongoing challenges we experience in our work with sexual minority women is identifying the optimal way to define "sexual minority" and operationalize our definition during the screening process. We initially planned to recruit participants who identified as lesbian women. However, based on some of our previous work [99,125] and in consultation with Community Marketing & Insights, the market research firm we worked with that specializes in recruiting LGBTQ+ adults for web-based research, we learned that young women are increasingly choosing to use other labels when describing their sexual identity (eg, queer or pansexual), use multiple labels (eg, lesbian and queer or gay and queer), or are resisting labels completely [126,127]. Therefore, from the start of this study, we decided to instead focus on recruiting based primarily on sexual attraction and, in some cases, relying also on behavior (ie, gender of the most recent romantic partner). We used a single attraction question that asked people to describe who they were attracted to, with response options including "only or mostly attracted to women," "only or mostly attracted to men," "equally attracted to men and women," or "attracted to people regardless of their gender identity" ("other" and "prefer not to answer" responses were also available). Potential participants were eligible for the heterosexual group if they selected "only or mostly attracted to men." Potential participants were eligible for the sexual minority group if they selected "only or mostly attracted to women" or if they selected "equally attracted" or "attracted regardless of gender" and also endorsed that their current or most recent relationship was with a woman. An ongoing challenge in research on sexual minority individuals is to balance our desire to be inclusive and respectful of the many ways in which identity (including multiple identities) can be defined against our desire to maximize study validity. A sample that is too heterogeneous in terms of identity creates challenges in applying previous literature to our work and interpreting our findings. Therefore, we settled on these criteria in an effort to be more broadly inclusive of sexual minority women who have diverse attractions (ie, including those with attractions to multiple genders or regardless of gender) but also

recognize that, because of the focus in this study on body image and eating behaviors, in the sexual minority women group, we wanted to enroll people who either were attracted to women or were currently or had been recently romantically involved with a woman.

In addition to the challenges in describing sexual identity, we also considered how we defined gender. The focus of this study was on women, and we decided to restrict the sample to people who reported that they were assigned female at birth. We also inquired about potential participants' gender identity, and our initial plan was to only include individuals who identified as "women." However, again in consultation with Community Marketing & Insights, we learned that they are increasingly seeing people identifying with more than one gender label, particularly nonbinary or gender nonconforming. Thus, for this study, we included participants who selected "woman" only or selected both "woman" and either "gender queer/nonconforming" or "nonbinary." Overall, when considering our inclusion criteria for sexual minority and heterosexual women, we tried to balance recruiting relatively homogeneous samples that were distinct from each other based on sexual attraction while also being inclusive of the diverse ways in which young adults describe and understand their identities and attractions [128-130]. These issues of how to define and describe sexual minority individuals will likely be an ongoing challenge for researchers and will continue to evolve as language and cultural understanding change over time.

Remote Data Collection Considerations

Given the large number of young women with diverse sexual identities that we are recruiting for this study, we planned for national recruitment across the United States, which requires that all data collection occur entirely remotely. From the start of the study, we implemented several strategies to enhance study engagement and compliance and also added new protocols throughout based on our experiences. First, to better describe the study to potential participants, we developed several training videos that described the study very generally and others that provided more specific details regarding the study procedures and explained study surveys and materials (eg, defining binge eating). These materials are distributed via email before and during the consent process and are embedded within Qualtrics (Qualtrics International Inc) surveys, allowing us to record whether and for how long the participants review the videos. Participants also have access to several of these relevant videos on the survey app on their phones and can review them throughout the study as needed. On the basis of our pilot work, these videos were well received, and pilot participants described them as useful in orienting them to the intensity of the study procedures so they had a better idea of what to expect when participating.

Second, as part of the screening process, participants shared with us whether they had an Android or Apple phone that they would be willing to use for the study. As a way to confirm potential participants' access to an appropriate smartphone, as part of the screening process (before consent), we ask participants to download the app to their phones. Although we cannot objectively confirm that they do so, we provide step-by-step downloading instructions as part of a Qualtrics survey and, at the end of the survey, participants indicate that they completed the installation. If participants are unable to install the app on their own phone or do not have a phone that the app is compatible with, we have phones that can be mailed to participants to use for the duration of the study. However, to date, all potential participants have had their own phones to use for the study. This is not surprising given that, in 2021, it was estimated that 96% of adults aged 18 to 29 years owned a smartphone [131]. Together, this suggests that future studies of young adults can expect that most if not all participants will have smartphones that are appropriate for a survey-based EMA study such as this one.

A third procedural consideration that has evolved over the course of the study is how we handle moving people through the study procedure remotely. As described in the Methods section, we developed a reminder system from the start of the study, which includes sending up to 2 reminders, typically several days apart, to participants who are not progressing through the study. Although most participants require very few or no reminders, for those who do receive all the planned reminders from our study team, before either withdrawing them from the study (if they previously consented) or assuming that they are not interested in enrolling (if before consent), the PI sends a final email inquiring about their interest in continuing. Although the PI email does not always result in re-engagement in the study, there have been many instances where it has helped bring a participant back to the study. Overall, this general approach of reminders is helping participants move efficiently through the study process while our study team primarily interacts with participants via email.

The onset of the COVID-19 pandemic and the associated safety protocols and guidelines limited face-to-face interactions in research settings. Given that our study onboarding and data collection procedures were designed to be remote, we experienced a rather seamless transition to conducting our research in the postpandemic era with little to no interruption. Our experiences, coupled with the likelihood of most young adults having a smartphone appropriate for survey-based EMA studies, suggest that entirely remote onboarding and data collection procedures are feasible for national recruitment and in other situations where bringing participants into the laboratory is not always feasible or possible.

Future Research Directions and Study Implications

The HER Life Project primarily focuses on exploring potential similarities and differences in predictors of binge eating between sexual minority and heterosexual young women given the documented health disparities in obesity rates and binge eating between these groups. However, as described in this protocol, part of aim 3 is to explore potential disparities that Black women may experience and consider how racial and sexual minority identities may intersect for Black sexual minority women. As described previously, there is very limited previous research on disordered eating among people who identify as both racial and sexual minority women [46] and, thus, this is a critically understudied area. Recent reports have highlighted the need for more research using an intersectional perspective and reiterated

the importance of such work for providing a more complete understanding of minority health more broadly. Although this study will provide some insight on these topics, it is only a first step, and future work to evaluate the role of other identities (eg, other racial or ethnic group identities, location [urban or rural], and socioeconomic status) and their interaction with sexual orientation is needed to advance the health and well-being of all sexual minority individuals [132]. Continuing to expand and incorporate an intersectional framework will enrich both research and intervention, with ultimate benefits to education, health care, and public policy.

Finally, we view the HER Life Project as 1 step in a large research program aimed at developing culturally sensitive interventions to address binge eating and obesity in sexual minority women. Data from this study can help inform future work in 2 ways. First, as we are including both sexual minority and heterosexual young women, this study will allow us to determine whether there are differential associations between the hypothesized predictors and binge eating or if sexual minority–specific factors (eg, experiencing sexual minority stressors and discrimination) are associated with binge eating. These findings could help in identifying intervention content for disordered eating or body image interventions that require tailoring for sexual minority women. For example, it is plausible that intervention components teaching strategies for coping with sexual minority stress (instead of engaging in binge eating) are needed. The HER Life Project is also uniquely designed to inform the development of ecological momentary interventions (EMIs). Binge eating EMIs that use mobile apps or SMS text messaging can deliver treatment in women's everyday lives and at specific times when most in need (ie, when likely to engage in binge eating) [133,134]. To develop EMIs, EMA data regarding within-person associations *with the target population* are first needed [135-137], and this study provides such data. In summary, the HER Life Project will provide foundational information needed to develop culturally tailored treatments and mobile technology–based interventions for sexual minority women with the ultimate goal of reducing binge eating and obesity disparities.

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Data Availability

Data will be available from the principal investigator upon reasonable request.

Authors' Contributions

KEH, ALB, and RJL conceptualized the research questions and designed the study and data collection procedures. CAD, CMS, LVB, and AM are responsible for data collection and management. All authors contributed to drafting the manuscript and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report from the Psychosocial Risk and Disease Prevention (PRDP) Study, Section - Risk, Prevention and Health Behavior Integrated Review, Group - Center for Scientific Review (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 179 KB - resprot_v11i10e41199_app1.pdf]

References

1. NHLBI Obesity Education Initiative Expert Panel on the Identification, Evaluation, and Treatment of Obesity in Adults (US). Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. Report No: 98-4083. Bethesda, MD, USA: National Heart, Lung, and Blood Institute; 1998.
2. National Academies of Sciences, Engineering, and Medicine, Division of Behavioral and Social Sciences and Education, Committee on Population, Committee on Understanding the Well-Being of Sexual and Gender Diverse Populations. In: White J, Sepúlveda MJ, Patterson CJ, editors. Understanding the Well-Being of LGBTQI+ Populations. Washington, DC, USA: National Academies Press (US); 2020.
3. Institute of Medicine (US) Committee on Lesbian, Gay, Bisexual, and Transgender Health Issues and Research Gaps and Opportunities. The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding. Washington, DC, USA: National Academies Press (US); 2011.
4. Carpenter C. Sexual orientation and body weight: evidence from multiple surveys. Gend Issues 2003 Jun;21(3):60-74. [doi: 10.1007/s12147-003-0006-z]

5. Conron KJ, Mimiaga MJ, Landers SJ. A population-based study of sexual orientation identity and gender differences in adult health. Am J Public Health 2010 Oct;100(10):1953-1960. [doi: 10.2105/AJPH.2009.174169] [Medline: 20516373]
6. Struble CB, Lindley LL, Montgomery K, Hardin J, Burcin M. Overweight and obesity in lesbian and bisexual college women. J Am Coll Health 2010;59(1):51-56. [doi: 10.1080/07448481.2010.483703] [Medline: 20670929]
7. Austin SB, Ziyadeh NJ, Corliss HL, Rosario M, Wypij D, Haines J, et al. Sexual orientation disparities in purging and binge eating from early to late adolescence. J Adolesc Health 2009 Sep;45(3):238-245 [FREE Full text] [doi: 10.1016/j.jadohealth.2009.02.001] [Medline: 19699419]
8. Mehl MR, Conner TS. Handbook of Research Methods for Studying Daily Life. New York, NY, USA: The Guilford Press; 2013.
9. Smyth JM, Heron KE. Health psychology. In: Mehl MR, Conner TS, editors. Handbook of Research Methods for Studying Daily Life. New York, NY, USA: The Guilford Press; 2013:569-584.
10. Smyth J, Wonderlich S, Crosby R, Miltenberger R, Mitchell J, Rorty M. The use of ecological momentary assessment approaches in eating disorder research. Int J Eat Disord 2001 Jul;30(1):83-95. [doi: 10.1002/eat.1057] [Medline: 11439412]
11. Smyth JM, Wonderlich SA, Heron KE, Sliwinski MJ, Crosby RD, Mitchell JE, et al. Daily and momentary mood and stress are associated with binge eating and vomiting in bulimia nervosa patients in the natural environment. J Consult Clin Psychol 2007 Aug;75(4):629-638. [doi: 10.1037/0022-006X.75.4.629] [Medline: 17663616]
12. Haedt-Matt AA, Keel PK. Revisiting the affect regulation model of binge eating: a meta-analysis of studies using ecological momentary assessment. Psychol Bull 2011 Jul;137(4):660-681 [FREE Full text] [doi: 10.1037/a0023660] [Medline: 21574678]
13. Mason TB, Lewis RJ, Heron KE. Daily discrimination and binge eating among lesbians: a pilot study. Psychol Sex 2017 Mar 04;8(1-2):96-103. [doi: 10.1080/19419899.2017.1296484]
14. Hawkins RC, Clement PF. Binge eating: measurement problems and a conceptual model. In: Hawkins RC, Fremouw WJ, Clement PF, editors. The Binge-Purge Syndrome: Diagnosis, Treatment, and Research. New York, NY, USA: Springer Publishing Company; 1984:229-251.
15. Srivastava P, Michael ML, Manasse SM, Juarascio AS. Do momentary changes in body dissatisfaction predict binge eating episodes? An ecological momentary assessment study. Eat Weight Disord 2021 Feb;26(1):395-400. [doi: 10.1007/s40519-020-00849-z] [Medline: 31989487]
16. Jones MD, Crowther JH, Ciesla JA. A naturalistic study of fat talk and its behavioral and affective consequences. Body Image 2014 Sep;11(4):337-345. [doi: 10.1016/j.bodyim.2014.05.007] [Medline: 24976570]
17. Leahey TM, Crowther JH, Ciesla JA. An ecological momentary assessment of the effects of weight and shape social comparisons on women with eating pathology, high body dissatisfaction, and low body dissatisfaction. Behav Ther 2011 Jun;42(2):197-210 [FREE Full text] [doi: 10.1016/j.beth.2010.07.003] [Medline: 21496506]
18. Mills J, Fuller-Tyszkiewicz M, Holmes M. State body dissatisfaction and social interactions: an experience sampling study. Psychol Women Q 2014 Feb 03;38(4):551-562. [doi: 10.1177/0361684314521139]
19. Morrison MA, Morrison TG, Sager C. Does body satisfaction differ between gay men and lesbian women and heterosexual men and women? A meta-analytic review. Body Image 2004 May;1(2):127-138. [doi: 10.1016/j.bodyim.2004.01.002] [Medline: 18089146]
20. Levine MP, Smolak L. The Prevention of Eating Problems and Eating Disorders: Theories, Research, and Applications. Mahwah, NJ, USA: Lawrence Erlbaum Associates; 2006.
21. Stice E. Risk and maintenance factors for eating pathology: a meta-analytic review. Psychol Bull 2002 Sep;128(5):825-848. [doi: 10.1037/0033-2909.128.5.825] [Medline: 12206196]
22. Thompson JK, Stice E. Thin-ideal internalization: mounting evidence for a new risk factor for body-image disturbance and eating pathology. Curr Dir Psychol Sci 2001 Oct 1;10(5):181-183. [doi: 10.1111/1467-8721.00144]
23. VanKim NA, Porta CM, Eisenberg ME, Neumark-Sztainer D, Laska MN. Lesbian, gay and bisexual college student perspectives on disparities in weight-related behaviours and body image: a qualitative analysis. J Clin Nurs 2016 Dec;25(23-24):3676-3686 [FREE Full text] [doi: 10.1111/jocn.13106] [Medline: 27878900]
24. Fingerhut AW, Peplau LA, Ghavami N. A dual-identity framework for understanding lesbian experience. Psychol Women Q 2005;29(2):129-139. [doi: 10.1111/j.1471-6402.2005.00175.x]
25. Gadalla T, Piran N. Co-occurrence of eating disorders and alcohol use disorders in women: a meta analysis. Arch Womens Ment Health 2007;10(4):133-140. [doi: 10.1007/s00737-007-0184-x] [Medline: 17533558]
26. Mason TB, Lewis RJ. Minority stress, depression, relationship quality, and alcohol use: associations with overweight and obesity among partnered young adult lesbians. LGBT Health 2015 Dec;2(4):333-340 [FREE Full text] [doi: 10.1089/lgbt.2014.0053] [Medline: 26788774]
27. Vancampfort D, Vanderlinden J, Stubbs B, Soundy A, Pieters G, De Hert M, et al. Physical activity correlates in persons with binge eating disorder: a systematic review. Eur Eat Disord Rev 2014 Jan;22(1):1-8. [doi: 10.1002/erv.2255] [Medline: 24014460]
28. Crandall KJ, Eisenman PA, Ransdell L, Reel J. Exploring binge eating and physical activity among community-dwelling women. Int J Psychol Behav Sci 2011 Nov 31;1(1):1-8 [FREE Full text] [doi: 10.5923/j.ijpbs.20110101.01]

29. Yancey AK, Cochran SD, Corliss HL, Mays VM. Correlates of overweight and obesity among lesbian and bisexual women. Prev Med 2003 Jun;36(6):676-683 [FREE Full text] [doi: 10.1016/s0091-7435(03)00020-3] [Medline: 12744910]
30. Drabble L, Midanik LT, Trocki K. Reports of alcohol consumption and alcohol-related problems among homosexual, bisexual and heterosexual respondents: results from the 2000 National Alcohol Survey. J Stud Alcohol 2005 Jan;66(1):111-120. [doi: 10.15288/jsa.2005.66.111] [Medline: 15830911]
31. McCabe SE, Hughes TL, Bostwick WB, West BT, Boyd CJ. Sexual orientation, substance use behaviors and substance dependence in the United States. Addiction 2009 Aug;104(8):1333-1345 [FREE Full text] [doi: 10.1111/j.1360-0443.2009.02596.x] [Medline: 19438839]
32. Wilsnack SC, Hughes TL, Johnson TP, Bostwick WB, Szalacha LA, Benson P, et al. Drinking and drinking-related problems among heterosexual and sexual minority women. J Stud Alcohol Drugs 2008 Jan;69(1):129-139. [doi: 10.15288/jsad.2008.69.129] [Medline: 18080073]
33. Calzo JP, Roberts AL, Corliss HL, Blood EA, Kroshus E, Austin SB. Physical activity disparities in heterosexual and sexual minority youth ages 12-22 years old: roles of childhood gender nonconformity and athletic self-esteem. Ann Behav Med 2014 Feb;47(1):17-27 [FREE Full text] [doi: 10.1007/s12160-013-9570-y] [Medline: 24347406]
34. Laska MN, VanKim NA, Erickson DJ, Lust K, Eisenberg ME, Rosser BR. Disparities in weight and weight behaviors by sexual orientation in college students. Am J Public Health 2015 Jan;105(1):111-121. [doi: 10.2105/AJPH.2014.302094] [Medline: 25393177]
35. Meyer IH. Prejudice, social stress, and mental health in lesbian, gay, and bisexual populations: conceptual issues and research evidence. Psychol Bull 2003 Sep;129(5):674-697 [FREE Full text] [doi: 10.1037/0033-2909.129.5.674] [Medline: 12956539]
36. Hatzenbuehler ML. How does sexual minority stigma "get under the skin"? A psychological mediation framework. Psychol Bull 2009 Sep;135(5):707-730 [FREE Full text] [doi: 10.1037/a0016441] [Medline: 19702379]
37. Ancheta AJ, Caceres BA, Zollweg SS, Heron KE, Veldhuis CB, VanKim NA, et al. Examining the associations of sexual minority stressors and past-year depression with overeating and binge eating in a diverse community sample of sexual minority women. Eat Behav 2021 Dec;43:101547. [doi: 10.1016/j.eatbeh.2021.101547] [Medline: 34412003]
38. Watson LB, Grotewiel M, Farrell M, Marshik J, Schneider M. Experiences of sexual objectification, minority stress, and disordered eating among sexual minority women. Psychol Women Q 2015 Mar 02;39(4):458-470. [doi: 10.1177/0361684315575024]
39. Mason TB, Lewis RJ. Minority stress and binge eating among lesbian and bisexual women. J Homosex 2015;62(7):971-992. [doi: 10.1080/00918369.2015.1008285] [Medline: 25603175]
40. Panza E, Fehling KB, Pantalone DW, Dodson S, Selby EA. Multiply marginalized: linking minority stress due to sexual orientation, gender, and weight to dysregulated eating among sexual minority women of higher body weight. Psychol Sex Orientat Gend Divers 2021 Dec;8(4):420-428. [doi: 10.1037/sgd0000431] [Medline: 34926715]
41. Heffernan K. Eating disorders and weight concern among lesbians. Int J Eat Disord 1996 Mar;19(2):127-138. [doi: 10.1002/(SICI)1098-108X(199603)19:2<127::AID-EAT3>3.0.CO;2-P] [Medline: 8932551]
42. Striegel-Moore RH, Tucker N, Hsu J. Body image dissatisfaction and disordered eating in lesbian college students. Int J Eat Disord 1990 Sep;9(5):493-500. [doi: 10.1002/1098-108X(199009)9:5<493::AID-EAT2260090504>3.0.CO;2-C]
43. Fitzgibbon ML, Spring B, Avellone ME, Blackman LR, Pingitore R, Stolley MR. Correlates of binge eating in Hispanic, Black, and White women. Int J Eat Disord 1998 Jul;24(1):43-52. [doi: 10.1002/(sici)1098-108x(199807)24:1<43::aid-eat4>3.0.co;2-0] [Medline: 9589310]
44. Howard LM, Heron KE, MacIntyre RI, Myers TA, Everhart RS. Is use of social networking sites associated with young women's body dissatisfaction and disordered eating? A look at Black-White racial differences. Body Image 2017 Dec;23:109-113. [doi: 10.1016/j.bodyim.2017.08.008] [Medline: 28965051]
45. Pike KM, Dohm FA, Striegel-Moore RH, Wilfley DE, Fairburn CG. A comparison of black and white women with binge eating disorder. Am J Psychiatry 2001 Sep;158(9):1455-1460. [doi: 10.1176/appi.ajp.158.9.1455] [Medline: 11532731]
46. Feldman MB, Meyer IH. Eating disorders in diverse lesbian, gay, and bisexual populations. Int J Eat Disord 2007 Apr;40(3):218-226 [FREE Full text] [doi: 10.1002/eat.20360] [Medline: 17262818]
47. Herek GM, Garnets LD. Sexual orientation and mental health. Annu Rev Clin Psychol 2007;3:353-375. [doi: 10.1146/annurev.clinpsy.3.022806.091510] [Medline: 17716060]
48. Fingerhut A, Peplau LA, Gable SL. Identity, minority stress and psychological well-being among gay men and lesbians. Psychol Sex 2010 Jun 03;1(2):101-114. [doi: 10.1080/19419899.2010.484592]
49. Doty ND, Willoughby BL, Lindahl KM, Malik NM. Sexuality related social support among lesbian, gay, and bisexual youth. J Youth Adolesc 2010 Oct;39(10):1134-1147. [doi: 10.1007/s10964-010-9566-x] [Medline: 20593304]
50. O'Hara RE, Armeli S, Scott DM, Covault J, Tennen H. Perceived racial discrimination and negative-mood-related drinking among African American college students. J Stud Alcohol Drugs 2015 Mar;76(2):229-236 [FREE Full text] [doi: 10.15288/jsad.2015.76.229] [Medline: 25785798]
51. Wood SM, Schott W, Marshal MP, Akers AY. Disparities in body mass index trajectories from adolescence to early adulthood for sexual minority women. J Adolesc Health 2017 Dec;61(6):722-728 [FREE Full text] [doi: 10.1016/j.jadohealth.2017.06.008] [Medline: 28935384]

52. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007 May;39(2):175-191. [doi: 10.3758/bf03193146] [Medline: 17695343]
53. West SG, Ryu E, Kwok OM, Cham H. Multilevel modeling: current and future applications in personality research. J Pers 2011 Feb;79(1):2-50. [doi: 10.1111/j.1467-6494.2010.00681.x] [Medline: 21223263]
54. Heron KE, Braitman AL, Lewis RJ, Shappie AT, Hitson PT. Measuring sexual minority stressors in lesbian women's daily lives: initial scale development. Psychol Sex Orientat Gend Divers 2018 Sep;5(3):387-395 [FREE Full text] [doi: 10.1037/sgd0000287] [Medline: 30221178]
55. Heron KE, Scott SB, Sliwinski MJ, Smyth JM. Eating behaviors and negative affect in college women's everyday lives. Int J Eat Disord 2014 Dec;47(8):853-859 [FREE Full text] [doi: 10.1002/eat.22292] [Medline: 24797029]
56. Fritz MS, Mackinnon DP. Required sample size to detect the mediated effect. Psychol Sci 2007 Mar;18(3):233-239 [FREE Full text] [doi: 10.1111/j.1467-9280.2007.01882.x] [Medline: 17444920]
57. Forbush KT, Wildes JE, Pollack LO, Dunbar D, Luo J, Patterson K, et al. Development and validation of the Eating Pathology Symptoms Inventory (EPSI). Psychol Assess 2013 Sep;25(3):859-878. [doi: 10.1037/a0032639] [Medline: 23815116]
58. Mond JM, Hay PJ, Rodgers B, Owen C. Eating Disorder Examination Questionnaire (EDE-Q): norms for young adult women. Behav Res Ther 2006 Jan;44(1):53-62. [doi: 10.1016/j.brat.2004.12.003] [Medline: 16301014]
59. Cooper PJ, Taylor MJ, Cooper Z, Fairbum CG. The development and validation of the body shape questionnaire. Int J Eat Disord 1987 Jul;6(4):485-494. [doi: 10.1002/1098-108X(198707)6:4<485::AID-EAT2260060405>3.0.CO;2-O]
60. Schaefer LM, Harriger JA, Heinberg LJ, Soderberg T, Kevin Thompson J. Development and validation of the sociocultural attitudes towards appearance questionnaire-4-revised (SATAQ-4R). Int J Eat Disord 2017 Feb;50(2):104-117. [doi: 10.1002/eat.22590] [Medline: 27539814]
61. Tylka TL. Development and psychometric evaluation of a measure of intuitive eating. J Couns Psychol 2006 Apr;53(2):226-240. [doi: 10.1037/0022-0167.53.2.226]
62. Royal S, Macdonald DE, Dionne MM. Development and validation of the Fat Talk Questionnaire. Body Image 2013 Jan;10(1):62-69. [doi: 10.1016/j.bodyim.2012.10.003] [Medline: 23201392]
63. Howard LM, Heron KE, Cramer RJ. The deliberate denial of disordered eating behaviors scale: development and initial validation in young women with subclinical disordered eating. J Psychopathol Behav Assess 2020 Jun 18;42(4):774-786 [FREE Full text] [doi: 10.1007/s10862-020-09819-2]
64. Williams DR, Yu Y, Jackson JS, Anderson NB. Racial differences in physical and mental health: socio-economic status, stress and discrimination. J Health Psychol 1997 Jul;2(3):335-351. [doi: 10.1177/135910539700200305] [Medline: 22013026]
65. Phinney JS. The Multigroup Ethnic Identity Measure: a new scale for use with diverse groups. J Adoles Res 1992 Apr 1;7(2):156-176. [doi: 10.1177/074355489272003]
66. Pearl RL, Puhl RM. Measuring internalized weight attitudes across body weight categories: validation of the modified weight bias internalization scale. Body Image 2014 Jan;11(1):89-92. [doi: 10.1016/j.bodyim.2013.09.005] [Medline: 24100004]
67. Szymanski DM. Does internalized heterosexism moderate the link between heterosexist events and lesbians' psychological distress? Sex Roles 2006 Feb;54(3-4):227-234. [doi: 10.1007/s11199-006-9340-4]
68. Mohr JJ, Kendra MS. Revision and extension of a multidimensional measure of sexual minority identity: the Lesbian, Gay, and Bisexual Identity Scale. J Couns Psychol 2011 Apr;58(2):234-245. [doi: 10.1037/a0022858] [Medline: 21319899]
69. Frost DM, Meyer IH. Measuring community connectedness among diverse sexual minority populations. J Sex Res 2012;49(1):36-49 [FREE Full text] [doi: 10.1080/00224499.2011.565427] [Medline: 21512945]
70. Zimmerman L, Darnell DA, Rhew IC, Lee CM, Kaysen D. Resilience in community: a social ecological development model for young adult sexual minority women. Am J Community Psychol 2015 Mar;55(1-2):179-190 [FREE Full text] [doi: 10.1007/s10464-015-9702-6] [Medline: 25572956]
71. Boyle SC, Omoto AM. Lesbian community oughts and ideals: normative fit, depression, and anxiety among young sexual minority women. Psychol Women Q 2014;38(1):33-45. [doi: 10.1177/0361684313484900]
72. Luhtanen R, Crocker J. A collective self-esteem scale: self-evaluation of one's social identity. Pers Soc Psychol Bull 1992 Jun 1;18(3):302-318. [doi: 10.1177/0146167292183006]
73. Fischer AR, Tokar DM, Mergl MM, Good GE, Hill MS, Blum SA. Assessing women's feminist identity development: studies of convergent, discriminant, and structural validity. Psychol Women Q 2000 Mar;24(1):15-29. [doi: 10.1111/j.1471-6402.2000.tb01018.x]
74. Bargad A, Hyde JS. Women's studies: a study of feminist identity development in women. Psychol Women Q 1991 Jun 1;15(2):181-201. [doi: 10.1111/j.1471-6402.1991.tb00791.x]
75. Rickard KM. The relationship of self-monitored dating behaviors to level of feminist identity on the feminist identity scale. Sex Roles 1989 Feb;20(3-4):213-226. [doi: 10.1007/BF00287993]
76. Vaux A, Phillips J, Holly L, Thomson B, Williams D, Stewart D. The social support appraisals (SS-A) scale: studies of reliability and validity. Am J Commun Psychol 1986 Apr;14(2):195-218. [doi: 10.1007/BF00911821]

77. Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). Am J Prev Med 1994;10(2):77-84. [Medline: 8037935]
78. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006 May 22;166(10):1092-1097 [FREE Full text] [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
79. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983 Dec;24(4):385-396. [Medline: 6668417]
80. Nock MK, Holmberg EB, Photos VI, Michel BD. Self-injurious thoughts and behaviors interview: development, reliability, and validity in an adolescent sample. Psychol Assess 2007 Sep;19(3):309-317. [doi: 10.1037/1040-3590.19.3.309] [Medline: 17845122]
81. Miller GK, Piscopo KD, Batts K, Han B, Colpe L, Forman-Hoffman VL, et al. Measurement of suicidal thoughts, behaviors, and related health outcomes in the United States: comparison of NSDUH estimates with other data sources. Substance Abuse and Mental Health Services Administration. 2015 Jul. URL: https://www.samhsa.gov/data/sites/default/files/NSDUH-DR-N20Suicide-2015/NSDUH-DR-N20Suicide-2015.pdf [accessed 2020-10-15]
82. Smith BW, Dalen J, Wiggins K, Tooley E, Christopher P, Bernard J. The brief resilience scale: assessing the ability to bounce back. Int J Behav Med 2008;15(3):194-200. [doi: 10.1080/10705500802222972] [Medline: 18696313]
83. Gibbons FX, Buunk BP. Individual differences in social comparison: development of a scale of social comparison orientation. J Pers Soc Psychol 1999 Jan;76(1):129-142. [doi: 10.1037//0022-3514.76.1.129] [Medline: 9972558]
84. Pennebaker JW, Susman JR. Disclosure of traumas and psychosomatic processes. Soc Sci Med 1988;26(3):327-332. [doi: 10.1016/0277-9536(88)90397-8] [Medline: 3279521]
85. Collins RL, Parks GA, Marlatt GA. Social determinants of alcohol consumption: the effects of social interaction and model status on the self-administration of alcohol. J Consult Clin Psychol 1985 Apr;53(2):189-200. [doi: 10.1037//0022-006x.53.2.189] [Medline: 3998247]
86. Cooper ML. Motivations for alcohol use among adolescents: development and validation of a four-factor model. Psychol Assess 1994 Jun;6(2):117-128 [FREE Full text] [doi: 10.1037/1040-3590.6.2.117]
87. Kahler CW, Strong DR, Read JP. Toward efficient and comprehensive measurement of the alcohol problems continuum in college students: the brief young adult alcohol consequences questionnaire. Alcohol Clin Exp Res 2005 Jul;29(7):1180-1189. [doi: 10.1097/01.alc.0000171940.95813.a5] [Medline: 16046873]
88. Rahal CJ, Bryant JB, Darkes J, Menzel JE, Thompson JK. Development and validation of the Compensatory Eating and Behaviors in Response to Alcohol Consumption Scale (CEBRACS). Eat Behav 2012 Apr;13(2):83-87. [doi: 10.1016/j.eatbeh.2011.11.001] [Medline: 22365787]
89. Choquette EM, Dedrick R, Thompson JK, Rancourt D. Reexamination of the psychometric properties of the Compensatory Eating and Behaviors in Response to Alcohol Consumption Scale (CEBRACS) and exploration of alternative scoring. Eat Behav 2020 Aug;38:101410. [doi: 10.1016/j.eatbeh.2020.101410] [Medline: 32736310]
90. Johnson TJ, Cohen EA. College students' reasons for not drinking and not playing drinking games. Subst Use Misuse 2004 Jun;39(7):1137-1160. [doi: 10.1081/ja-120038033] [Medline: 15387207]
91. Carver CS. You want to measure coping but your protocol's too long: consider the brief COPE. Int J Behav Med 1997;4(1):92-100. [doi: 10.1207/s15327558ijbm0401_6] [Medline: 16250744]
92. Carver CS, Scheier MF, Weintraub JK. Assessing coping strategies: a theoretically based approach. J Pers Soc Psychol 1989 Feb;56(2):267-283. [doi: 10.1037//0022-3514.56.2.267] [Medline: 2926629]
93. Ware Jr JJ, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992 Jun;30(6):473-483. [Medline: 1593914]
94. Collins RL, Vincent PC, Yu J, Liu L, Epstein LH. A behavioral economic approach to assessing demand for marijuana. Exp Clin Psychopharmacol 2014 Jun;22(3):211-221 [FREE Full text] [doi: 10.1037/a0035318] [Medline: 24467370]
95. Ehlke SJ, Stamates AL, Kelley ML, Braitman AL. Bisexual women's reports of descriptive drinking norms for heterosexual, bisexual, and lesbian women. Psychol Sex Orientat Gend Divers 2019 Jun;6(2):256-263 [FREE Full text] [doi: 10.1037/sgd0000312] [Medline: 31106227]
96. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division of Nutrition and Physical Activity. Barriers to being active quiz. In: Brown DR, Heath G, Martin SL, editors. Promoting Physical Activity: A Guide for Community Action. Champaign, IL, USA: Human Kinetics; 1999:100-101.
97. Steinhardt MA, Dishman RK. Reliability and validity of expected outcomes and barriers for habitual physical activity. J Occup Med 1989 Jun;31(6):536-546. [doi: 10.1097/00043764-198906000-00011] [Medline: 2786559]
98. Buysse DJ, Reynolds 3rd CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989 May;28(2):193-213. [doi: 10.1016/0165-1781(89)90047-4] [Medline: 2748771]
99. Heron KE, Lewis RJ, Shappie AT, Dawson CA, Amerson R, Braitman AL, et al. Rationale and design of a remote Web-based daily diary study examining sexual minority stress, relationship factors, and alcohol use in same-sex female couples across

the United States: study protocol of project relate. JMIR Res Protoc 2019 Feb 04;8(2):e11718 [FREE Full text] [doi: 10.2196/11718] [Medline: 30714946]
100. Watson D, Clark LA. The PANAS-X: Manual for the Positive and Negative Affect Schedule - Expanded Form. The University of Iowa. 1994. URL: https://www2.psychology.uiowa.edu/faculty/clark/panas-x.pdf [accessed 2020-09-30]
101. Posner J, Russell JA, Peterson BS. The circumplex model of affect: an integrative approach to affective neuroscience, cognitive development, and psychopathology. Dev Psychopathol 2005;17(3):715-734 [FREE Full text] [doi: 10.1017/S0954579405050340] [Medline: 16262989]
102. Arigo D, Brown MM, Pasko K, Ainsworth MC, Travers L, Gupta A, et al. Rationale and design of the women's health and daily experiences project: protocol for an ecological momentary assessment study to identify real-time predictors of midlife women's physical activity. JMIR Res Protoc 2020 Oct 15;9(10):e19044 [FREE Full text] [doi: 10.2196/19044] [Medline: 33055065]
103. MacIntyre RI, Heron KE, Braitman AL, Arigo D. An ecological momentary assessment of self-improvement and self-evaluation body comparisons: associations with college women's body dissatisfaction and exercise. Body Image 2020 Jun;33:264-277 [FREE Full text] [doi: 10.1016/j.bodyim.2020.04.002] [Medline: 32473545]
104. Stice E, Telch CF, Rizvi SL. Development and validation of the eating disorder diagnostic scale: a brief self-report measure of anorexia, bulimia, and binge-eating disorder. Psychol Assess 2000 Jun;12(2):123-131. [doi: 10.1037//1040-3590.12.2.123] [Medline: 10887758]
105. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5). 5th edition. Washington, DC, USA: American Psychiatric Association; 2013.
106. Cash TF, Fleming EC, Alindogan J, Steadman L, Whitehead A. Beyond body image as a trait: the development and validation of the Body Image States Scale. Eat Disord 2002;10(2):103-113. [doi: 10.1080/10640260290081678] [Medline: 16864251]
107. Holland E, Koval P, Stratemeyer M, Thomson F, Haslam N. Sexual objectification in women's daily lives: a smartphone ecological momentary assessment study. Br J Soc Psychol 2017 Jun;56(2):314-333. [doi: 10.1111/bjso.12152] [Medline: 27484394]
108. Almeida DM, Wethington E, Kessler RC. The daily inventory of stressful events: an interview-based approach for measuring daily stressors. Assessment 2002 Mar;9(1):41-55. [doi: 10.1177/1073191102091006] [Medline: 11911234]
109. Heron KE, Scott SB, Mogle JA, Howard LM, Everhart RS. Ambulatory assessment of everyday stressors: a two-study experiment evaluating the effect of question format on self-reported daily and momentary stressors. J Technol Behav Sci 2022 May 07;7(3):368-380 [FREE Full text] [doi: 10.1007/s41347-022-00259-1]
110. Panza E, Olson K, Goldstein CM, Selby EA, Lillis J. Characterizing lifetime and daily experiences of weight stigma among sexual minority women with overweight and obesity: a descriptive study. Int J Environ Res Public Health 2020 Jul 07;17(13):4892 [FREE Full text] [doi: 10.3390/ijerph17134892] [Medline: 32645883]
111. Fairburn CG, Beglin S. Eating disorder examination questionnaire (EDE-Q6.0). In: Fairburn CG, editor. Cognitive Behavior Therapy and Eating Disorders. New York, NY, USA: Guilford Press; 2008:309-313.
112. Garaulet M, Canteras M, Morales E, López-Guimera G, Sánchez-Carracedo D, Corbalán-Tutau MD. Validation of a questionnaire on emotional eating for use in cases of obesity: the Emotional Eater Questionnaire (EEQ). Nutr Hosp 2012;27(2):645-651. [doi: 10.1590/S0212-16112012000200043] [Medline: 22732995]
113. Tylka TL, Kroon Van Diest AM. The Intuitive Eating Scale-2: item refinement and psychometric evaluation with college women and men. J Couns Psychol 2013 Jan;60(1):137-153. [doi: 10.1037/a0030893] [Medline: 23356469]
114. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003 Aug;35(8):1381-1395. [doi: 10.1249/01.MSS.0000078924.61453.FB] [Medline: 12900694]
115. Schaefer LM, Burke NL, Thompson JK, Dedrick RF, Heinberg LJ, Calogero RM, et al. Development and validation of the Sociocultural Attitudes Towards Appearance Questionnaire-4 (SATAQ-4). Psychol Assess 2015 Mar;27(1):54-67. [doi: 10.1037/a0037917] [Medline: 25285718]
116. Bernstein MJ, Zawadzki MJ, Juth V, Benfield JA, Smyth JM. Social interactions in daily life: within-person associations between momentary social experiences and psychological and physical health indicators. J Soc Pers Relationships 2017 Feb 16;35(3):372-394 [FREE Full text] [doi: 10.1177/0265407517691366]
117. Zhaoyang R, Sliwinski MJ, Martire LM, Smyth JM. Age differences in adults' daily social interactions: an ecological momentary assessment study. Psychol Aging 2018 Jun;33(4):607-618 [FREE Full text] [doi: 10.1037/pag0000242] [Medline: 29708385]
118. Wilson CJ, Deane FP, Ciarrochi JV, Rickwood D. Measuring help seeking intentions: Properties of the General Help Seeking Questionnaire. University of Wollongong. 2005. URL: https://ro.uow.edu.au/cgi/viewcontent.cgi?referer=&httpsredir=1&article=2580&context=hbspapers [accessed 2020-10-18]
119. Cramer RJ, Wright S, Wilsey CN, Kaniuka AR, Bowling J, Crocker T, et al. Alternative sexuality, sexual orientation and mobile technology: findings from the National Coalition for Sexual Freedom technology and health enhancement feasibility study. Psychol Sex 2022;13(2):344-359 [FREE Full text] [doi: 10.1080/19419899.2020.1777188]
120. Whittaker F, Kingston S. Stress, social support, and substance use in the COVID-19 pandemic. Transl Issues Psychol Sci (forthcoming) 2022 Apr 14. [doi: 10.1037/tps0000322]

121. Grasso DJ, Briggs-Gowan MJ, Ford JD, Carter AS. Epidemic – Pandemic Impacts Inventory (EPII). University of Connecticut School of Medicine. 2020. URL: https://www.phenxtoolkit.org/toolkit_content/PDF/Grasso_EPII.pdf [accessed 2020-09-16]
122. Allison PD. Missing data. In: Quantitative Applications in the Social Sciences. Thousand Oaks, CA, USA: Sage Publications; 2001.
123. Preacher KJ, Zyphur MJ, Zhang Z. A general multilevel SEM framework for assessing multilevel mediation. Psychol Methods 2010 Sep;15(3):209-233. [doi: 10.1037/a0020141] [Medline: 20822249]
124. Preacher KJ, Selig JP. Advantages of Monte Carlo confidence intervals for indirect effects. Commun Methods Meas 2012 Apr;6(2):77-98. [doi: 10.1080/19312458.2012.679848]
125. Lewis RJ, Dawson CA, Shappie AT, Braitman AL, Heron KE. Recruiting cisgender female couples for health disparity-focused daily diary research: challenges, successes, and lessons learned. Psychol Sex (forthcoming) 2021 Jun 23:1-21 [FREE Full text] [doi: 10.1080/19419899.2021.1942177]
126. Savin-Williams R. Refusing and resisting sexual identity labels. In: Browning DL, editor. Adolescent Identities: A Collection of Readings. Milton Park, UK: Taylor & Francis; 2008:67-91.
127. Galupo MP, Mitchell RC, Davis KS. Sexual minority self-identification: multiple identities and complexity. Psychol Sex Orientat Gend Divers 2015 Dec;2(4):355-364 [FREE Full text] [doi: 10.1037/sgd0000131]
128. Savin-Williams RC, Joyner K, Rieger G. Prevalence and stability of self-reported sexual orientation identity during young adulthood. Arch Sex Behav 2012 Feb;41(1):103-110. [doi: 10.1007/s10508-012-9913-y] [Medline: 22302504]
129. Talley AE, Stevens JE. Sexual orientation self-concept ambiguity: scale adaptation and validation. Assessment 2017 Jul;24(5):632-645 [FREE Full text] [doi: 10.1177/1073191115617016] [Medline: 26643117]
130. Young RM, Meyer IH. The trouble with "MSM" and "WSW": erasure of the sexual-minority person in public health discourse. Am J Public Health 2005 Jul;95(7):1144-1149. [doi: 10.2105/AJPH.2004.046714] [Medline: 15961753]
131. Mobile Fact Sheet. Pew Research Center. 2021 Apr. URL: https://www.pewresearch.org/internet/fact-sheet/mobile/ [accessed 2022-06-29]
132. Else-Quest NM, Hyde JS. Intersectionality in quantitative psychological research: I. Theoretical and epistemological issues. Psychol Women Q 2016 Feb 26;40(2):155-170. [doi: 10.1177/0361684316629797]
133. Heron KE, Smyth JM. Ecological momentary interventions: incorporating mobile technology into psychosocial and health behaviour treatments. Br J Health Psychol 2010 Feb;15(Pt 1):1-39 [FREE Full text] [doi: 10.1348/135910709X466063] [Medline: 19646331]
134. Juarascio AS, Goldstein SP, Manasse SM, Forman EM, Butryn ML. Perceptions of the feasibility and acceptability of a smartphone application for the treatment of binge eating disorders: qualitative feedback from a user population and clinicians. Int J Med Inform 2015 Oct;84(10):808-816 [FREE Full text] [doi: 10.1016/j.ijmedinf.2015.06.004] [Medline: 26113461]
135. Borrelli B, Ritterband LM. Special issue on eHealth and mHealth: challenges and future directions for assessment, treatment, and dissemination. Health Psychol 2015 Dec;34S:1205-1208. [doi: 10.1037/hea0000323] [Medline: 26651461]
136. Smith KE, Juarascio A. From ecological momentary assessment (EMA) to ecological momentary intervention (EMI): past and future directions for ambulatory assessment and interventions in eating disorders. Curr Psychiatry Rep 2019 Jun 04;21(7):53. [doi: 10.1007/s11920-019-1046-8] [Medline: 31161276]
137. Spruijt-Metz D, Nilsen W. Dynamic models of behavior for just-in-time adaptive interventions. IEEE Pervasive Comput 2014 Jul;13(3):13-17. [doi: 10.1109/MPRV.2014.46]

Abbreviations

EMA: ecological momentary assessment
EMI: ecological momentary intervention
HER Life: Health and Experiences in Real Life
ICC: intraclass correlation coefficient
LGBTQ+: lesbian, gay, bisexual, transgender, and queer
PI: principal investigator

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Corrigenda and Addenda

Correction: The Facilitation of Clinical and Therapeutic Discoveries in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Related Diseases: Protocol for the You + ME Registry Research Platform

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Related Article:

Correction of: https://www.researchprotocols.org/2022/8/e36798

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In "The Facilitation of Clinical and Therapeutic Discoveries in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Related Diseases: Protocol for the You + ME Registry Research Platform" (JMIR Res Protoc 2022;11(8):e36798) the authors noted an error in the final paragraph of the Acknowledgments section.

In the originally published article, the final paragraph of the Acknowledgments section was published with an incorrect grant number as follows:

> *"The development of the Registry database and mobile app was supported in part by the National Institutes of Health (NIH) grant U24-NS-105525 as part of the ME/CFS Collaborative Research Network."*

The final paragraph of the Acknowledgments section has been updated with the correct grant number (U24-NS-105535), to read:

> *"The development of the Registry database and mobile app was supported in part by the National Institutes of Health (NIH) grant U24-NS-105535 as part of the ME/CFS Collaborative Research Network."*

The correction will appear in the online version of the paper on the JMIR Publications website on October 13th, 2022, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Metadata Correction: Social Support as a Stress Buffer or Stress Amplifier and the Moderating Role of Implicit Motives: Protocol for a Randomized Study

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In “Social Support as a Stress Buffer or Stress Amplifier and the Moderating Role of Implicit Motives: Protocol for a Randomized Study” ([JMIR Res Protoc 2022;11(8):e39509]) the authors noted three errors in the metadata.

First, in the originally published article, the authorship order was incorrect. The article was originally published with the following authorship order:

Julia Schüler, Alisa Haufler, Beate Ditzen

In the corrected article, the authorship order has been updated as follows:

Alisa Haufler, Beate Ditzen, Julia Schüler

Second, *Beate Ditzen* was listed as the Corresponding Author. However, the Corresponding Author has now been changed to *Julia Schüler*.

Third, one affiliation was incomplete and one affiliation was omitted for author Beate Ditzen. This author's affiliation was originally published as follows:

[2]Institute for Medical Psychology, Heidelberg, Germany

Beate Ditzen's affiliations have now been updated to:

[2]Institute for Medical Psychology, Heidelberg University Hospital, Heidelberg, Germany

[3]Heidelberg University, Heidelberg, Germany

The correction will appear in the online version of the paper on the JMIR Publications website on October 25, 2022, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Protocol

Soil-Transmitted Helminth Infection in Malaysia: Protocol for a Scoping Review

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Abstract

Background: Soil-transmitted helminth (STH) infection is 1 of the 20 notable neglected tropical diseases according to the Centers for Disease Control and Prevention and World Health Organization. In 2010, it is estimated that 1.73 billion people are infected with STH globally, of which 70% of cases occur in Asia. To date, there is a dearth of published literature on the prevalence of STH infection throughout Malaysia.

Objective: The objectives of this study are to review research activity on STH infection in Malaysia, to estimate the prevalence of STH infection among Malaysians, and to identify significant risk factors associated with the infection. This review aims to provide the current state of evidence pertaining to STH infections, focusing on the main areas, limitations, and biases of research and mapping out the morbidity distribution of the diseases and their causative agents, and to identify significant risk factors for preventive measures.

Methods: We will conduct a scoping review based on the 6-stage structured framework developed by Arksey and O'Malley. A comprehensive search strategy focusing on STH infection will be executed using electronic databases (Scopus, PubMed, Web of Science, and Embase). A systematic approach for searching, screening, reviewing, and data extraction will be applied based on the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines. Mendeley software and Microsoft Excel will be used to manage the references and to remove duplicates. Relevant data from selected articles will be extracted using a standardized data extraction form.

Results: A total of 164 potential manuscripts were retrieved. Data extraction is currently in progress and completion is expected by the end of 2022.

Conclusions: Our scoping review will summarize the current state of research in this field and provide comprehensive information regarding STH infections in Malaysia for future reference.

Trial Registration: National Medical Research Register NMRR-20-2889-54348; https://nmrr.gov.my/research-directory/e52ea778-d31c-4eb4-9163-a45bb3680bbf

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KEYWORDS

STH; soil-transmitted helminth; PRISMA-ScR; Malaysia; helminth; tropical disease

Introduction

Soil-transmitted helminth (STH) infection is among the most common diseases worldwide, primarily affecting those living in poor tropical and subtropical regions, especially households with inadequate sanitation facilities [1]. STH contamination can occur due to high soil moisture content in cramped living quarters, shared toilets, uncovered latrine pits, unhygienic practices, and pet (cat and dog) ownership, which increases the risk for zoonotic transmission [2]. STHs are nematodes including roundworms (*Ascaris lumbricoides*), whipworm (*Trichuris trichiura*), and anthropophilic hookworms (*Necator americanus* and *Ancylostoma duodenale*). STHs can infect humans through contact with parasitic eggs or larvae in soil [3].

According to the World Health Organization (WHO; 2005), STHs and schistosomes caused nearly 1.5 billion infections worldwide up to 2015. STH—namely, *Ascaris* spp, *Trichuris* spp, and hookworms—can affect physical and mental development in children, also contributing to poor nutritional status in the community [4,5]. Although it is known that hookworms can cause iron deficiency and protein malnutrition due to intestinal blood loss, STH infection does not necessarily cause death if early intervention and treatment are taken. STH infection can also cause anemia, where the intensity of hookworm infection is correlated to the depletion of host iron stores [6]. The prevalence of STH infections worldwide is overwhelming. According to Pullan et al (2014) [7], more than 50% of STH cases were recorded in South Asia and sub-Saharan Africa, with prevalence rates of *A lumbricoides*, *T trichiura*, and hookworm reported to be 819 million, 464 million, and 439 million, respectively. STH infection is very common in South Asia due to this region having tropical and moist climate areas, where these worms are endemic. It can also occur in several underdeveloped and developing countries in South Asia, which still do not have adequate clean water supply and do not have systematic sanitation infrastructure in some regions [8]. The highest prevalence of STH infections in South Asia was documented in India (21%) and China (18%), with the continent of Asia contributing to 67% of the global prevalence of STH infections [9]. Thirty-nine studies in India showed that *A lumbricoides* infection was the most prevalent parasite, with more than 50% prevalence reported in several states [10]. Conversely, the survey data of STH infection in China showed that the prevalence of STH infection in China considerably decreased from 2005 onward [11].

Although Malaysia is a developing country with rapid growth in socioeconomic and infrastructure in both urban and rural areas, the government is still grappling with the problem of STH infections, especially among very rural populations and indigenous communities. Many STH studies conducted in Malaysia focused on the indigenous people of Malaysia. Even though the government had built numerous resettlement areas for these indigenous tribes, they are still heavily dependent on the forest for their daily needs and sustenance, thereby retaining a high risk for intestinal parasitism [12]. A study by Sinniah et al (2014) [13] showed that STH infection was more common among those living in rural areas (32.3%), followed by urban squatters (20.6%) and those residing in flats or apartments (5.4%). The prevalence rate of STH infection among urban settlers, residents, and those living in flats showed a dramatic decrease, whereas STH infection prevalence in indigenous communities was over 90% previously (1970s) and is currently fluctuating below 70% (2000-2013) [13]. Another study revealed that the most prevalent types of STH in Malaysia are *T trichiura* (2.1%-98.2%), followed by *A lumbricoides* (4.6%-86.7%) and hookworm (0%-37%).

There are many recommendation documents published by the WHO to eliminate STH as a public health problem. The strategic plan for STH elimination included routine control activities in low-transmission areas, intensive control of STH infection in areas of high transmission (WHO 2001), and the delivery of anthelminthic treatment in school-age children to reduce worm loads (WHO 2012) [14]. In 1974, Malaysia launched a worm control program aimed at controlling STH infection [15]. The program targeted schoolchildren aged 7-15 years; a total of 1486 schools with more than 220,000 pupils were involved in this program. The national mass deworming program in Malaysia, which used a single dose of pyrantel pamoate once or twice per year, was discontinued in 1983 due to the drug's low effectiveness against *Trichuris* and hookworm. Albendazole tablets are still given to children in some rural areas. The government also attempted to improve sanitation in rural households by providing pour-flush latrines and safe drinking water to diminish STH infection [16].

This review aims to provide the current state of evidence pertaining to STH infections, focusing on the main areas, limitations, and biases of research and mapping out the morbidity distribution of the diseases and their causative agents, and to identify significant risk factors for preventive measures.

Methods

Protocol Design

This study protocol is registered at the National Medical Research Register (NMRR-20-2889-54348) [17]. This scoping review will adhere to the 6-stage structured framework proposed by Arksey and O'Malley [18], which was further developed by Levac et al [19] and the Joanna Briggs Institute [20], where it is recommended that the review process be structured in at least 5 stages. These stages include (1) identifying the research question; (2) identifying relevant studies; (3) selecting studies; (4) charting the data; and (5) collating, summarizing, and reporting the results. Although stage 6 (consulting with relevant stakeholders) would be beneficial in terms of getting insights and updates on the present circumstances of STH infection in Malaysia, this scoping review will not include this stage due to time and budget constraints. However, experts with scoping review–writing experience and statisticians (for data analysis) may be consulted throughout the preparation of this scoping review. This protocol was not submitted to PROSPERO (International Prospective Register of Systematic Reviews), as they do not currently accept scoping review protocols. The report will follow the 22 items in the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) [21] guidelines. Clinical trial

registration and ethics board approval are not needed since the review does not involve any human subjects.

Stage 1: Identifying the Research Questions

An exploratory review of the literature on STH infection in Malaysia was conducted to refine the scope of this protocol and develop the research questions. Based on this review and through consultation with the research team, the following research questions were identified:

1. What types of research activity on STH infection have been carried out in Malaysia?
2. What is the prevalence of STH infection in Malaysia?
3. What are the significant risk factors associated with STH infection in Malaysia?

Stage 2: Identifying Relevant Studies

A comprehensive search strategy will be executed by a team of investigators. Website sources will include published scientific journals, grey literature, and annual reports as below:

1. Electronic databases including PubMed, Scopus, Web of Science, and Embase
2. Relevant research websites such as ClinicialTrials.gov, the WHO, Global Atlas of Helminth Infections, Ministry of Health Malaysia, and Virtual Library Ministry of Health
3. Grey literature including website searches of universities, Google Scholar, and research institutes

A systematic approach to searching, screening, reviewing, and data extraction will be applied based on PRISMA-ScR guidelines. Titles, abstracts, and keywords will be examined for eligibility independently by 2 investigators. The proposed initial search strategy, keywords, and search terms for a search for related articles are attached. Medical Subject Headings (MeSH) terms were applied to assist the keyword search for different databases used (Multimedia Appendix 1). All selected search results will be downloaded and imported into Microsoft Word and Excel (Microsoft Corp) in duplicate; they will then be shared through Google Drive. Mendeley software and Microsoft Excel will be used to manage the references and to remove duplicates.

A hand search of the grey literature will be conducted through university visits and meetings with academics for further data retrieval and consultation, whenever relevant. The reference lists of publications by WHO-Western Pacific will be screened for additional sources of information.

Stage 3: Study Selection

Overview

The study selection will be based on the objectives of this review, which are (1) to identify the trend of research activity (the extent and nature of study), (2) to estimate the prevalence of STH infection, and (3) to identify significant risk factors associated with STH infection in Malaysia. We will include all original articles, either observational (cohort study, case-control study, cross-sectional study, case report, ecological report, and descriptive report) or interventional (randomized and nonrandomized). The first level for the review process consists of the screening of titles and abstracts. Investigators will independently screen the title and abstract from all retrieved citations that meet the minimal inclusion criteria. Abstracts that do not meet the scope of the study will be excluded. The second level of screening will take place once relevant abstracts are selected. The full-text review will include any articles that are considered significant and applicable to the research question. Cohen κ statistic will be applied to determine interobserver agreement and ensure consistent application of the eligibility criteria for inclusion in the review [22]. The third investigator will review any full-text article assessment that does not meet perfect agreement ($\kappa<1$), and the discordance will be resolved through discussion until full consensus is reached.

Inclusion Criteria

The following principles will be used to determine the studies that meet the criteria:

1. Studies that present evidence that was published between 2000 and 2020.
2. Studies that present evidence that was carried out in Malaysia with the Malaysian population.
3. Studies that present evidence on STH infection incidents in Malaysia.
4. Studies published in the English language.

Exclusion Criteria

Studies with the following characteristics will be excluded:

1. Studies published before 2000.
2. Studies with no evidence on STH infection incidents in Malaysia.
3. Studies published in languages other than English.

Stage 4: Charting the Data

The significant study characteristics from the articles will be extracted by a standardized data extraction framework using Google Sheets. It includes 7 sections that assist in data information extraction from the full review articles retrieved. Section 1 will provide standard bibliographical information (title, author, journal, year of publication, language, location of the study, sample size, and period of study), together with details pertaining to the specific STH involved in the study (parasite species of focus, predominant species, mixed infection, if a study was describing more than a single species of parasite, and the intensity of infection if mentioned). Sections 2 to 7 will describe the type of study, primary outcome, risk factors, treatment efficacy, laboratory investigation, and other valuable information, respectively. These sections will provide significant information about the study and facilitate data analysis (Multimedia Appendix 2). The data extraction framework will be distributed to all investigators through a link and can be easily accessed through email and mobile apps. Each investigator will be assigned articles in duplicate, and the results of the data extraction will be cross-checked with other investigators in the research team to ensure data extraction accuracy. Any aberrant findings and disagreements will be further discussed to ensure consistency and achieve consensus between investigators. A thorough discussion will be conducted whenever any questions or uncertainties arise throughout the whole data extraction process.

Stage 5: Collating, Summarizing, and Reporting the Results

Results will be retrieved and downloaded through a spreadsheet generated using Google Sheets. All relevant information will be collated into its appropriate category and will be reported according to the selection criteria. The characteristics of the outcome from the selected articles will be described based on the types of interventions, study design, settings, tools used, and the outcomes of each study. The findings of this study will summarize all data and information from the relevant articles and emphasize the scope of STH infection in Malaysia. Topics and areas that have been under-studied and may require further attention might be identified and will be highlighted in this study.

Ethical Considerations

Since the scoping review analysis seeks to synthesize information from publicly accessible publications and no primary data will be collected, formal ethical approval regarding dissemination activities is not necessary for this study.

Results

The search was performed in December 2021, in the abovementioned electronic databases; a total of 164 results were retrieved. Data extraction from all potential manuscripts will be completed by the end of 2022. Data will be summarized descriptively in tabular form including types of interventions, study design, settings, tools used, and the outcomes of each study.

Discussion

Overview

Many publications focus on the prevalence and distribution of STH infections among the indigenous population in Malaysia based on sociodemographic characteristics. There are limited publications that specify the general population, laboratory investigation, and treatment efficacy. Those studies highlighted a single issue and were not as collaborative. There were also Knowledge, Attitude, and Practice studies that emphasized risk factors and disease prevention measures; however, those studies will not be selected for data collection in this scoping review. To ensure the report's quality and reliability, only significant findings with $P \leq .05$ will be included in this study.

This scoping review will determine the types of research activities that have been carried out in Malaysia, whether epidemiological, clinical, treatment efficacy, preventive measures, or others, where related to the research topic. It will include all studies published between 2000 and 2020, as this time frame will provide adequate data to compare and summarize. We would like to provide further evidence on the prevalence of STH in terms of the parasite species that predominately cause the infection and the intensity of the infection. Prevalence figures provided by selected studies were calculated, considering each study's sample size. Prevalence maps will be produced based on the geographical coordinates of the studies' sites. Finally, we will present the significant risk factors that contribute to STH infection and discuss prevention measures taken by considering the government and private sector's involvement toward curbing this issue. We hope that the findings of this scoping review will provide information for policy makers and strengthen policy guidelines to eradicate STH infection, as well as for researchers to further study and investigate any STH-related issue in Malaysia.

Dissemination

An article detailing the scoping review findings will be submitted to a scientific journal for publication and will be presented at relevant meetings and conferences, as well as for continuous medical education at the departmental level. The scoping review results are expected to provide a comprehensive overview of the available evidence on the prevalence of STH infection in Malaysia and to highlight areas of controversy or where evidence is lacking. It will also offer essential information to policy makers and health practitioners involved in designing, funding, and delivering evidence-based and effective strategies to prevent STH infection. The findings will also be disseminated as part of future seminars and workshops.

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Authors' Contributions

MFMH conceived the idea, developed the research question, developed the study methods, was involved in data extraction, and contributed to the drafting and editing of the manuscript. FHA, HMH, NAL, NY, ENM, and RA aided data extraction and contributed to the drafting and editing. NAM supervised the preparation of the protocol and reviewed the manuscript. All authors have approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Table S1.
[PDF File (Adobe PDF File), 426 KB - resprot_v11i10e36077_app1.pdf]

Multimedia Appendix 2
Table S2.
[PDF File (Adobe PDF File), 458 KB - resprot_v11i10e36077_app2.pdf]

References

1. Chico ME, Vaca MG, Rodriguez A, Cooper PJ. Soil-transmitted helminth parasites and allergy: observations from Ecuador. Parasite Immunol 2019 Jun;41(6):e12590 [FREE Full text] [doi: 10.1111/pim.12590] [Medline: 30229947]
2. Steinbaum L, Mboya J, Mahoney R, Njenga SM, Null C, Pickering AJ. Effect of a sanitation intervention on soil-transmitted helminth prevalence and concentration in household soil: a cluster-randomized controlled trial and risk factor analysis. PLoS Negl Trop Dis 2019 Feb;13(2):e0007180 [FREE Full text] [doi: 10.1371/journal.pntd.0007180] [Medline: 30742614]
3. Bethony J, Brooker S, Albonico M, Geiger SM, Loukas A, Diemert D, et al. Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. Lancet 2006 May 06;367(9521):1521-1532. [doi: 10.1016/S0140-6736(06)68653-4] [Medline: 16679166]
4. WHO Expert Committee on the Control of Schistosomiasis. Prevention and control of schistosomiasis and soil-transmitted helminthiasis: report of a WHO expert committee. World Health Organization. URL: https://apps.who.int/iris/handle/10665/42588 [accessed 2021-12-02]
5. Stephenson LS, Latham MC, Ottesen EA. Malnutrition and parasitic helminth infections. Parasitology 2000;121 Suppl:S23-S38. [doi: 10.1017/s0031182000006491] [Medline: 11386688]
6. Stoltzfus RJ, Dreyfuss ML, Chwaya HM, Albonico M. Hookworm control as a strategy to prevent iron deficiency. Nutr Rev 1997 Jun;55(6):223-232. [doi: 10.1111/j.1753-4887.1997.tb01609.x] [Medline: 9279058]
7. Pullan RL, Smith JL, Jasrasaria R, Brooker SJ. Global numbers of infection and disease burden of soil transmitted helminth infections in 2010. Parasit Vectors 2014 Jan 21;7:37 [FREE Full text] [doi: 10.1186/1756-3305-7-37] [Medline: 24447578]
8. Dunn JC, Turner HC, Tun A, Anderson RM. Epidemiological surveys of, and research on, soil-transmitted helminths in Southeast Asia: a systematic review. Parasit Vectors 2016 Jan 27;9:31 [FREE Full text] [doi: 10.1186/s13071-016-1310-2] [Medline: 26813007]
9. Pullan R, Brooker SJ. The global limits and population at risk of soil-transmitted helminth infections in 2010. Parasit Vectors 2012 Apr 26;5:81 [FREE Full text] [doi: 10.1186/1756-3305-5-81] [Medline: 22537799]
10. Salam N, Azam S. Prevalence and distribution of soil-transmitted helminth infections in India. BMC Public Health 2017 Feb 16;17(1):201 [FREE Full text] [doi: 10.1186/s12889-017-4113-2] [Medline: 28209148]
11. Lai Y, Zhou XN, Utzinger J, Vounatsou P. Bayesian geostatistical modelling of soil-transmitted helminth survey data in the People's Republic of China. Parasit Vectors 2013 Dec 18;6:359 [FREE Full text] [doi: 10.1186/1756-3305-6-359] [Medline: 24350825]
12. Muslim A, Mohd Sofian S, Shaari SA, Hoh BP, Lim Y. Prevalence, intensity and associated risk factors of soil transmitted helminth infections: a comparison between Negritos (indigenous) in inland jungle and those in resettlement at town peripheries. PLoS Negl Trop Dis 2019 Apr;13(4):e0007331 [FREE Full text] [doi: 10.1371/journal.pntd.0007331] [Medline: 31009476]
13. Sinniah B, Hassan AR, Sabaridah I, Soe MM, Ibrahim Z, Ali O. Prevalence of intestinal parasitic infections among communities living in different habitats and its comparison with one hundred and one studies conducted over the past 42 years (1970 to 2013) in Malaysia. Trop Biomed 2014 Jun;31(2):190-206 [FREE Full text] [Medline: 25134888]
14. Becker SL, Liwanag HJ, Snyder JS, Akogun O, Belizario V, Freeman MC, et al. Toward the 2020 goal of soil-transmitted helminthiasis control and elimination. PLoS Negl Trop Dis 2018 Aug;12(8):e0006606 [FREE Full text] [doi: 10.1371/journal.pntd.0006606] [Medline: 30106975]
15. Oothuman P. Prevalence and reinfection of intestinal helminthiases among school children in an estate. Trop Biomed 1995;12:159-164.
16. Annual Report Ministry of Health Malaysia 2017. Ministry of Health Malaysia. 2017 Dec 19. URL: https://www.moh.gov.my/moh/resources/Penerbitan/Penerbitan%20Utama/Annual%20Report%20MoH%202017.pdf [accessed 2022-09-07]
17. Soil-transmitted helminths infection in Malaysia: a scoping review protocol. National Medical Research Register. URL: https://nmrr.gov.my/research-directory/e52ea778-d31c-4eb4-9163-a45bb3680bbf [accessed 2022-09-07]
18. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol 2005 Feb;8(1):19-32. [doi: 10.1080/1364557032000119616]
19. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implement Sci 2010 Sep 20;5:69 [FREE Full text] [doi: 10.1186/1748-5908-5-69] [Medline: 20854677]
20. Joanna Briggs Institute Reviewers' Manual: 2015 edition / Supplement. The Joanna Briggs Institute. 2015. URL: https://nursing.lsuhsc.edu/jbi/docs/reviewersmanuals/scoping-.pdf [accessed 2021-12-02]

21. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018 Oct 02;169(7):467-473 [FREE Full text] [doi: 10.7326/M18-0850] [Medline: 30178033]
22. McHugh ML. Interrater reliability: the kappa statistic. Biochem Med (Zagreb) 2012;22(3):276-282 [FREE Full text] [Medline: 23092060]

Abbreviations

MeSH: Medical Subject Headings
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
STH: soil-transmitted helminth
WHO: World Health Organization

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Protocol

Methodological Frameworks and Dimensions to Be Taken Into Consideration in Digital Health Technology Assessment: Protocol for a Scoping Review

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Abstract

Background: Health technology assessment (HTA) is one of the main tools that health systems have to appraise evidence and determine the value of a given health technology. Although the existing HTA frameworks are useful tools for the evaluation of a wide range of health technologies, more and more experts, organizations across the world, and HTA agencies are highlighting the need to update or develop specific methodological frameworks for the evaluation of digital health technologies in order to take into account additional domains that cover these technologies' intrinsic characteristics.

Objective: The purpose of our scoping review is to identify the methodological frameworks that are used worldwide for the assessment of digital health technologies; determine what dimensions and aspects are being considered; and generate, through a thematic analysis, a proposal for a methodological framework that is based on the most frequently described dimensions in the literature.

Methods: The scoping review will be performed in accordance with the guidelines established in the updated statement of the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews). We will search for peer-reviewed and grey literature published between 2011 and the date of the search execution. The retrieved references will be reviewed in a single-blind manner by 2 independent authors, and their quality will be assessed by using the Critical Appraisal Skills Program tool. The ATLAS.ti software (Scientific Software Development GmbH) will be used for data extraction and to perform the thematic analysis.

Results: The scoping review is currently (May 2022) in progress. It is expected to be completed in October 2022, and the final results of the research will be presented and published by November 2022.

Conclusions: To our knowledge, no studies have been published to date that identify the existing methodological frameworks for digital HTA, determine which dimensions must be evaluated for correct decision-making, and serve as a basis for the development of a methodological framework of reference that health care systems can use to carry out this kind of assessment. This work is intended to address this knowledge gap of key relevance for the field of HTA.

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KEYWORDS

digital health; eHealth; mobile health; artificial intelligence; framework; health technology assessment

Introduction

Background

European health systems, including the Spanish National Health System, face different challenges associated mainly with the progressive aging of the population [1-3]; the increasing prevalence of chronic conditions [2]; the growing need to medicalize citizens [1]; the rapid growth of health care expenditures, which are exceeding national incomes [1,4]; or the unequal distribution of health services throughout the territories [2,5]. Likewise, the health crisis caused by the SARS-CoV-2 (COVID-19) pandemic has increased the stress on health systems, challenging their sustainability and the values of universality, equity, and quality on which they are based [1,6-9]. Further, the COVID-19 pandemic has forced a hasty change from the face-to-face care model to a non–face-to-face model [7].

In this context, digital health, which is defined by the World Health Organization (WHO) as "the field of knowledge and practice associated with the development and use of digital technologies to improve health" [10] and by the European Commission as "the set of tools and services that use information and communication technologies to improve prevention, diagnosis, treatment, monitoring and management of health-related issues and to monitor and manage lifestyle-habits that impact health" [11], offers a unique opportunity to face these challenges and improve the accessibility, efficiency, sustainability, and quality of health systems [7,12].

The integration of digital health technologies (eg, mobile health [mHealth] apps, artificial intelligence [AI]–based solutions, etc) in health systems, however, entails certain challenges that hinder its implementation. Generally, these challenges are related to the rights of patients, the ownership of data, acceptance by users, the absence of adequate technological infrastructures, the literacy of professionals and patients, or the lack of robust evidence that makes the decision-making process difficult and can result in the development and reproduction of low-value technologies with a short, useful life span [7,10].

With regard to this last aspect, one of the main tools that the Spanish National Health System uses to generate evidence and determine the value of a given health technology is the health technology assessment (HTA) [13]. HTA, as well as its definition, has evolved since the 1980s, incorporating different dimensions in addition to safety, efficacy, effectiveness, and efficiency, such as the inclusion of the patient perspective, organizational aspects, or social impacts [6]. Currently, *health technology assessment* is defined as a "multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its life cycle," and it is intended to inform decision-making processes in order to promote an equitable, efficient, and high-quality health system [13].

HTA is generally carried out by using specific methodological frameworks, such as the HTA Core Model of the European Network for Health Technology Assessment (EUnetHTA; known since 2022 as the *EUnetHTA 21 Consortium*) [14]. In Spain, HTA is performed by using the Guideline for the Development and Adaptation of Rapid Health Technology Assessment Reports of the Spanish Network of Agencies for Assessing National Health System Technologies and Performance, which was developed based on the HTA Core Model and other methodological frameworks [15]. Generally, these frameworks specify and standardize methods for evaluating the quality and value of health technologies, as well as the relevant information or elements that must be reported for a complete HTA. In this sense, the HTA Core Model 3.0 describes the following nine domains to be evaluated [14]: health problem and current use of technology, description and technical characteristics, safety, clinical effectiveness, costs and economic effectiveness, ethical analysis, organizational aspects, patient and social aspects, and legal aspects.

Although these frameworks are useful tools for the evaluation of a wide range of health technologies, more and more experts, organizations across the world (eg, the WHO), and HTA agencies (eg, National Institute for Health and Care Excellence [NICE], Canada's Drug and Health Technology Agency, Finnish Coordinating Center for Health Technology Assessment [FinCCHTA], etc) are highlighting the need to update or develop specific methodological frameworks for the evaluation of digital health technologies that take into account additional domains (eg, interoperability, usability, etc) that cover these technologies' intrinsic characteristics [7,10,16]. For this reason, some initiatives have emerged, such as the Evidence Standard Framework of the NICE [17] or the Digi-HTA Framework of the FinCCHTA [18]. However, most of these initiatives have some limitations, such as the development being conducted according to a specific socioeconomic or national context that hinders the transferability or applicability of the tool or framework to other countries, the specificity or exclusion of certain digital health technologies with limitations in their use, or the low evidence available in relation to the real usefulness of the methodological frameworks.

In this context, we intend to develop a scoping review with the aim of identifying the methodological frameworks that are used worldwide for the evaluation of digital health technologies; determining what dimensions and aspects are being considered; and generating, through a thematic analysis, a proposal for a methodological framework that is based on the most frequently described dimensions in the literature.

Identifying the Research Questions

The scoping review will answer the following research questions:

- What methodological frameworks currently exist for digital HTA?
- What dimensions are being considered for the digital HTA?
- What dimensions are being described in more frequency in existing methodological frameworks?
- Are different dimensions being considered depending on whether the HTA is for a non–face-to-face care model of health care provision, a mobile device (mHealth), or a device that incorporates AI?

Methods

Overview of Methods for Conducting the Scoping Review

The scoping review of the available scientific literature will be carried out in accordance with the guidelines established in the updated statement of the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews, see Multimedia Appendix 1) [19], with the aim of guaranteeing the transparency and reproducibility of the results.

Different experts in the fields of HTA and digital health technology participated in the planning of the study. Furthermore, they will be involved in its execution.

Identifying Relevant Studies

The search strategy will be designed by an information specialist (RPP) and be based on the validated filter of Ayiku et al [20] for health apps; we will add the terms for concepts related to mHealth, remote care models, AI, digital health, methodological frameworks, and HTA. Taking into account the research questions, the initial search strategy for MEDLINE Ovid was designed by the information specialist (RPP) and peer-reviewed according to the Peer Review of Electronic Search Strategies Statement by JSF and CMP. The initial search strategy (Multimedia Appendix 2) will be exported to the following electronic databases: Ovid via MEDLINE, CINAHL Plus, Embase, Cochrane Library, Scopus, Web of Science, and TripDatabase. The characteristics of each database related to syntax, controlled vocabulary, and proximity operators will be taken into account. No time, language, or other filters will be used.

The identification of the studies will be complemented with a manual search that will be based on the references of the included studies, as well as the websites of the HTA agencies detected through the web pages of the EUnetHTA, the International Network for Agencies for Health Technology Assessment, and Health Technology Assessment International. Finally, a search will be carried out in Google Scholar, which will include the first 250 items to ensure that no relevant results are missed [21].

Inclusion Criteria

The criteria for the selection of studies in the reference screening process will be based on the previously detailed research questions, and these criteria are described in Textbox 1, using the PICo-D (Population, Phenomenon of Interest, Context, and Design) format [22]. It should be noted that the PICo-D format has been used instead of the traditional PICO-D (Population, Intervention, Comparator, Outcomes, Design) format due to the qualitative nature of the research questions and the characteristics of the phenomenon of interest.

Textbox 1. Research questions in the PICo-D (Population, Phenomenon of Interest, Context, and Design) format (inclusion criteria).

Problem

- Digital health technology assessment

Phenomenon of interest

- Specific methodological frameworks for the evaluation of digital health (with a special focus on mobile health, non–face-to-face models, and devices that incorporate artificial intelligence) that describe the domains that must be taken into account in this type of process, as well as the levels of evidence that should be considered for this process

Context

- Health technology assessment

Design

- Methodological guidelines and frameworks, scoping reviews, systematic reviews, consensus documents, and qualitative studies

In the study selection process, studies published before 2011, studies that do not describe dimensions or evaluation criteria, studies that are based on methodological frameworks that are not intended for this purpose (eg, EUnetHTA Core Model 3.0), comments, editorials, letters, and conference abstracts will be excluded. Likewise, methodological frameworks or tools that focus on the evaluation of digital health technologies by users (eg, user version of the Mobile App Rating Scale) and documents in languages other than English, Spanish, or Catalan will also be excluded. Nevertheless, in the case that we identify any methodological frameworks written in languages other than those mentioned above, the authors of those documents will be contacted to confirm the absence of an English version. Additionally, the translation of the documents will be considered.

All identified references will be imported into the EndNote bibliographic citation manager (version 20.2.1; Clarivate) [23], and duplicates will be removed according to the guidelines of Bramer et al [24].

The selection of studies will be carried out in 2 different phases. The first one will be the selection of studies via a single-blind peer review of the titles and abstracts of the references identified in the bibliographic search. This will be conducted by authors CMP and JSF. The second one will be a full-text, single-blind review of the studies included in the first phase, and this will be carried out by the same authors (CMP and JSF) in accordance with the selection criteria detailed above.

The quality of the evidence will be assessed by CMP and JSF using the Critical Appraisal Skills Program tool [25]. However,

it should be noted that this tool cannot be used to obtain an overall score of the quality of the studies. Therefore, no references will be excluded due to their quality.

Charting the Data

After the selection of the articles, the data of the included studies will be extracted. This task will be carried out by 3 reviewers (CMP, RPP, and JSF) using the web and desktop versions of the ATLAS.ti software (version 22.0; Scientific Software Development GmbH) [26] and the data extraction sheets that were designed ad hoc for this purpose according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* [27]. The data to be extracted through the tables will be authors, publication dates, methodological framework/tool names, HTA agencies, countries, study designs, technology characteristics, the number of dimensions and criteria, dimensions, and detailed criteria.

For cases of discrepancies in either of the two processes (selection of studies or data extraction), a consensus will be reached among 3 reviewers (CMP, RPP, and JSF). If a discrepancy remains, a fourth reviewer (RVH) will be consulted.

Collecting, Summarizing, and Reporting the Results

The evidence will be analyzed by using 2 approaches. First, a descriptive analysis will be carried out to evaluate and report the existing methodological frameworks and their characteristics. Second, a thematic analysis will be carried out according to the following three phases, which are described by Thomas and Harden [28], to identify HTA dimensions for digital health technologies: (1) line-by-line text coding, (2) the development of descriptive topics, and (3) the generation of analytical themes. Both analyses will be executed by three of the authors (CMP, RPP, and JSF) using the web and desktop versions of the ATLAS.ti software (version 22.0) [26].

The synthesis of the evidence will be carried out in a narrative manner, taking into account the selection criteria and the research questions detailed above.

Dimensions identified from systematic reviews that derived data from primary studies that are also identified in our systematic search will only be counted once in order to avoid the duplication of data and the risk of bias.

Ethical Considerations

No ethical board approval is necessary to conduct this scoping review.

Results

The scoping review is currently (May 2022) in progress. It is expected to be completed in October 2022, and the final results of the research will be presented and published by November 2022.

A dissemination plan has been developed to share the knowledge generated from the scoping review. Specifically, the results obtained from our work will be openly published in a scientific paper by March 2023, and they will also be presented at a national congress and an international congress. Furthermore, the results will be shared with the Spanish Ministry of Health, other relevant Spanish health care stakeholders, and national and international HTA agencies via direct emails and webinars.

Discussion

Principal Findings

Our scoping review is expected to identify and evaluate the existing frameworks for digital HTA and generate, through a thematic analysis, a proposal for a methodological framework that is based on the most frequently described dimensions in the literature. Although there are not many published frameworks that specifically address the assessment of digital health technologies, it is expected that considerable differences will be found among them (eg, in terms of the dimensions considered or the kinds of digital health technology addressed). Besides, additional domains that can be compared to those of conventional HTA methodological frameworks (eg, HTA Core Model) will probably be found. Finally, this work can be useful for the HTA field, as it will outline the main additional dimensions that should be considered for digital HTA and propose a framework that covers the intrinsic characteristics of digital health technologies [7,10,16].

Comparison With Previous Works

There are some publications that focus on analyzing—through qualitative studies, narrative reviews, or systematic reviews—what information related to the dimensions of the EUnetHTA HTA Core Model are reported by studies on digital health, what methodological frameworks and tools exist for the evaluation of digital health technologies, and what dimensions are considered by these frameworks. However, none of the articles identified through the preliminary literature search, which was done before the development of this protocol, addresses the same research questions from the perspective of HTA. For example, a review by Moshi et al [29] analyzed 45 tools for the evaluation of mobile apps, regardless of their intended audience, and a review by von Huben et al [30] analyzed the degree to which such tools cover the evaluation domains of the EUnetHTA HTA Core Model 3.0.

Strengths and Limitations

There are 2 main strengths to our study. First, different experts in the fields of HTA and digital health technology will participate in the planning and development of the study. Second, the validated filter of Ayiku et al [20] has been used to develop the search strategy. The main limitation of our study is the exclusion of frameworks published in languages other than English, Spanish, or Catalan. Another limitation is the use of controlled vocabulary that is not suited to the current state of knowledge in the digital health field.

Future Directions

According to the WHO [10], there is low evidence available in relation to the real usefulness of the existing methodological frameworks for digital HTA. Future work will be conducted to explore the utility of the methodological framework that will be developed based on our scoping review and compare it to existing frameworks.

Conclusions

To our knowledge, no study has been published so far with the aim of identifying the existing methodological frameworks for digital HTA, determining which dimensions must be evaluated for correct decision-making from the HTA perspective, and serving as a basis for the development of a methodological framework of reference that health care systems can use to carry out this kind of assessment. This work is intended to address this knowledge gap and may be useful in the field of HTA.

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Authors' Contributions

JSF, CMP, RPP, and RMVH contributed to the development of the protocol. RPP was in charge of developing the search strategy. JSF, CMP, and RPP will develop the rest of the tasks of the scoping review.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist.
[DOC File , 66 KB - resprot_v11i10e39905_app1.doc]

Multimedia Appendix 2
Search strategy.
[DOC File , 61 KB - resprot_v11i10e39905_app2.doc]

References

1. Avanzas P, Pascual I, Moris C. The great challenge of the public health system in Spain. J Thorac Dis 2017 May;9(Suppl 6):S430-S433 [FREE Full text] [doi: 10.21037/jtd.2017.04.59] [Medline: 28616336]
2. European semester thematic factsheet: Health systems. European Commission. 2016. URL: https://ec.europa.eu/info/sites/default/files/file_import/european-semester_thematic-factsheet_health-systems_en_0.pdf [accessed 2022-09-26]
3. Pla Director de Sistemes d'Informació del SISCAT: Construint junts una estratègia de salut digital per a Catalunya. Generalitat de Catalunya, Departament de Salut. 2017. URL: https://salutweb.gencat.cat/web/.content/_ambits-actuacio/Linies-dactuacio/Plans-sectorials/pd_sistemes_informacio/pla_director_final_v27.pdf [accessed 2022-09-26]
4. Health 2020: A European policy framework and strategy for the 21st century. World Health Organization. 2020. URL: https://www.euro.who.int/__data/assets/pdf_file/0011/199532/Health2020-Long.pdf [accessed 2022-09-26]
5. World Health Organization. WHO Guideline: Recommendations on Digital Interventions for Health System Strengthening. Geneva, Switzerland: World Health Organization; Jun 06, 2019.
6. The NICE methods of health technology evaluation: the case for change. National Institute for Health and Care Excellence. 2020. URL: https://www.bioindustry.org/static/e9c9093d-8a4b-4e1e-b01590df056d7f6a/BIA-response-to-the-NICE-methods-of-health-technology-evaluation-the-case-for-change.pdf [accessed 2022-09-26]
7. Kickbusch I, Piselli D, Agrawal A, Balicer R, Banner O, Adelhardt M, Secretariat of the Lancet and Financial Times Commission. The Lancet and Financial Times Commission on governing health futures 2030: growing up in a digital world. Lancet 2021 Nov 06;398(10312):1727-1776. [doi: 10.1016/S0140-6736(21)01824-9] [Medline: 34706260]
8. Catalonia, Spain. World Health Organization. 2018. URL: https://cdn.who.int/media/docs/librariesprovider2/country-sites/catalonia.pdf?sfvrsn=d000806_3&download=true [accessed 2022-09-26]
9. Spain: Health care and long-term care systems. European Commission. 2016. URL: https://ec.europa.eu/info/sites/default/files/file_import/joint-report_es_en_2.pdf [accessed 2022-09-26]
10. Global strategy on digital health 2020-2025. World Health Organization. 2021. URL: https://www.who.int/docs/default-source/documents/gs4dhdaa2a9f352b0445bafbc79ca799dce4d.pdf [accessed 2022-09-26]
11. eHealth: Digital health and care. European Commission. 2019. URL: https://pbu2020.eu/files/uploads/annual%20conference_2019/EB0219277ENN.en.pdf [accessed 2022-09-26]

12. Reeves JJ, Ayers JW, Longhurst CA. Telehealth in the COVID-19 era: A balancing act to avoid harm. J Med Internet Res 2021 Feb 01;23(2):e24785 [FREE Full text] [doi: 10.2196/24785] [Medline: 33477104]
13. O'Rourke B, Oortwijn W, Schuller T, International Joint Task Group. The new definition of health technology assessment: A milestone in international collaboration. Int J Technol Assess Health Care 2020 Jun;36(3):187-190. [doi: 10.1017/S0266462320000215] [Medline: 32398176]
14. EUnetHTA JA2 WP8 deliverable: HTA Core Model version 3. European Network for Health Technology Assessment. 2016. URL: https://www.eunethta.eu/wp-content/uploads/2018/03/HTACoreModel3.0-1.pdf [accessed 2022-04-07]
15. Puñal-Riobóo J, Álvarez EB, Varela LL, Muñoz MAC, Merino GA, Pérez RU, et al. Guía para la elaboración y adaptación de informes rápidos de evaluación de tecnologías sanitarias. Ministerio de Sanidad, Servicios Sociales e Igualdad. 2016. URL: https://extranet.sergas.es/catpb/Docs/gal/Publicaciones/Docs/avalia-t/PDF-2496-ga.pdf [accessed 2022-09-26]
16. Hussain MS, Silvera-Tawil D, Farr-Wharton G. Technology assessment framework for precision health applications. Int J Technol Assess Health Care 2021 May 26;37(1):e67. [doi: 10.1017/S0266462321000350] [Medline: 34034854]
17. Evidence standards framework for digital health technologies. National Institute for Health and Care Excellence. 2018. URL: https://www.nice.org.uk/corporate/ecd7/resources/evidence-standards-framework-for-digital-health-technologies-pdf-1124017457605 [accessed 2022-09-26]
18. Haverinen J, Keränen N, Falkenbach P, Maijala A, Kolehmainen T, Reponen J. Digi-HTA: Health technology assessment framework for digital healthcare services. Finnish Journal of eHealth and eWelfare 2019 Nov 02;11(4):326-341. [doi: 10.23996/fjhw.82538]
19. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and explanation. Ann Intern Med 2018 Oct 02;169(7):467-473 [FREE Full text] [doi: 10.7326/M18-0850] [Medline: 30178033]
20. Ayiku L, Hudson T, Glover S, Walsh N, Adams R, Deane J, et al. The NICE MEDLINE and Embase (Ovid) health apps search filters: development of validated filters to retrieve evidence about health apps. Int J Technol Assess Health Care 2020 Oct 27;37:e16. [doi: 10.1017/S026646232000080X] [Medline: 33107420]
21. Bramer WM, Rethlefsen ML, Kleijnen J, Franco OH. Optimal database combinations for literature searches in systematic reviews: a prospective exploratory study. Syst Rev 2017 Dec 06;6(1):245 [FREE Full text] [doi: 10.1186/s13643-017-0644-y] [Medline: 29208034]
22. Lockwood C, Munn Z, Porritt K. Qualitative research synthesis: methodological guidance for systematic reviewers utilizing meta-aggregation. Int J Evid Based Healthc 2015 Sep;13(3):179-187. [doi: 10.1097/XEB.0000000000000062] [Medline: 26262565]
23. EndNote 20. Clarivate. URL: https://endnote.com [accessed 2022-09-26]
24. Bramer WM, Giustini D, de Jonge GB, Holland L, Bekhuis T. De-duplication of database search results for systematic reviews in EndNote. J Med Libr Assoc 2016 Jul;104(3):240-243 [FREE Full text] [doi: 10.3163/1536-5050.104.3.014] [Medline: 27366130]
25. CASP Qualitative Checklist 2018. Critical Appraisal Skills Programme. URL: https://casp-uk.net/casp-tools-checklists/ [accessed 2022-04-07]
26. ATLAS.ti 22. Scientific Software Development GmbH. URL: https://atlasti.com [accessed 2022-09-26]
27. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, The Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions (v6.3). London, United Kingdom: The Cochrane Collaboration; 2022.
28. Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. BMC Med Res Methodol 2008 Jul 10;8:45 [FREE Full text] [doi: 10.1186/1471-2288-8-45] [Medline: 18616818]
29. Moshi MR, Tooher R, Merlin T. Suitability of current evaluation frameworks for use in the health technology assessment of mobile medical applications: a systematic review. Int J Technol Assess Health Care 2018 Jan;34(5):464-475. [doi: 10.1017/S026646231800051X] [Medline: 30201060]
30. von Huben A, Howell M, Howard K, Carrello J, Norris S. Health technology assessment for digital technologies that manage chronic disease: a systematic review. Int J Technol Assess Health Care 2021 May 26;37(1):e66. [doi: 10.1017/S0266462321000362] [Medline: 34034851]

Abbreviations

AI: artificial intelligence
EUnetHTA: European Network for Health Technology Assessment
FinCCHTA: Finnish Coordinating Center for Health Technology Assessment
HTA: health technology assessment
mHealth: mobile health
NICE: National Institute for Health and Care Excellence
PICO-D: Population, Intervention, Comparator, Outcomes, Design
PICo-D: Population, Phenomenon of Interest, Context, and Design

PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
WHO: World Health Organization

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Protocol

Interactive Conversational Agents for Health Promotion, Prevention, and Care: Protocol for a Mixed Methods Systematic Scoping Review

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Abstract

Background: Interactive conversational agents, also known as “chatbots,” are computer programs that use natural language processing to engage in conversations with humans to provide or collect information. Although the literature on the development and use of chatbots for health interventions is growing, important knowledge gaps remain, such as identifying design aspects relevant to health care and functions to offer transparency in decision-making automation.

Objective: This paper presents the protocol for a scoping review that aims to identify and categorize the interactive conversational agents currently used in health care.

Methods: A mixed methods systematic scoping review will be conducted according to the Arksey and O’Malley framework and the guidance of Peters et al for systematic scoping reviews. A specific search strategy will be formulated for 5 of the most relevant databases to identify studies published in the last 20 years. Two reviewers will independently apply the inclusion criteria using the full texts and extract data. We will use structured narrative summaries of main themes to present a portrait of the current scope of available interactive conversational agents targeting health promotion, prevention, and care. We will also summarize the differences and similarities between these conversational agents.

Results: The search strategy and screening steps were completed in March 2022. Data extraction and analysis started in May 2022, and the results are expected to be published in October 2022.

Conclusions: This fundamental knowledge will be useful for the development of interactive conversational agents adapted to specific groups in vulnerable situations in health care and community settings.

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KEYWORDS

conversational agents; chatbots; scoping review; literature review; healthcare; health care; health promotion; prevention; care; computer; natural language processing; literature; community

Introduction

Digital technologies are an engine of transformation in the health sector and represent a promising avenue for improving access to care, care personalization, health prevention, and health promotion, particularly for those in vulnerable situations [1]. Health technologies are increasingly necessary to support and improve health care access [2,3].

Conversational agents, also known as "chatbots," are computer programs that use natural language processing to engage in conversations with humans to provide or collect information [4-6]. Chatbots use algorithms to simulate a human conversation via text or voice messages. They are easy to use for patients and require minimal computer literacy and knowledge [7,8]. Chatbots can use simple predetermined conversation algorithms to simulate conversation or more complex systems based on neural networks and deep learning to understand speech, produce a voiced answer, and simulate social interaction [9]. Chatbots allow for automated interventions with customizable, accessible, and cost-effective software [8].

Although the literature on the development and use of chatbots for patients' health is growing, there are still important knowledge gaps that remain, such as identifying design aspects relevant to health care and functions to offer transparency in decision-making automation [7,10,11]. Moreover, despite increasing developments in digital technologies and the implementation of conversational agents in a wide range of domains, their use in health care is still limited [12]. Chatbots are primarily developed for a specific context of care, so little is known about the greater contextual application of chatbots in health care. Providing an exhaustive portrait of current chatbots used in health care is a significant step toward understanding the position of chatbots in the current infrastructure of care. This review is interested in chatbots that were able to adapt and simulate interactive conversations as opposed to chatbots offering users constrained multiple-choice options, thus limiting the impression of real and meaningful interactions.

The goal of this mixed methods systematic scoping review is to identify and categorize interactive conversational technologies currently used in health promotion, prevention, and care.

Methods

Overview

A mixed methods systematic scoping review will be conducted according to the Arksey and O'Malley [13] framework and the guidance of Peters et al [14] for systematic scoping reviews. This literature review will focus on studies on interactive conversational agents for health promotion, prevention, and care. As this topic is complex and heterogeneous, a review of the scope of the literature will help tailor future systematic reviews and research endeavors. The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) criteria will be used to report the results [15].

Our key synthesis question is as follows: (1) in which population and settings are interactive conversational agents used for health promotion, prevention, and care? and (2) what are the characteristics of the technologies supporting these interactive conversational agents?

Eligibility Criteria

We will address all types of evidence matching the PICOS (population, intervention, comparison, outcomes, setting or context) criteria:

- Participants or population: we will include all studies targeting laypeople (eg, patients, students, citizens). Studies targeting only health care providers will be excluded.
- Interventions or phenomena of interest: we will include all interactive conversational agents, that is, those involving a 2-way exchange (written, oral, and visual dialogue), directed at laypeople for health promotion, prevention, and care.
- Comparator: no restrictions will be applied.
- Outcomes: we will consider all outcomes reported in the studies. We will seek outcomes related to patients, caregivers, health care providers, and policy makers. Those could include barriers, facilitators, acceptability, feasibility, adoption, fidelity, morbidity, mortality, quality of life, satisfaction, cost, and cost-effectiveness.
- Setting: we will include studies taking place in a health care or community setting, in any geographical area. All types of studies will be included (qualitative, quantitative, and mixed methods).

Search Strategy

The search strategy was developed in collaboration with a university librarian who has experience in literature reviews (FB) (Multimedia Appendix 1). An iterative process of revision by members of the research team took place, and all relevant comments were integrated into the final version of the search strategy. The final version was approved by all team members. A specific search strategy was formulated for each of the following databases: MEDLINE (Ovid), Embase, Inspec (Engineering Village), Web of Science, and CINAHL. The search will be restricted to studies from the last 20 years because of the recent nature of conversational agents. No restriction on language was applied to the search. Terms such as *chatbot*, *conversational agent*, *virtual embodied agent*, and their spelling variants were used for the search. Additionally, since innovation implementations are often conducted by the private sector, we performed an internet search in the following sources and databases: Google, Google Scholar, Institut national d'excellence en santé et en services sociaux, Canadian Evaluation Society, EuroScan, OpenGrey, Grey Literature Report, GreyNet, and Grey Matters. The search also included a hand search, and bibliographies were reviewed for additional relevant references. The search strategy is presented in Multimedia Appendix 1.

Data Collection

All citations will be exported to the online collaboration tool Covidence (Veritas Health Innovation) [16], where duplicates will be removed by its automated function. An independent assessment of inclusion criteria will be done by at least 2 reviewers. Reviewers will search and obtain all the full texts of the selected references and will import the PDF files in Covidence. Two reviewers will independently apply the inclusion criteria using the full texts. Reasons for exclusion will be recorded in Covidence. A PRISMA flowchart will be used to describe the identifications of studies, the screening process, and the application of inclusion and exclusion criteria [17].

Data Extraction

Team members will complete the extraction, and the data will be reviewed by an experienced researcher (MPG or MS). We will extract descriptive data (title, year of publication, authors, country), study type (published or gray literature, study design), intervention data (name of the technology, language of the technology, implementation channel, and features like audio, text, voice, avatar), setting data (target population, place of implementation), sample data (comparator, number of participants, sample sizes), outcomes (process, patients, providers, or systems related), and outcome type (qualitative and quantitative). We will appraise the quality of the studies included by applying the Mixed Methods Appraisal Tool [18].

Data Synthesis

We will complete the data synthesis using structured narrative summaries of main themes and provide a portrait of the current scope of available technologies using descriptive analysis. A summary of the differences and similarities between conversational agents will highlight the following points: strengths and weaknesses, main outcomes, main resources used, and trade-offs. A map of outcomes and targeted populations will be built and presented [14].

Results

The search strategy and screening steps of the review were completed in March 2022. Data extraction and analysis began in May 2022, and the results are expected to be published in October 2022.

Discussion

Main Contributions of This Scoping Review

Literature reviews on chatbots in health care are available in specific contexts, such as mental health management [19-21], prevention of COVID-19 [22], health behavior change [23,24], chronic conditions management [25], and medical education [26]. A systematic review by Laranjo et al [12] was completed in 2018 with a global scope, but it was aimed at patients and providers and focused only on verbal communication. To our knowledge, our review is the first endeavor aiming to offer an overarching map of the research on interactive conversational agents targeting laypeople in all contexts of care. As there are many pilot and usability studies on the topic, summarizing evidence by context and type of technology will offer a unique view of how and for whom conversational agents are used. This review will also explore whether these technologies are useful and successful in managing health issues.

Potential Impact and Future Directions

There is a human resources crisis in health care. Worldwide shortages in health care professionals, increasing burnout rates, and an aging population are 3 major factors causing an imbalance in the offering and demand of health care services [27,28]. Focused technologies and tools such as interactive conversational agents are needed to overcome the potential abyss of human resource shortage in health care by reducing cost and improving access. Understanding what is currently offered in health care has the potential to help researchers, health care professionals, and decision-makers to develop, implement, or test solutions.

Accelerated by the COVID-19 pandemic, the shift to digital care has caused health inequities [29]. This review will thus pay particular attention to how equity, diversity, and inclusion have been considered in the development of conversational agents. Vulnerable populations often do not have the skills and opportunities to use chatbots [30]. Indeed, personal characteristics (eg, advanced age, chronic diseases, disability situation, lack of digital literacy) or contextual factors (eg, poverty, housing, irregular migrant status) may make chatbots unfavorable for use. Moreover, in their interaction with individuals, chatbots cannot always evolve with time and adapt to the user's literacy skills and language level. Thus, they sometimes are unable to adapt to dynamic user behavior and offer customized responses tailored to the user's personality [31,32]. Therefore, the development of conversational agents adapted to the needs of individuals, especially those in vulnerable situations, remains a major challenge for researchers [33]. This review could contribute to the inclusion of the needs of vulnerable populations when designing conversational agents [30].

Finally, the widespread implementation of conversational agents is still burdened by ethical and clinical implications [23]. Shifting to an artificial relationship removes human-to-human communication from the care process. Understanding the level of involvement of professionals in the human-machine relationship remains an area of research worth considering. The burden of decision-making also emanates from that problem. As professionals are assisted by technological tools, we need to think about who is responsible for the information and decisions offered by technology that can be potentially harmful to patients [34]. On a more macro level, the use of conversational agents could support a shift toward disease prevention rather than treatment, thus leading to large-scale benefits for the whole society [7].

Conclusion

The results of this scoping review will provide a portrait of interactive conversational agents and their various applications in health promotion, prevention, and care. This fundamental knowledge will be useful for the development of interactive conversational agents adapted to specific users and people in vulnerable situations.

Acknowledgments

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Data Availability

The data for this review will be deposited and made available online in the Open Science Framework depository.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Detailed search strategy.
[PDF File (Adobe PDF File), 166 KB - resprot_v11i10e40265_app1.pdf]

References

1. de Cock C, Milne-Ives M, van Velthoven MH, Alturkistani A, Lam C, Meinert E. Effectiveness of conversational agents (virtual assistants) in health care: protocol for a systematic review. JMIR Res Protoc 2020 Mar 9;9(3):e16934. [doi: 10.2196/16934]
2. El Alami LSE, Nemoto A, Nakata Y. Investigation of users' experiences for online access to their electronic health records in Japan. Glob Health Med 2021 Feb 28;3(1):37-43 [FREE Full text] [doi: 10.35772/ghm.2020.01073] [Medline: 33688594]
3. François J, Audrain-Pontevia AF. La santé numérique: un levier pour améliorer l'accessibilité aux soins de santé au Québec. Revue Organisations & Territoires 2020;29(3):41-55 [FREE Full text] [doi: 10.1522/revueot.v29n3.1196]
4. Denecke K, Tschanz M, Dorner TL, May R. Intelligent conversational agents in healthcare: hype or hope? Stud Health Technol Inform 2019;259:77-84. [Medline: 30923277]
5. Montenegro JLZ, da Costa CA, da Rosa Righi R. Survey of conversational agents in health. Expert Syst Appl 2019 Sep;129:56-67. [doi: 10.1016/j.eswa.2019.03.054]
6. Tudor Car L, Dhinagaran DA, Kyaw BM, Kowatsch T, Joty S, Theng Y, et al. Conversational agents in health care: scoping review and conceptual analysis. J Med Internet Res 2020 Aug 07;22(8):e17158 [FREE Full text] [doi: 10.2196/17158] [Medline: 32763886]
7. Gabarron E, Larbi D, Denecke K, Årsand E. What do we know about the use of chatbots for public health? Stud Health Technol Inform 2020 Jun 16;270:796-800. [doi: 10.3233/SHTI200270] [Medline: 32570492]
8. Parmar P, Ryu J, Pandya S, Sedoc J, Agarwal S. Health-focused conversational agents in person-centered care: a review of apps. NPJ Digit Med 2022 Feb 17;5(1):21 [FREE Full text] [doi: 10.1038/s41746-022-00560-6] [Medline: 35177772]
9. Oh KJ, Lee D, Ko B, Choi HJ. A chatbot for psychiatric counseling in mental healthcare service based on emotional dialogue analysis and sentence generation. 2017 Presented at: 8th IEEE International Conference on Mobile Data Management (MDM); May 29 - Jun 1; Daejeon, Korea p. 371-375 URL: https://ieeexplore.ieee.org/document/7962482 [doi: 10.1109/mdm.2017.64]
10. Jovanovic M, Baez M, Casati F. Chatbots as conversational healthcare services. IEEE Internet Comput 2021 May;25(3):44-51 [FREE Full text] [doi: 10.1109/MIC.2020.3037151]
11. Chew HSJ, Achananuparp P. Perceptions and needs of artificial intelligence in health care to increase adoption: scoping review. J Med Internet Res 2022 Jan 14;24(1):e32939 [FREE Full text] [doi: 10.2196/32939] [Medline: 35029538]
12. Laranjo L, Dunn AG, Tong HL, Kocaballi AB, Chen J, Bashir R, et al. Conversational agents in healthcare: a systematic review. J Am Med Inform Assoc 2018 Sep 01;25(9):1248-1258 [FREE Full text] [doi: 10.1093/jamia/ocy072] [Medline: 30010941]
13. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res 2005 Feb;8(1):19-32. [doi: 10.1080/1364557032000119616]
14. Peters MDJ, Godfrey C, McInerney P, Munn Z, Tricco AC, Khalil H. Chapter 11: Scoping reviews (2020 version). In: Aromataris E, Munn Z, editors. JBI Manual for Evidence Synthesis. Adelaide, Australia: JBI; 2020.
15. Selçuk AA. A guide for systematic reviews: PRISMA. Turk Arch Otorhinolaryngol 2019 Mar 10;57(1):57-58 [FREE Full text] [doi: 10.5152/tao.2019.4058] [Medline: 31049257]
16. Covidence. Veritas Health Innovation. URL: https://www.covidence.org/ [accessed 2022-10-03]
17. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021 Mar 29;372:n71 [FREE Full text] [doi: 10.1136/bmj.n71] [Medline: 33782057]
18. Pace R, Pluye P, Bartlett G, Macaulay AC, Salsberg J, Jagosh J, et al. Testing the reliability and efficiency of the pilot Mixed Methods Appraisal Tool (MMAT) for systematic mixed studies review. Int J Nurs Stud 2012 Jan;49(1):47-53. [doi: 10.1016/j.ijnurstu.2011.07.002] [Medline: 21835406]
19. Abd-Alrazaq AA, Rababeh A, Alajlani M, Bewick BM, Househ M. Effectiveness and safety of using chatbots to improve mental health: systematic review and meta-analysis. J Med Internet Res 2020 Jul 13;22(7):e16021 [FREE Full text] [doi: 10.2196/16021] [Medline: 32673216]

20. Vaidyam AN, Wisniewski H, Halamka JD, Kashavan MS, Torous JB. Chatbots and conversational agents in mental health: a review of the psychiatric landscape. Can J Psychiatry 2019 Jul;64(7):456-464 [FREE Full text] [doi: 10.1177/0706743719828977] [Medline: 30897957]
21. Abd-Alrazaq AA, Alajlani M, Alalwan AA, Bewick BM, Gardner P, Househ M. An overview of the features of chatbots in mental health: a scoping review. Int J Med Inform 2019 Dec;132:103978. [doi: 10.1016/j.ijmedinf.2019.103978] [Medline: 31622850]
22. Almalki M, Azeez F. Health chatbots for fighting COVID-19: a scoping review. Acta Inform Med 2020 Dec;28(4):241-247 [FREE Full text] [doi: 10.5455/aim.2020.28.241-247] [Medline: 33627924]
23. Zhang J, Oh YJ, Lange P, Yu Z, Fukuoka Y. Artificial intelligence chatbot behavior change model for designing artificial intelligence chatbots to promote physical activity and a healthy diet: viewpoint. J Med Internet Res 2020 Sep 30;22(9):e22845 [FREE Full text] [doi: 10.2196/22845] [Medline: 32996892]
24. Pereira J, Díaz Ó. Using health chatbots for behavior change: a mapping study. J Med Syst 2019 Apr 04;43(5):135. [doi: 10.1007/s10916-019-1237-1] [Medline: 30949846]
25. Schachner T, Keller R, V Wangenheim F. Artificial intelligence-based conversational agents for chronic conditions: systematic literature review. J Med Internet Res 2020 Sep 14;22(9):e20701 [FREE Full text] [doi: 10.2196/20701] [Medline: 32924957]
26. Frangoudes F, Hadjiaros M, Schiza EC, Matsangidou M, Tsivitanidou O, Neokleous K. An overview of the use of chatbots in medical and healthcare education. In: Zaphiris P, Ioannou A, editors. Learning and Collaboration Technologies: Games and Virtual Environments for Learning. Lecture Notes in Computer Science, vol 12785. Cham: Springer; 2021:170-184.
27. Meara JG, Leather AJM, Hagander L, Alkire BC, Alonso N, Ameh EA, et al. Global Surgery 2030: evidence and solutions for achieving health, welfare, and economic development. The Lancet 2015 Aug;386(9993):569-624. [doi: 10.1016/s0140-6736(15)60160-x]
28. Shanafelt TD, Hasan O, Dyrbye LN, Sinsky C, Satele D, Sloan J, et al. Changes in burnout and satisfaction with work-life balance in physicians and the general us working population between 2011 and 2014. Mayo Clin Proc 2015 Dec;90(12):1600-1613. [doi: 10.1016/j.mayocp.2015.08.023] [Medline: 26653297]
29. Yao R, Zhang W, Evans R, Cao G, Rui T, Shen L. Inequities in health care services caused by the adoption of digital health technologies: scoping review. J Med Internet Res 2022 Mar 21;24(3):e34144 [FREE Full text] [doi: 10.2196/34144] [Medline: 35311682]
30. Luxton DD. Ethical implications of conversational agents in global public health. Bull World Health Organ 2020 Jan 27;98(4):285-287. [doi: 10.2471/blt.19.237636]
31. Ahmad R, Siemon D, Gnewuch U, Robra-Bissantz S. Designing personality-adaptive conversational agents for mental health care. Inf Syst Front 2022 Mar 02;24(3):923-943 [FREE Full text] [doi: 10.1007/s10796-022-10254-9] [Medline: 35250365]
32. Parviainen J, Rantala J. Chatbot breakthrough in the 2020s? An ethical reflection on the trend of automated consultations in health care. Med Health Care Philos 2022 Mar 04;25(1):61-71 [FREE Full text] [doi: 10.1007/s11019-021-10049-w] [Medline: 34480711]
33. Kocaballi AB, Berkovsky S, Quiroz JC, Laranjo L, Tong HL, Rezazadegan D, et al. The personalization of conversational agents in health care: systematic review. J Med Internet Res 2019 Nov 07;21(11):e15360 [FREE Full text] [doi: 10.2196/15360] [Medline: 31697237]
34. Powell J. Trust me, I'm a chatbot: how artificial intelligence in health care fails the Turing Test. J Med Internet Res 2019 Oct 28;21(10):e16222 [FREE Full text] [doi: 10.2196/16222] [Medline: 31661083]

Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
PICOS: population, intervention, comparison, outcomes, setting or context

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Protocol

The Influence of Sex, Gender, or Age on Outcomes of Digital Technologies for Treatment and Monitoring of Chronic Obstructive Pulmonary Disease: Protocol for an Overview of Systematic Reviews

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a common chronic disease that can be treated and monitored with various digital technologies. Digital technologies offer unique opportunities for treating and monitoring people with chronic diseases, but little is known about whether the outcomes of such technologies depend on sex, gender, or age in people with COPD.

Objective: The general objective of this study is to assess the possible influence of sex, gender, or age on outcomes of digital technologies for treatment and monitoring of COPD through an overview of systematic reviews.

Methods: The study is planned as an overview of systematic reviews. Study reporting is based on the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 2020 guidelines because guidelines for overviews are not available as of this writing. The information sources for the overview will include 4 bibliographic databases (MEDLINE, Cochrane Library, Epistemonikos, and Web of Science) as well as the bibliographies of the included systematic reviews. The electronic search strategy will be developed and conducted in collaboration with an experienced database specialist. The search results will be presented in accordance with the PRISMA 2020 guidelines. The eligibility of studies is based on the population, intervention, comparison, outcomes, and study design (PICOS) criteria: (1) people with COPD (population), (2) digital technology intervention for treatment or monitoring (intervention), (3) any control group or no control group (comparison), (4) any outcome, and (5) systematic review of randomized controlled trials or non–randomized controlled trials with or without a meta-analysis (study design). Critical appraisal of the included systematic reviews will be performed using A Measurement Tool to Assess Systematic Reviews, version 2 (AMSTAR 2). Data will be extracted using a standardized data extraction sheet.

Results: The literature search is scheduled for June 2022. We expect to select the relevant systematic reviews, code the data, and appraise the systematic reviews by December 2022.

Conclusions: There is a growing recognition that the influence of sex, gender, or age should be considered in research design and outcome reporting in the context of health care interventions. Our overview will identify systematic reviews of various digital technologies for treatment or monitoring of COPD. The most interesting aspect of the overview will be to investigate if any systematic reviews considered the influence of sex, gender, or age on the outcomes of such digital technologies in COPD. Evidence from the overview could be used to guide more individualized (sex, gender, or age-based) recommendations for the use of digital technologies among people with COPD.

Trial Registration: PROSPERO International Prospective Register of Systematic Reviews CRD42022322924; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=322924

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KEYWORDS

digital technologies; digital intervention; COPD; AMSTAR 2; chronic obstructive pulmonary disease; gender; sex; age; overview; systematic review; treatment; monitoring; chronic disease; chronic illness; outcome reporting; review methodology; critical appraisal

Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent chronic disease associated with a high disease burden and premature death [1,2]. The prevalence increases with age [3], and differences in diagnostic and therapeutic responses depending on sex, gender, or age have been found [4-12]. For example, although females manifest more severe COPD symptoms across their life course than males [9], they also benefit to a greater extent from certain therapeutic interventions [10]. Female sex is also associated with severe early-onset COPD [11].

In general, sex and gender appear to be inconsistently defined in the literature on COPD. Some studies refer exclusively to sex [10-12], others exclusively or predominantly to gender [4,5], and some use both terms [8,9]. We refer to "sex" as a genetic or biological construct that distinguishes between males and females and to "gender" as a social construct [2,13]. Despite these distinctions, sex and gender cannot be neatly separated because the concepts are multidimensional and interrelated [13]. It is increasingly understood that sex-specific biological factors and social factors influence each other and interact to affect health behaviors, opportunities, and outcomes [8]. Owing to such complexity of definitions, we aim to use any definition of sex or gender used in the context of COPD.

Digital technologies offer unique opportunities for treatment and monitoring of people with chronic diseases [14-17]. Digital technologies can help shift from reactive to proactive treatment approaches [18], but it is known that the uptake of digital technologies varies and depends, among other factors, on sex, gender, or age [19,20].

In recent years, many systematic reviews have been published on the use of digital technologies in COPD. If methodologically sound systematic reviews on a similar topic already exist, a new method of research synthesis, a so-called overview (a systematic review of systematic reviews) [21], can be conducted. Overviews can summarize the outcomes of multiple systematic reviews with similar objectives and address new objectives using existing data reported in such reviews. Although compared to systematic reviews, the number of overviews is still relatively low, the popularity of the latter is growing exponentially [22]. The main difference between an overview and a systematic review is that the units of searching, inclusion, and data analysis are systematic reviews (in overviews) and primary studies (in systematic reviews).

Systematic reviews should provide a comprehensive and objective assessment of existing evidence. This includes appropriate consideration of sex, gender, or age differences in the outcomes of any health care intervention. It is unclear if and to what extent systematic reviews have thus far addressed the influence of sex, gender, or age on the outcomes of digital technologies for treatment and monitoring of COPD. According to a search of the International Prospective Registry of Systematic Reviews (PROSPERO), MEDLINE, and the Cochrane Database of Systematic Reviews, no currently planned or completed overviews of systematic reviews on this topic were identified.

Thus, our main objectives are to (1) describe the terminology and definitions of sex or gender used in the systematic reviews; (2) determine if the systematic reviews focus on sex, gender, or age in any planned analyses and result reporting; (3) assess whether the systematic reviews include sex, gender, or age in their implications for clinical practice or policy and regulation development; and (4) create an evidence map that could inform individualized recommendations for people with COPD that take into account sex, gender, or age.

Methods

Study Design

The study is planned as an overview of systematic reviews [21]. Study reporting is based on the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 2020 guidelines [23] because guidelines for overviews are not available at the time of this writing. However, a new set of guidelines (Preferred Reporting Items for Overviews of Reviews [PRIOR]) is expected to be published shortly [24]. Since the wording and structure of the PRIOR items resemble those of the PRISMA 2020 items, we intend to adhere to the PRIOR statement once it is published. The PRISMA 2020 or the PRIOR checklist will be made available once the overview is complete.

Protocol and Registration

The overview of systematic reviews was prospectively registered on PROSPERO (CRD42022322924). Any changes to the protocol will be amended in PROSPERO and reported once the overview is complete.

Patient and Public Involvement

Patients and the public were not involved in the design of this protocol. Thus, ethics approval is not required for the overview of systematic reviews.

Eligibility Criteria

The eligibility criteria for this overview of systematic reviews are based on the population, intervention, comparison, outcomes, and study design (PICOS) criteria (Textbox 1). Our overview aims to (1) identify systematic reviews of digital technologies for the treatment and monitoring of COPD and (2) systematically assess if the outcomes reported in such reviews were analyzed or discussed in terms of sex, gender, or age. Consequently, we shall include neither the terms "sex," "gender," or "age" among

the inclusion or exclusion criteria nor the search terms because we are interested in both types of systematic reviews in this field (ie, systematic reviews that either consider or do not consider the influence of sex, gender, or age on their outcomes).

We intend to include only systematic reviews in the languages in which we are proficient (English and German). We will report the number of systematic reviews that were excluded in the full-text screening owing to language considerations and discuss any possible implications of excluding such literature on the results of the overview.

Textbox 1. Eligibility criteria for the overview of systematic reviews.

Inclusion criteria

- Population: diagnosis of chronic obstructive pulmonary disease (COPD) with or without any comorbidities
- Intervention: any digital technology for treatment and monitoring of COPD. Digital technologies are defined as any intervention delivered or supported by digital tools with the aim of targeted client communication or personal health tracking [25]; for example, remote and Web 2.0–based interventions that provide patients access to eHealth information regarding behavior change for self-management of COPD
- Comparison: any other intervention or no intervention
- Outcome: any outcome
- Study type: systematic review of randomized controlled trials (RCTs), non-RCTs, or both with or without meta-analysis. A study will be classified as a systematic review if it has explicitly stated objectives and reproducible methodology, including a literature search in at least 2 bibliographic databases
- Publication status: systematic review published in a peer-reviewed journal
- Publication language: English or German
- Full text accessible

Exclusion criteria

- Population without COPD
- Digital interventions are not applied or are not the primary intervention
- Other study type: rapid, scoping, or narrative review; overview of systematic review; primary study; comment; correction; letter; editorial; or protocol
- Other publication status: conference paper, unpublished report, thesis, or book
- Language other than English or German
- A review that does not fulfill the requirements for a systematic review (eg, no explicitly stated objectives or reproducible methodology or a literature search in only one bibliographic database) or has low or critically low appraisal ratings on AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews, version 2) [26]
- Full text not accessible

Information Sources

The information sources for the overview will include 4 bibliographic databases (MEDLINE, Cochrane Library, Epistemonikos, and Web of Science) as well as the bibliographies of the included systematic reviews. These databases were selected because they identified the most relevant studies in our preliminary search for systematic reviews and were accessible at our institution.

Search Strategy

The electronic search strategy will be developed iteratively by the team in consultation with an experienced database specialist. The development and reporting of the search strategy adheres to the Peer Review of Electronic Search Strategies [27] and PRISMA Statement for Reporting Literature Searches in Systematic Reviews [28] guidelines. The search terms and corresponding Medical Subject Headings terms will be derived to address the 2 main search topics: (1) COPD and (2) digital technologies. The electronic search will be conducted in English by the first author and will not use any restrictions regarding language or time frame. We will use an incorporated and validated filter in MEDLINE to identify systematic reviews [29]. A summary of the electronic search in MEDLINE is shown in Table 1.

Table 1. Summary of the search strategy in MEDLINE.

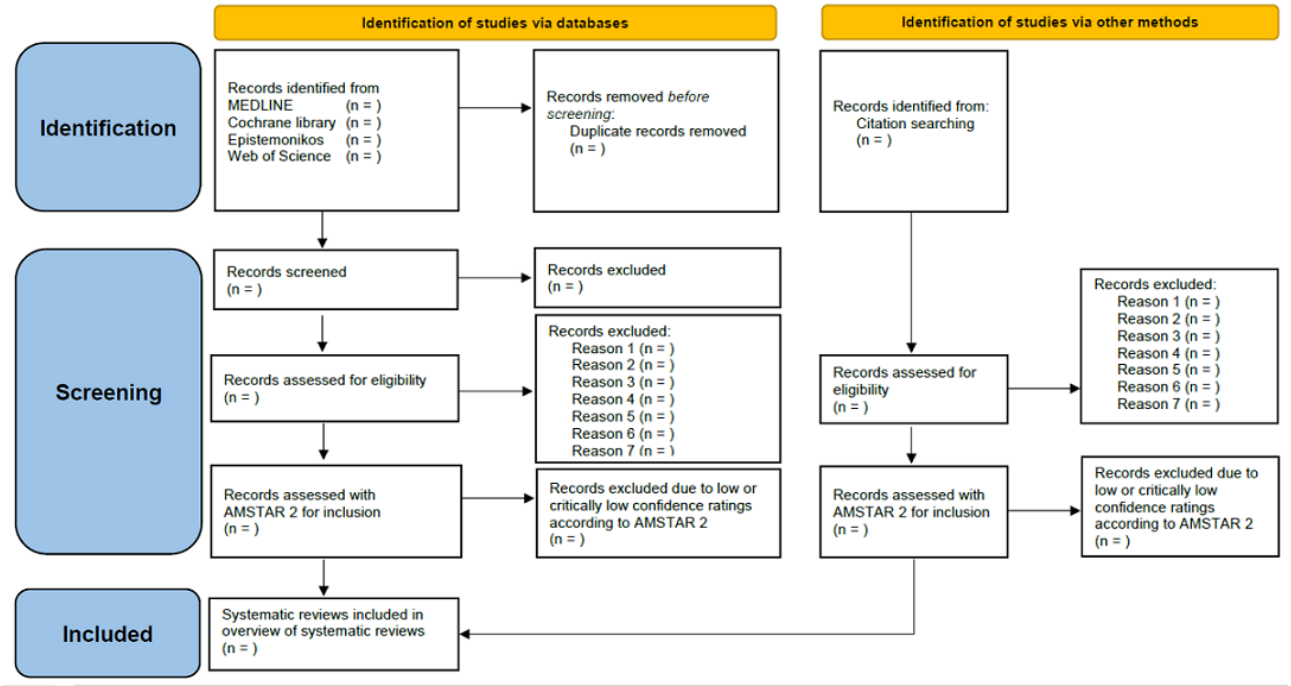
Variable	Search topic 1: digital technologies	Search topic 2: chronic obstructive pulmonary disease
Example search terms	Telemed*, telehealth*, ehealth*, mhealth*, mobile applications, wearable electronic devices, digital*, healthcare application*, internet*	Chronic obstructive pulmonary disease*, chronic obstructive airways disease*, COPD, COAD
Search fields	Titles or abstracts	Titles or abstracts
Comments	Relevant Medical Subject Headings terms were included	Relevant Medical Subject Headings terms were included

Selection of Sources of Evidence

The electronic search results will be stored in EndNote 20 (Clarivate). Following the removal of duplicates in EndNote, the remaining studies will be screened by 2 authors for inclusion in 3 steps using Covidence (Veritas Health Innovation). First, 2 authors will independently screen all titles and abstracts and reach consensus by discussion. Second, 2 authors will independently screen the studies selected for full-text inspection and reach consensus through discussion. In the case of no consensus, a third author will intervene. Third, once the study selection from the electronic search is complete, all systematic reviews will be appraised with AMSTAR 2 [26], and any systematic reviews with low or critically low appraisal ratings will be excluded owing to poor confidence in their results. One author will also manually screen the bibliographies of the included systematic reviews for additional literature. The results of the literature search will be reported in full once the overview is complete and presented on a PRISMA 2020 flow diagram [23] modified in accordance with our eligibility criteria and screening procedure (Figure 1).

A list of included and excluded studies following full-text screening and individual reasons for exclusion will be reported once the overview is complete.

Figure 1. Modified Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram.



Critical Appraisal of Individual Sources of Evidence

The critical appraisal of systematic reviews will be performed using AMSTAR 2 [26]. AMSTAR 2 has acceptable psychometric properties and is an appropriate tool to appraise systematic review of health care interventions [26,30]. The tool includes 16 items that need to be rated to derive the overall confidence rating in the results of a systematic review (critically low, low, moderate, or high) [26]. The overall confidence rating will be derived for each systematic review on the basis of a combination of scores on 7 critical and 9 noncritical items in accordance with AMSTAR 2 guidelines [26].

A form for appraising systematic reviews with AMSTAR 2 will be self-developed in Excel (version 10; Microsoft Corp). AMSTAR 2 appraisals will be performed in 2 phases independently by 2 authors as described in our protocol for a scoping review [31] and consensus will be reached through discussion. In the case of no consensus, a third author will intervene. The overall confidence rating for each systematic review according to AMSTAR 2 will be reported once the overview is complete.

Overlap in Primary Studies Included in Systematic Reviews

An overlap in overviews occurs when the same primary studies are cited in 2 or more systematic reviews. We will determine

the overlap among primary studies in the included systematic reviews. Although there is currently no standardized methodological approach for addressing overlap in overviews [32], the creation of citation matrices and the calculation of the overall corrected covered area (CCA) can be used to visualize the overlap. In general, CCA refers to an overall degree in overlap in primary studies among all systematic reviews and can be computed using the Graphical Representation of Overlap for OVErviews tool [33]. The primary studies included in each systematic review will be inserted into this tool and compared among the systematic reviews (sorted from the oldest to the newest). The tool reports the absolute number of overlapped and nonoverlapped primary studies and an overall outcome of the CCA assessment (degree of overlap in the overview) [33].

Data Charting

A form for coding and capturing of all data will be self-developed in Excel and calibrated within the team. Part of the data charting form will be adapted from the Sex and Gender Equity in Research guidelines [34]. Two authors will code all data independently in a 10% sample of the included systematic reviews. If the agreement in the sample is high (ie, reaching a κ of ≥ 0.80), the data in remaining systematic reviews will be charted by 1 author. We will resolve any discrepancies through discussion. In the case of no consensus, a third author will intervene. We will not contact the authors of the systematic reviews to obtain missing information or further clarification.

Data Items

Data items that will be coded in the overview are reported in Textbox 2. These items were chosen to address the objectives of our overview. Data items will include descriptive characteristics of the systematic reviews and their included primary studies and any sex, gender, or age effects on any intervention outcomes. Data items (Textbox 2) will be coded either quantitatively into predefined categories or qualitatively using definitions or author statements from the included systematic reviews. All data will be reported once the overview is complete.

Textbox 2. Data items in the overview of systematic reviews.

Data items

- Bibliographic information
- Population characteristics
- Intervention details
- Comparison type
- Outcome type
- Study (systematic review) type: Cochrane or non-Cochrane review
- Study aim according to review authors
- Primary studies in systematic review (number of studies, designs, and overlap among published studies)
- Risk of bias in primary studies according to review authors
- Data items for sex, gender, or age (eg, sensitivity analyses of outcomes taking into account sex, gender, or age)

Synthesis of Results

The data will be synthesized using descriptive statistics (absolute frequencies) or narratively. The overall confidence ratings for all systematic reviews, obtained using AMSTAR 2, will be graphically synthesized using a bar graph to visualize the outcomes of the critical appraisal.

Subgroup Analyses

Subgroup analyses will be performed to assess if considerations of sex, gender, or age in a systematic review are associated with the type or AMSTAR 2 appraisal rating of systematic reviews in accordance with methods applied in our previous work [22]. Proportions of studies with sex, gender, or age considerations (yes or no) will be compared on the basis of (1) the type of systematic review (Cochrane vs non-Cochrane) and (2) AMSTAR 2 confidence rating (high vs moderate) using chi-square tests and odds ratios with 95% CIs. These analyses will be performed because Cochrane reviews are associated with a higher quality than non-Cochrane reviews [35] and because high AMSTAR 2 ratings indicate high confidence in the results of a systematic review.

Results

The literature search is scheduled for June 2022. We expect to select the relevant systematic reviews, code the data, and appraise the systematic reviews by December 2022.

Discussion

Principal Findings

Preliminary literature searches have shown that systematic reviews so far identified various digital technologies for the treatment or monitoring of COPD, including remote and Web 2.0–based interventions, internet-based telecommunication with health care professionals, telerehabilitation, smartphone interventions, and home telemonitoring. The overview will provide a detailed list of such technologies once the studies are selected. We will also assess the outcomes of such digital technologies in the context of COPD. The most interesting

aspect of the overview will be to investigate if any systematic reviews have considered sex, gender, or age in their data synthesis or discussion of outcomes of such digital technologies in COPD.

Comparison to Prior Work

There is a growing recognition of the importance of sex, gender, or age considerations in research design and reporting [36-39]. This applies to not only primary studies but also systematic reviews. This can be challenging because the use of multiple subgroup analyses can cause methodological problems [40,41]. Methodological studies assessing the consideration of sex or gender, mostly included in Cochrane reviews, show room for improvement [42-45]. A recent methodological study evaluating a sample of 113 Cochrane reviews of interventions to prevent health care–associated infections found that only 10 reviews (10%) planned to conduct a subgroup analysis based on sex and only 3 (3%) reported the results of such an analysis [45]. It remains unclear whether this is also an issue with systematic reviews of digital technologies for COPD. According to the literature identified in the context of preparing this protocol, we have noticed that the terms "sex" and "gender" are not used in a standardized way in studies on COPD [4,5,8-12]. This is consistent with the findings of Adisso et al [46], who conducted a secondary analysis of a Cochrane systematic review that assessed sex and gender terminology in shared decision-making studies. Adisso et al [46] concluded the following:

> *In SDM implementation studies, sex and gender terms and concepts are in a state of confusion. Our results suggest the urgency of adopting a standardized use of sex and gender terms and concepts before these considerations can be properly integrated into implementation research.*

Thus, our overview will provide all terminology and definitions of sex and gender used in the systematic reviews of digital technologies for COPD.

Our overview focuses on the potential influence of only 3 sociodemographic variables (sex or gender and age) on the outcomes of digital technologies in COPD. We assume that these variables are regularly collected and reported in primary studies, at least in aggregate form (ie, as frequencies or means). According to the Global Burden of Disease Study 2019 [47], complex interactions exist between sex or gender and age in terms of prevalence, deaths, and disability-adjusted life years of COPD. Thus, we aim to assess if systematic reviews consider any of the 3 variables either individually or as part of interactions on the outcomes of digital technologies in COPD. In addition, a number of other participant characteristics could be worth investigating in COPD, such as the age of onset [11], race [48], or education and socioeconomic status [49]. Furthermore, the focus on digital health technologies is also a reason to choose sex, gender, or age as the variables of interest in our overview. For example, the interest in and the actual use of digital health technologies in COPD may decline with age and depend on digital health literacy as is the case in the general population [19]. Studies assessing the acceptance and use of digital technologies often take into account sex, gender, or age as explanatory variables. For example, the gender gap in internet use (favoring males) was approximately 1.8% in 2020 [50]. However, when splitting the sample to assess older individuals (aged 75 years or older), a gender gap of 55% (favoring males) still persists [50]. When it comes to searching health-related information on the internet or using other technologies for health purposes, females outperform males [51], although internet use for health purposes declined with age (faster in females than in males). Indeed, while people with COPD had a positive attitude toward mobile health adoption for COPD management, especially the older participants who faced difficulties using such technologies owing to their age [52], we expect that sex, gender, or age could influence the outcomes of digital technologies for COPD. However, it is unclear if and how these variables are considered in systematic reviews of digital technologies for COPD.

Strengths and Limitations

This protocol has been rigorously developed, and the electronic search syntax was iteratively tested and revised by an experienced database specialist. Nevertheless, we cannot exclude the possibility that some relevant systematic reviews in this new field may have been overlooked in our electronic search. Hence, a manual search for additional literature will be performed by screening the bibliographies of the included systematic reviews. The overview will also have further limitations. We have decided not to search the gray literature—this choice is guided by the general difficulty in assessing any financial interests associated with digital health technologies that may be present in gray literature. Our appraisal of systematic reviews will be based on AMSTAR 2 [26]. Another possible appraisal tool could be the risk of bias in systematic reviews (ROBIS), which was designed to evaluate the level of bias present within a systematic review [53]. So far, there are no clear recommendations as to which instrument is more suitable for overviews [54]. We have chosen AMSTAR 2 because the tool is easier to implement [55] and has a higher interrater reliability than ROBIS [30,56]. For the overall confidence rating required in the overview, AMSTAR 2 showed high agreement with ROBIS [30]. In addition, we will only include systematic reviews in English or German, which may further limit the relevant literature for this overview.

Implications for Practice and Dissemination Plan

Evidence from the overview could be used to guide more individualized (sex-, gender-, or age-based) recommendations for the use of digital technologies by people with COPD. Considering the rapid technological advancement in the field of digital health technologies, the findings from the overview could be of interest for various stakeholder groups, including researchers, policy makers, health professionals, people with COPD, and companies that develop digital technologies for COPD. Therefore, the dissemination plan for this overview is to publish the findings in a peer-reviewed journal and present them at scientific conferences. We will also attempt to summarize the findings using a plain-language summary designed for the nonscientific community, which can be uploaded on our research profiles on the internet.

Conclusions

There is a growing recognition that the influence of sex, gender, or age should be considered in reporting research designs and outcomes in the context of health care interventions. Our overview will help identify systematic reviews of various digital technologies for the treatment or monitoring of COPD. The most interesting aspect of the overview will be the ability to investigate if any systematic reviews considered the influence of sex, gender, or age on the outcomes of such digital technologies in COPD. Evidence from the overview could be used to guide more individualized (sex-, gender-, or age-based) recommendations for use of digital technologies by people with COPD.

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Data Availability

This overview of systematic reviews will be based on previously published data. All relevant data will be made available once the overview is complete.

Authors' Contributions

KM conceptualized the study, developed the methodology, wrote the first draft of the manuscript, and reviewed and edited the manuscript. IH conceptualized the study and reviewed and edited the manuscript. KKDS conceptualized the study, developed the methodology, and reviewed and edited the manuscript.

Conflicts of Interest

None declared.

References

1. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016 Oct 08;388(10053):1545-1602 [FREE Full text] [doi: 10.1016/S0140-6736(16)31678-6] [Medline: 27733282]
2. Mauvais-Jarvis F, Bairey Merz N, Barnes PJ, Brinton RD, Carrero J, DeMeo DL, et al. Sex and gender: modifiers of health, disease, and medicine. The Lancet 2020 Aug;396(10250):565-582. [doi: 10.1016/s0140-6736(20)31561-0]
3. Steppuhn H, Kuhnert R, Scheidt-Nave C. 12-month prevalence of known chronic obstructive pulmonary disease (COPD) in Germany. J Health Monit 2017;1(4). [doi: 10.17886/RKI-GBE-2017-065]
4. Robles PG, Brooks D, Goldstein R, Salbach N, Mathur S. Gender-associated differences in pulmonary rehabilitation outcomes in people with chronic obstructive pulmonary disease: a systematic review. J Cardiopulm Rehabil Prev 2014;34(2):87-97. [doi: 10.1097/HCR.0000000000000018] [Medline: 24280903]
5. Ntritsos G, Franek J, Belbasis L, Christou MA, Markozannes G, Altman P, et al. Gender-specific estimates of COPD prevalence: a systematic review and meta-analysis. COPD 2018 May;Volume 13:1507-1514. [doi: 10.2147/copd.s146390]
6. Somayaji R, Chalmers JD. Just breathe: a review of sex and gender in chronic lung disease. Eur Respir Rev 2022 Mar 31;31(163) [FREE Full text] [doi: 10.1183/16000617.0111-2021] [Medline: 35022256]
7. Martinez CH, Diaz AA, Parulekar AD, Rennard SI, Kanner RE, Hansel NN, COPDGeneSPIROMICS Investigators. Age-related differences in health-related quality of life in COPD: an analysis of the COPDGene and SPIROMICS cohorts. Chest 2016 Apr;149(4):927-935 [FREE Full text] [doi: 10.1016/j.chest.2015.11.025] [Medline: 26836895]
8. Aryal S, Diaz-Guzman E, Mannino DM. COPD and gender differences: an update. Transl Res 2013 Oct;162(4):208-218. [doi: 10.1016/j.trsl.2013.04.003] [Medline: 23684710]
9. DeMeo DL, Ramagopalan S, Kavati A, Vegesna A, Han MK, Yadao A, COPDGene Investigators. Women manifest more severe COPD symptoms across the life course. Int J Chron Obstruct Pulmon Dis 2018;13:3021-3029 [FREE Full text] [doi: 10.2147/COPD.S160270] [Medline: 30319250]
10. Tsiligianni I, Mezzi K, Fucile S, Kostikas K, Shen S, Banerji D, et al. Response to Indacaterol/Glycopyrronium (IND/GLY) by sex in patients with COPD: a pooled analysis from the IGNITE program. COPD 2017 Aug;14(4):375-381. [doi: 10.1080/15412555.2017.1324837] [Medline: 28594587]
11. Foreman MG, Zhang L, Murphy J, Hansel NN, Make B, Hokanson JE, COPDGene Investigators. Early-onset chronic obstructive pulmonary disease is associated with female sex, maternal factors, and African American race in the COPDGene Study. Am J Respir Crit Care Med 2011 Aug 15;184(4):414-420 [FREE Full text] [doi: 10.1164/rccm.201011-1928OC] [Medline: 21562134]

12. Lambert A, Dieter B, Barjaktarevic I, Barr R, Bhatt S, Christenson S, et al. Women with COPD experience increased symptom burden, frequent and severe exacerbation, and impaired functional capacity as compared to men in SPIROMICS. In: D23 COPD: DIAGNOSIS AND EPIDEMIOLOGY. p. A5941-A. 2019 Presented at: American Thoracic Society 2019 International Conference; May 17-22, 2019; Dallas, TX p. A5941. [doi: 10.1164/ajrccm-conference.2019.199.1_MeetingAbstracts.A5941]
13. Doull M, Welch V, Puil L, Runnels V, Coen SE, Shea B, et al. Development and evaluation of 'briefing notes' as a novel knowledge translation tool to aid the implementation of sex/gender analysis in systematic reviews: a pilot study. PLoS One 2014;9(11):e110786 [FREE Full text] [doi: 10.1371/journal.pone.0110786] [Medline: 25372876]
14. MacKinnon GE, Brittain EL. Mobile health technologies in cardiopulmonary disease. Chest 2020 Mar;157(3):654-664 [FREE Full text] [doi: 10.1016/j.chest.2019.10.015] [Medline: 31678305]
15. Fekete M, Fazekas-Pongor V, Balazs P, Tarantini S, Nemeth AN, Varga JT. Role of new digital technologies and telemedicine in pulmonary rehabilitation: smart devices in the treatment of chronic respiratory diseases. Wien Klin Wochenschr 2021 Nov;133(21-22):1201-1207 [FREE Full text] [doi: 10.1007/s00508-021-01930-y] [Medline: 34460006]
16. Bashi N, Fatehi F, Mosadeghi-Nik M, Askari MS, Karunanithi M. Digital health interventions for chronic diseases: a scoping review of evaluation frameworks. BMJ Health Care Inform 2020 Mar;27(1) [FREE Full text] [doi: 10.1136/bmjhci-2019-100066] [Medline: 32156751]
17. Hanlon P, Daines L, Campbell C, McKinstry B, Weller D, Pinnock H. Telehealth interventions to support self-management of long-term conditions: a systematic metareview of diabetes, heart failure, asthma, chronic obstructive pulmonary disease, and cancer. J Med Internet Res 2017 May 17;19(5):e172 [FREE Full text] [doi: 10.2196/jmir.6688] [Medline: 28526671]
18. Empowering the health workforce: strategies to make the most of the digital revolution. OECD. URL: https://www.oecd.org/health/health-systems/Empowering-Health-Workforce-Digital-Revolution.pdf [accessed 2022-11-09]
19. De Santis KK, Jahnel T, Sina E, Wienert J, Zeeb H. Digitization and health in Germany: cross-sectional nationwide survey. JMIR Public Health Surveill 2021 Nov 22;7(11):e32951 [FREE Full text] [doi: 10.2196/32951] [Medline: 34813493]
20. Safi S, Danzer G, Schmailzl KJ. Empirical research on acceptance of digital technologies in medicine among patients and healthy users: questionnaire study. JMIR Hum Factors 2019 Nov 29;6(4):e13472 [FREE Full text] [doi: 10.2196/13472] [Medline: 31782741]
21. Hunt H, Pollock A, Campbell P, Estcourt L, Brunton G. An introduction to overviews of reviews: planning a relevant research question and objective for an overview. Syst Rev 2018 Mar 01;7(1):39 [FREE Full text] [doi: 10.1186/s13643-018-0695-8] [Medline: 29490699]
22. De Santis KK, Lorenz RC, Lakeberg M, Matthias K. The application of AMSTAR2 in 32 overviews of systematic reviews of interventions for mental and behavioural disorders: A cross-sectional study. Res Synth Methods 2022 Jul 28;13(4):424-433. [doi: 10.1002/jrsm.1532] [Medline: 34664766]
23. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev 2021 Mar 29;10(1):89 [FREE Full text] [doi: 10.1186/s13643-021-01626-4] [Medline: 33781348]
24. Pollock M, Fernandes RM, Pieper D, Tricco AC, Gates M, Gates A, et al. Preferred Reporting Items for Overviews of Reviews (PRIOR): a protocol for development of a reporting guideline for overviews of reviews of healthcare interventions. Syst Rev 2019 Dec 23;8(1):335 [FREE Full text] [doi: 10.1186/s13643-019-1252-9] [Medline: 31870434]
25. World Health Organization. WHO guideline: recommendations on digital interventions for health system strengthening. Geneva: World Health Organization; 2018.
26. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017 Sep 21;358:j4008 [FREE Full text] [doi: 10.1136/bmj.j4008] [Medline: 28935701]
27. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. J Clin Epidemiol 2016 Jul;75:40-46 [FREE Full text] [doi: 10.1016/j.jclinepi.2016.01.021] [Medline: 27005575]
28. Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, PRISMA-S Group. PRISMA-S: an extension to the PRISMA statement for reporting literature searches in systematic reviews. Syst Rev 2021 Jan 26;10(1):39 [FREE Full text] [doi: 10.1186/s13643-020-01542-z] [Medline: 33499930]
29. Shojania KG, Bero LA. Taking advantage of the explosion of systematic reviews: an efficient MEDLINE search strategy. Eff Clin Pract 2001;4(4):157-162. [Medline: 11525102]
30. Lorenz RC, Matthias K, Pieper D, Wegewitz U, Morche J, Nocon M, et al. A psychometric study found AMSTAR 2 to be a valid and moderately reliable appraisal tool. J Clin Epidemiol 2019 Oct;114:133-140. [doi: 10.1016/j.jclinepi.2019.05.028] [Medline: 31152864]
31. De Santis KK, Jahnel T, Mergenthal L, Zeeb H, Matthias K. Evaluation of digital interventions for physical activity promotion: protocol for a scoping review. JMIR Res Protoc 2022 Mar 3;11(3):e35332. [doi: 10.2196/35332]
32. Lunny C, Pieper D, Thabet P, Kanji S. Managing overlap of primary study results across systematic reviews: practical considerations for authors of overviews of reviews. BMC Med Res Methodol 2021 Jul 07;21(1):140 [FREE Full text] [doi: 10.1186/s12874-021-01269-y] [Medline: 34233615]

33. Pérez-Bracchiglione J, Meza N, Bangdiwala SI, Niño de Guzmán E, Urrútia G, Bonfill X, et al. Graphical Representation of Overlap for OVErviews: GROOVE tool. Res Synth Methods 2022 May;13(3):381-388. [doi: 10.1002/jrsm.1557] [Medline: 35278030]
34. Heidari S, Babor TF, De Castro P, Tort S, Curno M. Sex and gender equity in research: rationale for the SAGER guidelines and recommended use. Res Integr Peer Rev 2016;1:2 [FREE Full text] [doi: 10.1186/s41073-016-0007-6] [Medline: 29451543]
35. Goldkuhle M, Narayan VM, Weigl A, Dahm P, Skoetz N. A systematic assessment of Cochrane reviews and systematic reviews published in high-impact medical journals related to cancer. BMJ Open 2018 Mar 25;8(3):e020869 [FREE Full text] [doi: 10.1136/bmjopen-2017-020869] [Medline: 29581210]
36. Tannenbaum C, Greaves L, Graham ID. Why sex and gender matter in implementation research. BMC Med Res Methodol 2016 Oct 27;16(1):145 [FREE Full text] [doi: 10.1186/s12874-016-0247-7] [Medline: 27788671]
37. Gogovor A, Mollayeva T, Etherington C, Colantonio A, Légaré F, GIKT Group. Sex and gender analysis in knowledge translation interventions: challenges and solutions. Health Res Policy Syst 2020 Sep 23;18(1):108 [FREE Full text] [doi: 10.1186/s12961-020-00625-6] [Medline: 32967674]
38. Gogovor A, Zomahoun HTV, Ekanmian G, Adisso É, Deom Tardif A, Khadhraoui L, et al. Sex and gender considerations in reporting guidelines for health research: a systematic review. Biol Sex Differ 2021 Nov 20;12(1):62 [FREE Full text] [doi: 10.1186/s13293-021-00404-0] [Medline: 34801060]
39. Schiebinger L, Leopold SS, Miller VM. Editorial policies for sex and gender analysis. Lancet 2016 Dec 10;388(10062):2841-2842. [doi: 10.1016/S0140-6736(16)32392-3] [Medline: 27979394]
40. Petticrew M, Tugwell P, Kristjansson E, Oliver S, Ueffing E, Welch V. Damned if you do, damned if you don't: subgroup analysis and equity. J Epidemiol Community Health 2012 Jan;66(1):95-98. [doi: 10.1136/jech.2010.121095] [Medline: 21652518]
41. Oxman AD, Lavis JN, Lewin S, Fretheim A. SUPPORT Tools for evidence-informed health policymaking (STP) 10: taking equity into consideration when assessing the findings of a systematic review. Health Res Policy Syst 2009 Dec 16;7 Suppl 1:S10 [FREE Full text] [doi: 10.1186/1478-4505-7-S1-S10] [Medline: 20018100]
42. Antequera A, Stallings E, Henry RS, Lopez-Alcalde J, Runnels V, Tudiver S, et al. Sex and gender appraisal tool-systematic reviews-2 and participation-to-prevalence ratio assessed to whom the evidence applies in sepsis reviews. J Clin Epidemiol 2022 Feb;142:119-132. [doi: 10.1016/j.jclinepi.2021.11.006] [Medline: 34763038]
43. Doull M, Runnels VE, Tudiver S, Boscoe M. Appraising the evidence: applying sex- and gender-based analysis (SGBA) to Cochrane systematic reviews on cardiovascular diseases. J Womens Health (Larchmt) 2010 May;19(5):997-1003. [doi: 10.1089/jwh.2009.1626] [Medline: 20384450]
44. Petkovic J, Trawin J, Dewidar O, Yoganathan M, Tugwell P, Welch V. Sex/gender reporting and analysis in Campbell and Cochrane systematic reviews: a cross-sectional methods study. Syst Rev 2018 Aug 2;7(1). [doi: 10.1186/s13643-018-0778-6]
45. López-Alcalde J, Stallings E, Cabir Nunes S, Fernández Chávez A, Daheron M, Bonfill Cosp X, et al. Consideration of sex and gender in Cochrane reviews of interventions for preventing healthcare-associated infections: a methodology study. BMC Health Serv Res 2019 Mar 15;19(1):169 [FREE Full text] [doi: 10.1186/s12913-019-4001-9] [Medline: 30876452]
46. Adisso É, Zomahoun HTV, Gogovor A, Légaré F. Sex and gender considerations in implementation interventions to promote shared decision making: a secondary analysis of a Cochrane systematic review. PLoS One 2020;15(10):e0240371 [FREE Full text] [doi: 10.1371/journal.pone.0240371] [Medline: 33031475]
47. Safiri S, Carson-Chahhoud K, Noori M, Nejadghaderi SA, Sullman MJM, Ahmadian Heris J, et al. Burden of chronic obstructive pulmonary disease and its attributable risk factors in 204 countries and territories, 1990-2019: results from the Global Burden of Disease Study 2019. BMJ 2022 Jul 27;378:e069679 [FREE Full text] [doi: 10.1136/bmj-2021-069679] [Medline: 35896191]
48. Nastars DR, Rojas JD, Ottenbacher KJ, Graham JE. Race/ethnicity and 30-day readmission rates in Medicare beneficiaries with COPD. Respir Care 2019 Aug;64(8):931-936 [FREE Full text] [doi: 10.4187/respcare.06475] [Medline: 30914490]
49. Jones PW, Gelhorn H, Wilson H, Benson VS, Karlsson N, Menjoge S, et al. Socioeconomic status as a determinant of health status treatment response in COPD trials. Chronic Obstr Pulm Dis 2017 Apr 01;4(2):150-158 [FREE Full text] [doi: 10.15326/jcopdf.4.2.2017.0132] [Medline: 28848924]
50. Garín-Muñoz T, Pérez-Amaral T, Valarezo Á. Evolution of the internet gender gaps in Spain and effects of the Covid-19 pandemic. Telecomm Policy 2022 Sep;46(8):102371 [FREE Full text] [doi: 10.1016/j.telpol.2022.102371] [Medline: 35542497]
51. Alvarez-Galvez J, Salinas-Perez JA, Montagni I, Salvador-Carulla L. The persistence of digital divides in the use of health information: a comparative study in 28 European countries. Int J Public Health 2020 Apr;65(3):325-333. [doi: 10.1007/s00038-020-01363-w] [Medline: 32277246]
52. Alwashmi MF, Fitzpatrick B, Farrell J, Gamble J, Davis E, Nguyen HV, et al. Perceptions of patients regarding mobile health interventions for the management of chronic obstructive pulmonary disease: mixed methods study. JMIR Mhealth Uhealth 2020 Jul 23;8(7):e17409 [FREE Full text] [doi: 10.2196/17409] [Medline: 32706697]

53. Whiting P, Savović J, Higgins JPT, Caldwell DM, Reeves BC, Shea B, ROBIS group. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol 2016 Jan;69:225-234 [FREE Full text] [doi: 10.1016/j.jclinepi.2015.06.005] [Medline: 26092286]
54. Hennessy EA, Johnson BT, Keenan C. Best practice guidelines and essential methodological steps to conduct rigorous and systematic meta-reviews. Appl Psychol Health Well Being 2019 Nov;11(3):353-381 [FREE Full text] [doi: 10.1111/aphw.12169] [Medline: 31290288]
55. Perry R, Whitmarsh A, Leach V, Davies P. A comparison of two assessment tools used in overviews of systematic reviews: ROBIS versus AMSTAR-2. Syst Rev 2021 Oct 25;10(1):273 [FREE Full text] [doi: 10.1186/s13643-021-01819-x] [Medline: 34696810]
56. Pieper D, Puljak L, González-Lorenzo M, Minozzi S. Minor differences were found between AMSTAR 2 and ROBIS in the assessment of systematic reviews including both randomized and nonrandomized studies. J Clin Epidemiol 2019 Apr;108:26-33. [doi: 10.1016/j.jclinepi.2018.12.004] [Medline: 30543911]

Abbreviations

AMSTAR2: A Measurement Tool to Assess Systematic Reviews, version 2
CCA: corrected covered area
COPD: chronic obstructive pulmonary disease
PICOS: population, intervention, comparison, outcomes, and study design
PRIOR: Preferred Reporting Items for Overviews of Reviews
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Registry of Systematic Reviews
RCT: randomized controlled trial
ROBIS: risk of bias in systematic reviews

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Protocol

The National and Global Impact of Systemic and Structural Violence on the Effective Prevention, Treatment, and Management of COVID-19 in African or Black Communities: Protocol for a Scoping Review

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Abstract

Background: As COVID-19 ravages the globe and cases increase rapidly, countries are presented with challenging policy choices to contain and mitigate its spread. In Canada and globally, the COVID-19 pandemic has added a new stratum to the debate concerning the root causes of global and racial health inequities and disparities. Individuals who exist as targets of systemic inequities are not only more susceptible to contracting COVID-19, but also more likely to bear the greatest social, economic, and physical burdens. Therefore, data collection that focuses on the impact of COVID-19 on the lives and health of African/Black communities worldwide is needed to develop intersectional, culturally relative, antiracist/antioppression, and empowerment-centered interventions and social policies for supporting affected communities.

Objective: The primary objective of this review is to investigate the impact and management of COVID-19 among African/Black individuals and communities, and understand how anti-Black racism and intersectional violence impact the health of African/Black communities during the pandemic. Moreover, the study aims to explore research pertaining to the impact of COVID-19 on Black communities in the global context. We seek to determine how Black communities are impacted with regard to structural violence, systematic racism, and health outcomes, and the ways in which attempts have been made to mitigate or manage the consequences of the pandemic and other injurious agents.

Methods: A systematic search of quantitative and qualitative studies published on COVID-19 will be conducted in MEDLINE (Ovid), Embase (Ovid), Cumulative Index to Nursing and Allied Health Literature (EBSCO), Cochrane Library, PsychInfo (Ovid), CAB Abstracts (Ovid), Scopus (Elsevier), Web of Science (Clarivate), and Global Index Medicus. To be included in the review, studies should present data on COVID-19 in relation to African/Black individuals, populations, and communities in the global sphere. Studies must discuss racism, oppression, antioppression, or systemic and structural violence and be published in English, French, Spanish, or Portuguese. According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews guidelines, the findings will be synthesized quantitatively and qualitatively through thematic analysis. The risk of bias will not be assessed.

Results: Title, abstract, and full-text screening concluded in June 2022. Data collection is in progress and is expected to be completed by December 2022. Data analysis and drafting of the manuscript will be done thereafter. Findings from the scoping review are expected to be provided for peer review in 2023.

Conclusions: This review will collect important data and evidence related to COVID-19 in African/Black communities. The findings could help identify existing gaps in COVID-19 management in African/Black communities and inform future research

paradigms. Furthermore, the findings could be applied to decision-making for health policy and promotion, and could potentially influence services provided by health care facilities and community organizations around the globe.

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KEYWORDS

African; Black people; COVID-19; systemic and structural barriers; health disparities; minority health; racism; racial health inequity; structural violence; anti-Black racism; decolonizing; resistance; social justice

Introduction

As SARS-CoV-2 ravaged the globe and the number of cases increased rapidly, countries were presented with challenging policy choices to contain the spread of COVID-19. Although this was a global effort, each country had a different response to the pandemic. For example, some countries, such as China and South Africa, elected to immediately close the national economy and apply strict and punishable rules regarding traditional public health measures (eg, social distancing, masking, isolation, and quarantine) [1]. In contrast, other countries, including the United States, opted for more loose public health recommendations. Although research has found that public health interventions and nonpharmaceutical control measures are effective in mitigating transmission of COVID-19, the differential timing of lockdown measures, including closing nonessential industries and limiting in-person capacity, may have significant social and economic implications [2,3]. One of the potential concerns is how the COVID-19 pandemic has differentially affected populations, as it appears that the burden of these interventions was not equal. The COVID-19 pandemic has created a wave of panic across the world. According to John Hopkins University, COVID-19 has taken the life of 4,310,354 people across the globe, with 26,633 deaths in Canada alone as of August 10, 2021 [4]. The COVID-19 pandemic has added a new stratum to the debate concerning the root causes of racial health disparities. The effects of COVID-19 have been shown to be linked to structural violence and racism [5]. The British and American governments have acknowledged that large proportions of their COVID-19 cases and deaths are among individuals of African descent. Due to the discrimination and oppression experienced by racialized groups, such as Black communities, it was reported that in England, Black people were more than 4 times likely to die from COVID-19 than their White counterparts [5,6]. Similarly, an analysis by the Washington Post reported that in the United States, counties where Black residents were in majority had 3 times the rate of COVID-19 infection and almost 6 times the rate of deaths compared with counties where White residents were in majority [7].

Multiple researchers have misattributed the morbidity and mortality disparities observed in England and America to the high prevalence of chronic diseases in Black communities [8,9]. Multinational data have reported poor outcomes for individuals aged over 65 years or with underlying health conditions, including diabetes, heart disease, asthma, and compromised immune systems [10].

The association between COVID-19 and pre-existing illness is especially troubling for Black individuals who are genetically misconceived as more likely to develop chronic comorbidities because they are Black [11].

Many social determinants of health, including anti-Black racism, intersectional violence (including sexism, heterosexism, classism, ageism, refugee status, etc), poverty, physical environment (eg, smoke exposure and homelessness), and race and ethnicity, can have a considerable effect on COVID-19 outcomes. Homeless families are at higher risk of viral transmission because of crowded living spaces and scarce access to COVID-19 screening and testing facilities [12].

Individuals who exist as targets of systemic inequities are not only more susceptible to contracting COVID-19, but also more likely to bear the greatest extent of the subsequent economic pandemic [13].

There is a need for data collection that specifically focuses on the impact of COVID-19 on the lives and health of African/Black communities across the globe in order to develop intersectional, culturally relative, antiracist/antioppression, and empowerment-centered interventions and social policies that support heterogeneous African/Black communities during and after the COVID-19 pandemic.

The collection of race-based data on COVID-19 is important to understand the impact of COVID-19 on the lives of African/Black people and its historical and current day context [14].

In most African countries, the response to the COVID-19 pandemic has been challenging due to continued colonial impacts, which lead to distrust in the government, and social, cultural, and religious resistance [15]. The COVID-19 global pandemic has exposed the world inequities and the racially based colonial demarcations with the North/South as the main geographical and sociological anchors [16]. In Brazil, the failure of the neoliberal government to protect the Black and Indigenous populations mostly exposed to COVID-19, has created the emergence of a new form of solidarity and mutual aid in “favelas” and Indigenous communities [17].

Standard systematic reviews and scoping reviews are different; scoping reviews investigate broad topics as opposed to a specific well-defined question. In the context of this paper, this review will assess the impact of COVID-19 on African/Black communities across the globe. The purpose of this scoping review is to employ a decolonizing, African feminist, Black resistance lens to examine the impact of COVID-19 on heterogeneous and intersectional Black communities throughout

the world, while also exploring the various forms of resistance that Black communities have established and employed during the global pandemic. Therefore, this review will attempt to answer the question of how COVID-19 is impacting African/Black communities, and what interventions are effective to prevent, treat, and reduce the impact of COVID-19 on these communities?

The primary objectives are to (1) investigate the impact of COVID-19 on African/Black individuals and communities; (2) explore how systemic and structural violence are barriers to the effective prevention, treatment, and management of COVID-19 in the African/Black population; and (3) understand how anti-Black racism and intersectional violence (violence related to race, gender, sexual orientation, gender identity, age, disabilities, language, educational attainment, immigration status, and social determinants of health) impact the health of African/Black communities during the COVID-19 pandemic. The secondary objective of the review is to identify intervention strategies to respond effectively to the impact of COVID-19 on African/Black individuals, communities, front-line health service workers, and essential service workers in Canada and transnationally.

Methods

Approach

A scoping review methodology has been selected as it can help to (1) identify review parameters, (2) identify a process of mapping the existing literature, and (3) explore a research gap [18].

The methodological framework as described by Arksey and O'Malley, and later advanced by Levac et al will be applied and followed in developing and disseminating this scoping review [19,20]. The scoping review approach will also endeavor to include recommendations by Peterson that are appropriate for policy change, education, and research purposes [21]. The protocol has been drafted with the intention to align with the reporting guidance provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist (Multimedia Appendix 1) [22-24]. This framework recommends organizing the scoping review in a 6-stage process that includes but is not limited to (1) identifying the research question; (2) identifying relevant studies; (3) selecting studies; (4) charting the data; (5) collating, summarizing, and reporting the results; and (6) consulting with relevant stakeholders and key informants.

Identifying the Research Question

The research question was developed in response to a knowledge gap in the literature surrounding the health of Black people in relation to the COVID-19 pandemic, and revised periodically with significant input from the principal investigator. The following research question was identified and guided the scoping review and effective search strategy: How is COVID-19 impacting African/Black communities nationally and globally, and what interventions are effective to prevent, treat, and reduce the impact of COVID-19 on these communities?

Identifying Relevant Studies

An expert liaison and education librarian familiar with systematic and scoping review processes was enlisted to assist with devising the search strategy and other essential resources. The research team conducted a preliminary assessment of a variety of electronic databases independently, such as PubMed and Google Scholar, using search terms associated with the domains of interest. Reference lists of articles deemed relevant were scanned much like their titles and abstracts, which culminated in many articles. On that basis, keywords were collected and used in the search strategy, and we found a need to expand the geographic inclusion beyond Canada.

To that extent, a comprehensive systematic search was developed and employed in multiple electronic databases: MEDLINE (Ovid), Embase (Ovid), Cumulative Index to Nursing and Allied Health Literature (EBSCO), Cochrane Library, APA PsychInfo (Ovid), CAB Abstracts (Ovid), Scopus (Elsevier), Web of Science (Clarivate), and Global Index Medicus. This electronic search strategy was developed by a health science librarian (JM) and was peer reviewed according to the peer review of electronic search strategies (PRESS) guidelines [25]. The literature search systematically searched the published literature of quantitative and qualitative studies published since the beginning of COVID-19 in December 2019, and will be documented in accordance with the PRISMA-ScR checklist [23].

Types of Studies

Experimental (randomized or nonrandomized), observational (longitudinal or cross-sectional), qualitative, and mixed methods studies will be considered for this review.

Eligibility Criteria

To be included in the review, studies should include data on COVID-19 in relation to African/Black individuals, populations, and communities, no matter the geographical status. The studies must discuss racism, oppression, antioppression, or systemic and structural violence, and be published in English, French, Spanish, or Portuguese. The research team includes members who are fluent in the aforementioned languages and will independently assess study articles to ensure relevant data can be extracted. Additionally, if non-English articles provide an English translation, this will be accepted so long as other criteria are met. Screening will be conducted to filter out studies based on their publication date and language. In particular, studies published between December 2019 and August 2021 will be included for review. Review papers (eg, scoping reviews, systematic reviews, and rapid reviews), reports, book chapters, and conference abstracts will be excluded from the review.

Outcomes

With regard to the primary outcomes of this scoping review, we will (1) evaluate COVID-19 prevention, infection, testing, comorbidity and mortality, and interventions in African/Black individuals and communities, as well as the global impact on these communities; (2) investigate the effect of systemic and structural barriers on the prevention, treatment, and management of COVID-19 in a population that has been reported to experience significantly higher COVID-19 complications and

negative outcomes; and (3) evaluate the impacts of social determinants of health and the intersections of dimensions, such as gender, sexual orientation, gender identity, age, disabilities, language, educational attainment, and immigration status, on COVID-19 in African/Black communities.

With regard to the secondary outcomes, we will assess (1) the resistance of African/Black communities in relation to the structural barriers that they face in the context of COVID-19 and (2) the population-based intervention strategies and tools to better prevent, treat, and manage COVID-19 in African/Black individuals and communities globally.

The search strategy can be found in Table 1, and it includes the concepts COVID-19, Black people, and racism. The search strategies for all the databases are detailed in Multimedia Appendix 2 and can also be found online [26].

Table 1. Proposed search strategy for MEDLINE (search on August 4, 2021).

#	Search	Results, n
1	exp Coronavirus/	87,181
2	exp Coronavirus Infections/	106,533
3	(coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars$coronavirus* or Severe Acute Respiratory Syndrome Coronavirus* or 2019$nCov or Severe Acute Respiratory Syndrome Corona Virus).tw,kf,ot.	173,610
4	((novel or new or nouveau) adj2 (CoV or nCoV or covid* or coronavirus* or corona virus or Pandemi*)).tw,kf,ot.	14,611
5	((Wuhan or Hubei) adj5 pneumonia).tw,kf,ot.	355
6	((new or novel or “19” or “2019” or Wuhan or Hubei or China or Chinese) adj3 (coronavirus* or corona virus* or betacoronavirus* or CoV or HCoV)).tw,kf,ot.	48,596
7	((coronavirus* or corona virus* or betacoronavirus*) adj3 (pandemic* or epidemic* or outbreak* or crisis)).tw,kf,ot.	8997
8	1 or 2 or 3 or 4 or 5 or 6 or 7	185,346
9	limit 8 to yr=“2019 -Current”	166,753
10	exp african continental ancestry group/ or ethnic groups/	150,584
11	Minority Groups/	15,130
12	Minority Health/	839
13	(people of colo$r or person* of colo$r or POC or BAME or BIPOC or ((african* or afro*) adj5 (americ* or canad* or asia* or caribbean* or australi* or european* or brazil* or minorit* or refugee or migrant* or immigrant* or ancest* or native* or hispanic* or latin* or indigenous* or diaspora* or communit* or descen* or provider* or nurse* or doctor* or worker* or service user* or patient* or front line* or frontline* or people* or man or men or wom$n or race or population* or person* or individual* or group* or female* or male*))).tw,kf.	97,176
14	((black or blacks) adj5 (americ* or canad* or asia* or caribbean* or australi* or european* or brazil* or minorit* or refugee or migrant* or immigrant* or ancest* or native* or hispanic* or latin* or indigenous* or diaspora* or communit* or descen* or provider* or nurse* or doctor* or worker* or service user* or patient* or front line* or frontline* or people* or man or men or wom$n or race or population* or person* or individual* or group* or female* or male*)).tw,kf.	57,326
15	(((ethnic* or racial* or race) adj5 (group* or minorit* or disparit* or divers* or equal* or inequal* or discriminat*)) or mixed race or mixed racial* or multi racial* or mutli race or multiracial* or multirace).tw,kf.	87,613
16	10 or 11 or 12 or 13 or 14 or 15	286,281
17	prejudice/ or racism/	28,679
18	(racism or racist* or racial* or anti-black* or antiblack* or structural violence* or systemic violence*).tw,kf.	54,130
19	(white supremac* or white hegemon*).tw,kf.	95
20	(prejudice* or discriminat* or intolerance* or oppress* or bias* or hostil*).tw,kf.	550,272
21	((structur* or institution* or systemic or systematic* or generational* or intersect* or health*) adj5 (violence* or polic* or barrier* or disparit* or inequalit* or trauma)).tw,kf.	145,097
22	(decoloni* or de coloni* or anti oppress* or antioppress*).tw,kf.	1798
23	17 or 18 or 19 or 20 or 21 or 22	744,913
24	9 and 16 and 23	1349

Study Selection

Search results will be deduplicated in EndNote before being uploaded to Covidence (JM), an online program that facilitates screening and data extraction [27].

Two reviewers will pilot test a screening form customized to reflect the aforementioned inclusion criteria. This screening form will be generated and used by 2 independent reviewers. A subset of records will be used as a sample to establish consistency of use and clarity of the instrument before its implementation. The Cohen kappa statistic will be estimated to measure interrater reliability, and screening will begin when 90% agreement is achieved [28].

With regard to study selection, initially, we will conduct title and abstract screening. Once an article is seen as potentially relevant, we will retrieve and screen the full text in detail. This occurs prior to data extraction. In duplicate, the authors RCS and PD will conduct all screening, data extraction, and quality assessment procedures. Disagreements will be resolved by consensus. If consensus cannot be reached, a third author (RT) will arbitrate.

The reference lists of all relevant citations will be searched for available related articles. We will search for available theses and conference posters. Furthermore, experts, authors, and relevant organizations will be contacted.

Charting the Data

For the purpose of this scoping review, we will extract bibliometric information, such as author names, journal, and year of publication, in addition to the location of the study, study design, number of participants, outcomes reported, and outcome measures. We will report where possible measures of the effect of the outcome on African/Black people with respect to COVID-19. We will not report measures of magnitude, such as mean (SD) and percentage (95% CI), or extract data, such as odds or risk ratios and mean differences.

Collating, Summarizing, and Reporting the Results

Our findings will be reported according to the PRISMA-ScR guidelines [23,29,30]. Our findings will be summarized narratively and using tables. Data will be grouped by outcomes, with the number of studies, their design, and their methodological quality. The key findings of each study will also be summarized using tables. We will conduct a narrative synthesis of the data to identify common themes and knowledge gaps. Since the review explores a variety of geographical regions across the globe, the results will be categorically interpreted based on common geographical demarcations (ie, North America, Latin America, Europe, Africa, Middle East, and Caribbean), grouped thematically, and compared. Similarly, data presentation will also include visualization on a geographical map to report the number of publications across the globe.

Throughout the reporting phase, we will follow the recommendations of the PRISMA-ScR guidelines when writing up the final review. Abstracted information from all the included articles will be synthesized, and the results will be presented to capture the extent of the literature. First, tables will provide basic information on the included articles, such as study characteristics, methodological quality, major findings, and the pedagogical and theoretical or conceptual approach used in the design. This overview will be followed by a narrative presentation of the synthesized mapping of the included literature. We will then report the output with an emphasis on describing how the findings relate to the research questions guiding the scoping review before discussing the implications for policy and practice in the realm of the health and well-being of Black people.

Consistent with the guidance on conducting scoping reviews, we will not assess the methodological quality or risk of bias of the included articles. Our goal is to provide an overview of the existing evidence and gap regardless of study quality.

Consultation With Stakeholders

Patients are not involved in the design of the scoping review. Experts in the health and well-being of Black people may be consulted for informing the scoping review and disseminating research findings during presentation, but this is not expected.

Ethical Considerations

Ethics approval is not required as secondary published data will be used.

Results

This project started in August 2021 with the development of the search strategy and literature search. As of June 2022, the study team has completed title, abstract, and full-text screening of imported citations. Data collection is in progress and is expected to be completed by December 2022. Data analysis and drafting of the manuscript will be done thereafter, with expected publication in 2023. All data generated or analyzed during this study will be included in the published article and its supplementary information files.

Discussion

Overview

The primary goal of this review is to investigate the global impact of COVID-19 on African/Black individuals and communities, and explore how systemic and structural violence are barriers to the effective prevention, treatment, and management of COVID-19 in these communities.

The global COVID-19 pandemic is still occurring more than a year after its initial emergence in late December 2019. Published studies highlight the inequity and disparity in COVID-19 infections and deaths. Data collected globally and research data indicate that African and Black populations are more likely to contract and die from COVID-19 [5,6,9,31].

Anti-Black racism and colonial institutions contribute to disparities in access to health care, employment, education, housing, and physical environments, and food insecurity [32,33]. These determinants have been shown to have an impact on COVID-19 infection [14,16,34]. Through this scoping review, we will employ a decolonizing, African feminist, Black resistance lens to investigate the impact of COVID-19 on

heterogeneous and intersectional Black communities in Canada and throughout the world. We will also explore the various forms of resistance that Black communities have established and employed during the global COVID-19 pandemic.

Our findings will be disseminated as peer-reviewed manuscripts and at conferences and student rounds, and could be of interest to government health agencies and organizations serving African/Black communities.

Strengths

The exhaustive search strategy across numerous global databases is one of the strengths of this review. Another strength is the innovative research topic that examines the global impact of COVID-19 on African/Black communities.

Limitations

One limitation of this scoping review is the wide range of inclusion criteria. Thus, the hand-searching of the literature by the research team could lead to personal interpretation of the criteria. Furthermore, the search was not translated into the 4 inclusion languages, and studies could be missed because of this. Moreover, it is generally understood that scoping reviews are not intended to be exhaustive, especially compared to systematic reviews and meta-analyses [35]. Still, the lack of critical appraisal and possibility of missing relevant studies have been reported as key challenges in conducting scoping reviews [36,37]. However, a narrative synthesis was found to be appropriate, which is both widely used and recommended in guidelines for scoping reviews. Another limitation to consider is associated with the differences and nuances in terminology across languages and regions. For example, systemic and structural racism may be described differently in different native languages using different terms. This may lead to a bias due to the lack of sufficient locally published articles in non-English journals in this review.

Implications

This review will collect important data and evidence on African/Black communities related to COVID-19. Most importantly, the findings of this review could be used in decision-making for health policy and promotion, and could influence the services provided by health care facilities and community organizations around the globe that serve individuals from African and Black communities and help mitigate COVID-19 risk and ameliorate health outcomes and trajectories. In addition, the findings could offer guidance for future initiatives and emerging needs.

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Authors' Contributions

The review was conceived by RT. All authors revised the research question and provided content to the design. The manuscript was written and edited by PD, RT, RACS, and JM. The principal investigator of the study is RT. All authors read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist.
[PDF File (Adobe PDF File), 535 KB - resprot_v11i10e40381_app1.pdf]

Multimedia Appendix 2
Detailed search strategies for all databases.
[PDF File (Adobe PDF File), 186 KB - resprot_v11i10e40381_app2.pdf]

References

1. Arndt C, Davies R, Gabriel S, Harris L, Makrelov K, Robinson S, et al. Covid-19 lockdowns, income distribution, and food security: An analysis for South Africa. Glob Food Sec 2020 Sep;26:100410 [FREE Full text] [doi: 10.1016/j.gfs.2020.100410] [Medline: 32834955]
2. Ayouni I, Maatoug J, Dhouib W, Zammit N, Fredj SB, Ghammam R, et al. Effective public health measures to mitigate the spread of COVID-19: a systematic review. BMC Public Health 2021 May 29;21(1):1015 [FREE Full text] [doi: 10.1186/s12889-021-11111-1] [Medline: 34051769]
3. Coibion O, Gorodnichenko Y, Weber M. The Cost of the Covid-19 Crisis: Lockdowns, Macroeconomic Expectations, and Consumer Spending. National Bureau of Economic Research. 2020. URL: https://www.nber.org/papers/w27141 [accessed 2022-10-10]
4. Coronavirus Resource Center. Johns Hopkins University. URL: https://coronavirus.jhu.edu/map.html [accessed 2021-08-10]

5. Khunti K, Singh AK, Pareek M, Hanif W. Is ethnicity linked to incidence or outcomes of covid-19? BMJ 2020 Apr 20;369:m1548. [doi: 10.1136/bmj.m1548] [Medline: 32312785]
6. Patel P, Hiam L, Sowemimo A, Devakumar D, McKee M. Ethnicity and covid-19. BMJ 2020 Jun 11;369:m2282. [doi: 10.1136/bmj.m2282] [Medline: 32527732]
7. Thebault R, Tran A, Williams V. The coronavirus is infecting and killing black Americans at an alarmingly high rate. Washington Post. 2020. URL: https://www.washingtonpost.com/nation/2020/04/07/coronavirus-is-infecting-killing-black-americans-an-alarmingly-high-rate-post-analysis-shows/ [accessed 2022-10-10]
8. Williamson E, Walker A, Bhaskaran K, Bacon S, Bates C, Morton C, et al. OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. MedRxiv. 2020. URL: https://www.medrxiv.org/content/10.1101/2020.05.06.20092999v1 [accessed 2022-10-10]
9. Aldridge RW, Lewer D, Katikireddi SV, Mathur R, Pathak N, Burns R, et al. Black, Asian and Minority Ethnic groups in England are at increased risk of death from COVID-19: indirect standardisation of NHS mortality data. Wellcome Open Res 2020 Jun 24;5:88 [FREE Full text] [doi: 10.12688/wellcomeopenres.15922.2] [Medline: 32613083]
10. Coronavirus disease 2019 (COVID-19) : situation report, 86. World Health Organization. 2020. URL: https://apps.who.int/iris/handle/10665/331784 [accessed 2022-10-10]
11. Etowa J, Hyman I. Unpacking the health and social consequences of COVID-19 through a race, migration and gender lens. Can J Public Health 2021 Feb 06;112(1):8-11 [FREE Full text] [doi: 10.17269/s41997-020-00456-6] [Medline: 33410121]
12. Abrams EM, Szefler SJ. COVID-19 and the impact of social determinants of health. Lancet Respir Med 2020 Jul;8(7):659-661 [FREE Full text] [doi: 10.1016/S2213-2600(20)30234-4] [Medline: 32437646]
13. Ruiz N, Horowitz J, Tamir C. Many Black and Asian Americans Say They Have Experienced Discrimination Amid the COVID-19 Outbreak. Pew Research Center. 2020. URL: https://www.pewresearch.org/social-trends/2020/07/01/many-black-and-asian-americans-say-they-have-experienced-discrimination-amid-the-covid-19-outbreak/ [accessed 2022-10-10]
14. Racial Data Transparency-The Demographics of COVID. Johns Hopkins University. URL: https://coronavirus.jhu.edu/data/racial-data-transparency [accessed 2022-10-10]
15. Adebisi YA, Rabe A, Lucero-Prisno Iii DE. Risk communication and community engagement strategies for COVID-19 in 13 African countries. Health Promot Perspect 2021;11(2):137-147 [FREE Full text] [doi: 10.34172/hpp.2021.18] [Medline: 34195037]
16. Oliveira RGD, Cunha APD, Gadelha AGDS, Carpio CG, Oliveira RBD, Corrêa RM. Racial inequalities and death on the horizon: COVID-19 and structural racism. Cad Saude Publica 2020;36(9):e00150120 [FREE Full text] [doi: 10.1590/0102-311X00150120] [Medline: 32965376]
17. Ortega F, Orsini M. Governing COVID-19 without government in Brazil: Ignorance, neoliberal authoritarianism, and the collapse of public health leadership. Glob Public Health 2020 Sep;15(9):1257-1277. [doi: 10.1080/17441692.2020.1795223] [Medline: 32663117]
18. Pham MT, Rajić A, Greig JD, Sargeant JM, Papadopoulos A, McEwen SA. A scoping review of scoping reviews: advancing the approach and enhancing the consistency. Res Synth Methods 2014 Dec;5(4):371-385 [FREE Full text] [doi: 10.1002/jrsm.1123] [Medline: 26052958]
19. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. International Journal of Social Research Methodology 2005 Feb;8(1):19-32. [doi: 10.1080/1364557032000119616]
20. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implement Sci 2010 Sep 20;5:69 [FREE Full text] [doi: 10.1186/1748-5908-5-69] [Medline: 20854677]
21. Peterson J, Pearce PF, Ferguson LA, Langford CA. Understanding scoping reviews: Definition, purpose, and process. J Am Assoc Nurse Pract 2017 Jan;29(1):12-16. [doi: 10.1002/2327-6924.12380] [Medline: 27245885]
22. Sarkis-Onofre R, Catalá-López F, Aromataris E, Lockwood C. How to properly use the PRISMA Statement. Syst Rev 2021 Apr 19;10(1):117 [FREE Full text] [doi: 10.1186/s13643-021-01671-z] [Medline: 33875004]
23. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med 2018 Oct 02;169(7):467-473 [FREE Full text] [doi: 10.7326/M18-0850] [Medline: 30178033]
24. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015 Jan 01;4:1 [FREE Full text] [doi: 10.1186/2046-4053-4-1] [Medline: 25554246]
25. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016 Jul;75:40-46 [FREE Full text] [doi: 10.1016/j.jclinepi.2016.01.021] [Medline: 27005575]
26. Search strategy replication data. Borealis-University of Toronto Dataverse. URL: https://borealisdata.ca/dataset.xhtml?persistentId=doi:10.5683/SP3/LKMEOO [accessed 2022-10-11]
27. Covidence. URL: https://www.covidence.org/ [accessed 2022-10-10]
28. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. Fam Med 2005 May;37(5):360-363 [FREE Full text] [Medline: 15883903]

29. Bernardo WM. PRISMA statement and PROSPERO. Int Braz J Urol 2017;43(3):383-384 [FREE Full text] [doi: 10.1590/S1677-5538.IBJU.2017.03.02] [Medline: 28520335]
30. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000 Apr 19;283(15):2008-2012. [doi: 10.1001/jama.283.15.2008] [Medline: 10789670]
31. Phiri P, Delanerolle G, Al-Sudani A, Rathod S. COVID-19 and Black, Asian, and Minority Ethnic Communities: A Complex Relationship Without Just Cause. JMIR Public Health Surveill 2021 Feb 01;7(2):e22581 [FREE Full text] [doi: 10.2196/22581] [Medline: 33481752]
32. Williams DR, Mohammed SA. Racism and Health II: A Needed Research Agenda for Effective Interventions. Am Behav Sci 2013 Aug 01;57(8) [FREE Full text] [doi: 10.1177/0002764213487341] [Medline: 24347667]
33. Czyzewski K. Colonialism as a Broader Social Determinant of Health. International Indigenous Policy Journal 2011 May 16;2(1). [doi: 10.18584/iipj.2011.2.1.5]
34. Kopel J, Perisetti A, Roghani A, Aziz M, Gajendran M, Goyal H. Racial and Gender-Based Differences in COVID-19. Front Public Health 2020;8:418 [FREE Full text] [doi: 10.3389/fpubh.2020.00418] [Medline: 32850607]
35. Levett-Jones T, Hoffman K, Dempsey J, Jeong SY, Noble D, Norton CA, et al. The 'five rights' of clinical reasoning: an educational model to enhance nursing students' ability to identify and manage clinically 'at risk' patients. Nurse Educ Today 2010 Aug;30(6):515-520. [doi: 10.1016/j.nedt.2009.10.020] [Medline: 19948370]
36. Hasan M, Singh H, Haffizulla F. Culturally Sensitive Health Education in the Caribbean Diaspora: A Scoping Review. Int J Environ Res Public Health 2021 Feb 04;18(4):1476 [FREE Full text] [doi: 10.3390/ijerph18041476] [Medline: 33557252]
37. Salami B, Fernandez-Sanchez H, Fouche C, Evans C, Sibeko L, Tulli M, et al. A Scoping Review of the Health of African Immigrant and Refugee Children. Int J Environ Res Public Health 2021 Mar 28;18(7):3514 [FREE Full text] [doi: 10.3390/ijerph18073514] [Medline: 33800663]

Abbreviations

PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Co-design of Digital Health Interventions for Young Adults: Protocol for a Scoping Review

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Abstract

Background: Digital health interventions, including apps and web-based services, are on the rise due to their facilitated access to target groups. The constant evolution of technology calls for participatory research methodologies to understand youth expectations and the use of technology. The creative and collaborative nature of co-design allows for the active integration of youth desires and may enhance acceptability when it comes to digital health tools.

Objective: The primary objective of this review is to assess the breadth of literature on digital health interventions that have been co-designed for and by young adults, including the types of available evidence, the identification of key characteristics relevant to young adult co-design, and the examination of research conduct in this space.

Methods: The proposed scoping review will be conducted in accordance with the Joanna Briggs Institute (JBI) Manual for Scoping Reviews. As well as the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist for reporting scoping reviews, an adaptation of Arksey and O'Malley's 6-stage framework for scoping reviews will be referenced. Peer-reviewed primary research, where young adults (aged 15-35 years) were actively involved in the design and development process of digital health interventions, will be collated for analyses. Five databases, including MEDLINE (Ovid), Cochrane, CINAHL Plus, Google Scholar, and Scopus, will be searched for relevant papers. Search strategies will be comprehensive to identify both published and unpublished literature. Relevant gray literature and secondary research will be excluded but pooled for separate analysis and citation chaining. Results will be presented in one or multiple forms, including narrative, tabular, or diagrammatic.

Results: Data collection commenced in October 2021. Following data extraction according to the JBI results extraction instrument and independent quality assurance of included studies, a narrative synthesis of each paper included in the final pool will allow for data charting. As of May 2022, 19 papers are included for analysis. We expect the results to be published by autumn 2022.

Conclusions: This protocol provides guidance for researchers who plan to conduct a similar style of investigation and promotes standardization of the scoping review process. We anticipate the provision of an overview of participatory digital health research involving young adults, highlighting any gaps in this research area, as well as potential areas for further study.

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KEYWORDS

digital health intervention; eHealth; mHealth; digital intervention; co-design; user participation; participatory research; participatory medicine; user feedback; participatory design; social media; web-based tool; young adult; youth; teenager; adolescent; review; protocol; search strategy; medical librarian; health librarian; library science; information science

Introduction

Background and Rationale

Digital technologies present ever-evolving opportunities for health professionals and researchers to effectively engage with young adults (YAs) online. Regardless of socioeconomic status, the vast majority of young people have access to a mobile device, with which they spend up to 10 hours per day interacting [1,2]. As such, smartphones and their capabilities, as well as personal computers with internet access, provide promising and potentially equitable platforms to influence a vast range of health behaviors.

Young adulthood is a critical development period, one in which health ethos and behaviors are, often for the first time, shaped outside of the home [3]. Health habits and behaviors that are adopted during this period often have a profound impact on long-term health status and general well-being [4].

Recent studies that have explored the health-seeking behaviors of YAs state a reliance on the internet for health information [5-7]. Actors in this space, including health influencers as well as health practitioners, are increasingly trusted with the provision of health information online [7]. The evolution of social media continues to add a more interactive element, as well as multiplying opportunities to encounter misinformation or succumb to "echo chambers" or confirmation bias [8]. The presence of health professionals in the digital space, via intervention apps or websites, introduces an opportunity to influence health behaviors online while also allowing for the dissemination of evidence-based health information in an environment where the voices of health professionals are typically outnumbered [9]. In this review, "digital technology" is used as an umbrella term that encompasses smartphone apps, SMS text messaging, social media, and web use, or a combination of multiple mediums.

Co-design, which originates from participatory research, has been defined as a "process of collective creativity or partnership with potential users and stakeholders, who are actively involved in the development of the technology, helping to ensure it meets the users' needs and preferences" [10]. Co-design with future users (FUs) enables researchers and designers to determine the attitudes and values of FUs, as well as their interests and capabilities [11]. An important distinction from a user-centered approach, co-design not only develops interventions *for* end users but also designs *with* users, consulting with target groups throughout the development process. The more creative and collaborative nature of co-design enables "greater participation and more effective responses to complex health issues" [12]. Increasingly, research uses co-design frameworks to create digital health interventions, especially for young people (ie, Young and Well Cooperative Research Centre) [13]. Where the evolution of technology is constant, participatory design methodologies are ever more valuable in the development of digital tools to sustain knowledge of youth expectations and use.

Evidence supports the notion that co-design or participatory design may enhance desired outcomes through increasing engagement and maintaining participation, while increasing the likelihood of developing a universally acceptable tool [11,14]. By way of example, Davis et al [15] coupled a patient-driven participatory design approach with professional respiratory expertise to develop a self-management app for young people with asthma. The digital app, which was found to be highly acceptable to young co-designers, highlights how co-design may result in more engaging, accessible, and acceptable intervention tools.

Prior reviews have explored the employment of co-design methodologies in the creation of digital health interventions for children and adolescents [10,16]. Further, a recent scoping review protocol seeks to investigate strategies for adolescent engagement in digital health interventions for obesity management [17]. Researchers have called for more participatory research in the development of such interventions due to an observed influence on engagement and subsequent health behaviors [16]. While research on the co-design of digital health interventions is gaining momentum, particularly for children and adolescents, there appears to be limited research concerning the young adult population. We, therefore, intend to explore the breadth of literature in this area to summarize and provide guidance for future participatory research with this age group.

Objectives

A preliminary search of MEDLINE, the Cochrane Database of Systematic Reviews, and the Joanna Briggs Institute (JBI) Evidence Synthesis journal was conducted, and no current or underway systematic or scoping reviews on the topic were identified. Presently, evidence surrounding the YA co-design of digital health interventions is scattered across health fields. An initial search outlined that the nature of the evidence is indicative of the need for a scoping review (ScR), rather than a systematic review, to synthesize relevant research. Where systematic reviews pose precise questions addressed to an established volume of literature, scoping reviews are suited to an "emerging" evidence base. The principal objective of an ScR is to "scope" a body of literature in order to "identify knowledge gaps, clarify concepts, or investigate research conduct" [18]. The overarching objective of this ScR is to assess the breadth of literature on digital health interventions that have been co-designed for and by YAs, including the types of available evidence, identification of key characteristics relevant to YA co-design, and examination of research conducted in this space [18,19].

Methods

Protocol Design

The proposed ScR will be conducted in accordance with the JBI Manual for Scoping Reviews [20]. The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist will be used (Multimedia Appendix 1) [21]. The PRISMA-ScR was developed to provide guidance on the reporting of scoping reviews. This reporting guideline is consistent with the JBI guidance for scoping reviews, which highlights the importance of methodological rigor in the conduct of such reviews [20]. As well as the PRISMA-ScR checklist, an adaptation of Arksey and O'Malley's 6-stage framework for ScR has been referenced [19,21]. The framework, which Levac et al [22] and Kahlil et al [23] adapted, consists of 5 core stages that will be used to address the primary research questions. The 5 stages include:

1. Identification of the research question
2. Identification of relevant studies
3. Selection of studies (search strategy)
4. Charting of data
5. Summary and report of research findings

Identification of the Research Question

As aforementioned, recent reviews have contributed to the evidence base concerning co-designed digital health interventions. However, such research primarily focuses on adults or adolescents and children, with limited research in the YA space. An ScR is performed in order to collate research findings from "scattered" evidence where research is insufficient to warrant a systematic review [18]. Following the preliminary literature search, it was deemed that a systematic review would limit findings, given the reductionist approach required. As such, this ScR intends to assess the breadth of literature on youth co-design of digital health interventions in order to inform future research in the digital health space.

The PCC (population/participants, concept, context) framework is recommended to identify the main concepts of primary review questions and inform search strategy development [19].

To comprehensively investigate how co-design with YAs is used in the development of digital health interventions, the overarching objective of this review has been translated into 4 key research questions according to the PCC framework [24];

1. Which theories and frameworks of co-design or participatory design have been used to involve YAs in the development of digital health interventions?
2. What health outcomes (if available) have been improved using co-design of digital health interventions in YAs?
3. How does co-design or participatory design support behavior change efforts such as reach, engagement, and accessibility of digital health interventions for YAs?
4. What is the potential to build credibility, trust, collaboration, and advocacy online?

The nature of reporting is such that papers are typically separated by a focus on either co-design processes or health outcomes. Where possible, all relevant papers from a study will be sought in order to comprehensively assess the co-design methodology as well as associated intervention outcomes. The intent of this ScR is to collate learnings and determinants of success in the co-design of digital interventions that endeavor to improve the health of YAs. Resolving the above research questions will enable the fulfillment of the primary research objective.

Identification of Relevant Studies

The following steps will be followed in order to obtain the final pool of studies for analysis:

1. An initial limited search of a selection of relevant databases
2. Analysis of text words contained in the title, abstract, and the keywords used to describe relevant articles
3. A second comprehensive search using all identified keywords and index terms across selected databases
4. Identification of additional studies via reference lists of all relevant reports and articles identified (citation chaining)

Search strategies have been developed via consultations with a University of Auckland science librarian (Textbox 1). Searches will be run on each selected database (n=5), as well as manual searching of gray literature to attain the final pool. Databases searched will include MEDLINE (Ovid), Scopus, CINAHL Plus, Cochrane, and Google Scholar (to be used for both an advanced and gray literature search).

Textbox 1. Search strategy (Cochrane) for the identification of papers for analysis.

1. MeSH descriptor: [Community-Based Participatory Research] this term only
2. MeSH descriptor: [Community Participation] this term only
3. (Co NEXT (design* or creat* or produc* OR youth led or youth?led or participatory design* or user?centered or user?centered):ti,ab,kw (Word variations have been searched for)
4. MeSH descriptor: [Digital Technology] this term only
5. MeSH descriptor: [Social Media] this term only
6. MeSH descriptor: [Online Social Networking] this term only
7. MeSH descriptor: [Internet-Based Intervention] this term only
8. MeSH descriptor: [Internet] this term only
9. MeSH descriptor: [Blogging] in all MeSH products
10. (digital* or web?based or social media or Instagram or Facebook or Twitter or Snapchat or social app* or online or internet):ti,ab,kw (Word variations have been searched)
11. MeSH descriptor: [Young Adult] this term only
12. (young adult* or YA or youth* or young person*):ti,ab,kw (Word variations have been searched
13. 1 or 2 or 3
14. 4 or 5 or 6 or 7 or 8 or 9 or 10
15. 11 or 12
16. 13 and 14 and 15 in Cochrane Reviews, Trials with 'Public Health' in Cochrane Groups (Word variations have been searched)

Date of most recent search: September 2021

Selection of Studies for Inclusion

The papers sourced will be exported to the reference management software EndNote X9 (Clarivate). Collated papers will be scanned and reviewed according to the inclusion criteria. Such criteria will be refined iteratively as the independent review is undertaken. Articles will be screened for duplicates, prior to title screening, by the primary author (JM). The remaining papers will be screened by 2 independent reviewers (JM and RR). Relevant secondary evidence will be citation chained by the primary author, with the paper source added to libraries to undergo a secondary independent abstract review. Following consultation and resolution of library discrepancies, a final list of papers eligible for full-text screening will be created. The full-text of the papers will be screened by the primary author (JM). Full-text articles will then be citation chained, with the above process repeated for newly sourced articles. The final list for inclusion will be assessed independently by 3 reviewers to ensure the eligibility criteria are upheld. Discrepancies regarding the final list will be discussed and resolved in meetings. The eligibility criteria will be iteratively refined where required, with ineligible papers excluded. The results of the search and the study inclusion process will be reported in full in a PRISMA-ScR flow diagram.

Eligibility Criteria (PCC)

Types of Participants (Population)

The classification of YAs differs across the literature, with the United Nations defining the age range as 15-24 years, whereas the World Health Organization describes this age group as "youth" [25]. Initially, the population group of interest for this review was further narrowed to focus on those in "young adulthood" aged 18-24 years, a scope which is inclusive of individuals classed as either Generation Z or "young" Millennials, as defined by the Massachusetts Institute of Technology [26]. Following consultation with the review team during study selection, the age range for inclusion was iteratively widened to include participants aged 15-35 years. This iteration was applied to ensure relevant studies were not excluded.

Concept

The literature will be searched for studies reporting on the participation or engagement of YAs in the design and development of interventions to improve health using digital tools or technologies. To be eligible, studies must include 2 core concepts: the use of co-design or similar methodologies, and digital health tools. For this review, "health interventions" encompass those aiming to improve chronic disease states, mental health conditions, dietary or physical activity habits, and risky health behaviors including binge drinking and smoking.

Health intervention studies that explicitly state co-design or participatory research design where there is active involvement of YAs for the duration of the research process in the form of leadership roles, design and knowledge sharing focus groups or workshops, ongoing interviews, and iterative development of the intervention will be included.

Health intervention studies that do not explicitly state co-design yet report the use of co-design or similar methodologies where the above criteria are met regarding active involvement of YAs in design and development processes will also be included for analyses. Eligible digital health interventions or technologies will include eHealth and mobile health (mHealth), and those

that are web-based or include social networking, blogging, engagement with social media, SMS text messaging, or general digital health communications.

Context

Peer-reviewed empirical research in all languages will be included and translated if required. Literature prior to 2006 will be excluded due to the emergence of social media and modern apps, and to ensure relevancy to YAs.

Types and Sources of Literature

Published peer-reviewed primary research (including both qualitative and quantitative studies) involving youth participation and decision-making in digital health interventions will be included.

Exclusion Criteria

Studies primarily targeting adolescents and children, older adults, or those with wide age inclusion criteria (eg, 16-50 years) will be excluded in order to target results to YAs. Conference abstracts, commentaries, discussion papers, book editorials, guidelines, frameworks, and thesis papers are to be excluded. Relevant secondary research, including systematic reviews, scoping reviews, critical reviews, and meta-analyses, will be excluded but pooled for subsequent citation chaining.

Gray Literature

The developed search strategy will be comprehensive to identify both published and unpublished evidence. Although excluded from this study, gray literature will be collated and assessed separately. Identified gray literature, including conference papers and organizational frameworks or guidance documents, provides a valuable overview of distinct co-design processes and offers insight into safe and effective implementation [12,13,27]. Although not always specific to digital interventions or young adults, these frameworks are useful in understanding the principles of participatory research and may be adapted to suit alternative population groups and tools.

Data Charting Process

To extract data on study and intervention characteristics, an adapted version of the JBI results extraction instrument will be used [28]. Independent quality assurance of included studies will be undertaken using the JBI critical appraisal tools for qualitative studies, randomized controlled trials, and quasi-experimental research [29]. A narrative synthesis of final studies will allow for insights to be mapped by digital health tools, co-design, or similar methodologies and their effectiveness regarding acceptability, feasibility, and usability, influence on health behaviors; or both.

As per the JBI Reviewer's Manual [20], key information to be collected from each paper will include:

- authors
- country of origin and year of publication
- study population and sample size
- intervention type
- purpose of study (aim)

By way of addressing the aforementioned research questions, intervention-specific data will be extracted on the use of co-design or similar theories and frameworks, description of digital health tools, health field and outcome, key findings, and limitations.

It will be assumed that the "purpose" or aim of studies may be characterized by:

- a description of the *development* of a digital health tool using co-design or participatory design;
- evaluation of the *acceptability, feasibility, or usability* of a co-designed digital health tool; or
- investigation and reporting of *direct or desired* health impacts of a co-designed digital health tool.

Author statements or discussions regarding the potential to build credibility, trust, collaboration, and advocacy online will be summarized, and we will provide a commentary on the use of developed interventions to support engagement, reach, segmentation, and accessibility for YAs.

Critical Appraisal of Individual Sources of Evidence

An independent critical appraisal of the included sources of information will be conducted in order to assess reliability, relevance, and value [30]. The JBI's critical appraisal tools for qualitative studies, randomized controlled trials, and quasi-experimental research will be used by 2 independent authors to guide the quality assurance process. The extent of co-design reporting will be added as an additional aspect of quality assurance, with those classified as "weak" to be reassessed for inclusion. Disagreements will be resolved by discussion with reviewers. Results will be compared and used in data synthesis to classify papers by quality.

Data Synthesis

Due to the potentially large volume, breadth, and heterogeneity of material included in a scoping review, it is not possible to predetermine the optimal method of collating and reporting the results. The evidence may be presented in one or multiple of the following formats: narrative, table, or visual (eg, map or diagram). A draft table outlining key data extracted from each study (Tables 1 and 2) has been developed for reference [31].

Table 1. Exemplar tabular data representation (types of available evidence)[a].

First author (Year)	Country sampling	Intervention (digital tool)	Purpose/aim	Key findings
Name (YYYY)	Country, population, sample size	App, website, online screening tool	Feasibility/acceptability, tool development, health impact	Engagement, health status, behavior, feasibility

[a]Adapted from Casu et al [31], which is published under Creative Commons Attribution 4.0 International License [32].

Table 2. Exemplar tabular data representation (cocreation process).

Study	Cocreation group	Sessions	Aim of session
First author (YYYY)	FU[a] or HP[b]	Type (n)	For example, exploration of concept

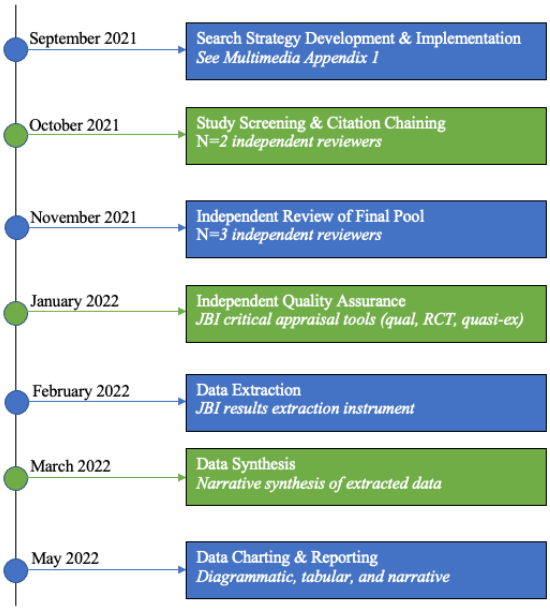
[a]FU: future user.

[b]HP: health practitioner.

Results

Data collection commenced in October 2021, once the search strategies were developed. As of May 2022, we have identified 19 papers for analysis. Prior to conducting the narrative synthesis, for each study in the final pool, all relevant peer-reviewed primary papers associated with the digital tool of interest are being sought if available (eg, reports of co-design methodology vs intervention implementation). Additional studies identified will undergo data extraction and independent quality assurance. Once complete, the research team will embark on a narrative synthesis of the finalized pool. We expect results to be published by spring 2023 (Figure 1).

Figure 1. Timeline for conduct of scoping literature review. JBI: Joanna Briggs Institute; qual: qualitative; quasi-ex: quasi-experimental; RCT: randomized controlled trial.



Discussion

Principal Findings

We hypothesize that a number of studies have implemented co-design or participatory design methodologies in distinct and creative ways to optimize engagement with and relevancy of developed digital tools with young adults. We foresee the exploration and dissemination of the insights regarding the strengths and challenges of participatory research with this age group, including effects on engagement, feasibility, and acceptability of developed digital tools. These insights will be summarized in order to inform the future cocreation of digital interventions for young people aged 15-35 years.

Prior participatory research indicates a number of key behaviors which have been targeted using co-designed digital tools [33-35]. As such, the types of behaviors likely to be targeted with the results from this review include risky health behaviors (eg, binge drinking, smoking), those associated with chronic disease states (eg, cancer, diabetes), and behaviors that have been identified as having positive influences on mental and physical well-being, such as healthy eating behaviors and physical activity.

Comparison to Prior Work

As aforementioned, co-design research with a principal focus on the young adult population is scarce. Prior studies have examined the effect of inclusive research processes such as co-design on the engagement of children and adolescents with digital health interventions, and its potential as a mediator of positive health outcomes [10,16]. Similarly, we intend to explore recent participatory research involving an older age group in the development of digital health tools, as well as any associated influences on engagement and health outcomes.

Strengths and Limitations

This protocol provides guidance for researchers who plan to conduct a similar style of investigation and promotes standardization of the scoping review process. Upon completion of data synthesis, the strengths and limitations of this review will be summarized.

Future Directions

The results of this review will provide a synopsis of the breadth of literature on the employment of co-design methodology in the development of digital health interventions for young adults. We anticipate the provision of an overview of any gaps in this

research area, as well as potential areas for further study. Regarding our plans for dissemination, we foresee the publication of the results of this review by spring 2023.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist.
[PDF File (Adobe PDF File), 805 KB - resprot_v11i10e38635_app1.pdf]

References

1. Mobile fact sheet. Pew Research Center Internet and Technology. 2017. URL: http://www.pewinternet.org/fact-sheet/mobile/ [accessed 2021-10-23]
2. Roberts JA, Yaya LHP, Manolis C. The invisible addiction: cell-phone activities and addiction among male and female college students. J Behav Addict 2014 Dec;3(4):254-265 [FREE Full text] [doi: 10.1556/JBA.3.2014.015] [Medline: 25595966]
3. Lawrence EM, Mollborn S, Hummer RA. Health lifestyles across the transition to adulthood: implications for health. Soc Sci Med 2017 Nov;193:23-32 [FREE Full text] [doi: 10.1016/j.socscimed.2017.09.041] [Medline: 28992538]
4. Committee on Improving the Health, Safety, and Well-Being of Young Adults; Board on Children, Youth, and Families; Institute of Medicine. In: Bonnie RJ, Stroud C, Breiner H, editors. Investing in the Health and Well-being of Young Adults. Washington (DC): National Academies Press (US); 2015.
5. Basch CH, MacLean SA, Romero R, Ethan D. Health information seeking behavior among college students. J Community Health 2018 Dec;43(6):1094-1099. [doi: 10.1007/s10900-018-0526-9] [Medline: 29779074]
6. Lim MSC, Molenaar A, Brennan L, Reid M, McCaffrey T. Young adults' use of different social media platforms for health information: insights from web-based conversations. J Med Internet Res 2022 Jan 18;24(1):e23656 [FREE Full text] [doi: 10.2196/23656] [Medline: 35040796]
7. Beck F, Richard J, Nguyen-Thanh V, Montagni I, Parizot I, Renahy E. Use of the internet as a health information resource among French young adults: results from a nationally representative survey. J Med Internet Res 2014 May 13;16(5):e128 [FREE Full text] [doi: 10.2196/jmir.2934] [Medline: 24824164]
8. Suarez-Lledo V, Alvarez-Galvez J. Prevalence of health misinformation on social media: systematic review. J Med Internet Res 2021 Jan 20;23(1):e17187 [FREE Full text] [doi: 10.2196/17187] [Medline: 33470931]
9. Ventola CL. Social media and health care professionals: benefits, risks, and best practices. P T 2014 Jul;39(7):491-520 [FREE Full text] [Medline: 25083128]
10. Jones RB, Stallard P, Agha SS, Rice S, Werner-Seidler A, Stasiak K, et al. Practitioner review: co-design of digital mental health technologies with children and young people. J Child Psychol Psychiatry 2020 Aug;61(8):928-940 [FREE Full text] [doi: 10.1111/jcpp.13258] [Medline: 32572961]
11. Latulippe K, Hamel C, Giroux D. Co-design to support the development of inclusive eHealth tools for caregivers of functionally dependent older persons: social justice design. J Med Internet Res 2020 Nov 09;22(11):e18399 [FREE Full text] [doi: 10.2196/18399] [Medline: 33164905]
12. Mark S, Hagen P. Co-design in Aotearoa New Zealand: a snapshot of the literature. Auckland Co-design Lab, Auckland Council. 2020. URL: https://knowledgeauckland.org.nz/media/1900/co-design-in-aotearoa-new-zealand-a-snapshot-of-the-literature-s-mark-p-hagen-tsi-june-2020.pdf [accessed 2021-02-11]
13. Hagen P, Collin P, Metcalf A, Nicholas M, Rahilly K, Swainston N. Participatory design of evidence-based online youth mental health promotion, intervention and treatment. Young and Well Cooperative Research Centre. 2012. URL: https://www.westernsydney.edu.au/__data/assets/pdf_file/0005/476330/Young_and_Well_CRC_IM_PD_Guide.pdf [accessed 2021-04-11]
14. Steen M. Co-design as a process of joint inquiry and imagination. Design Issues 2013 Apr;29(2):16-28. [doi: 10.1162/desi_a_00207]
15. Davis SR, Peters D, Calvo RA, Sawyer SM, Foster JM, Smith L. "Kiss myAsthma": using a participatory design approach to develop a self-management app with young people with asthma. J Asthma 2018 Sep;55(9):1018-1027. [doi: 10.1080/02770903.2017.1388391] [Medline: 29064746]
16. Partridge SR, Redfern J. Strategies to engage adolescents in digital health interventions for obesity prevention and management. Healthcare (Basel) 2018 Jun 21;6(3):70 [FREE Full text] [doi: 10.3390/healthcare6030070] [Medline: 29933550]
17. Mandoh M, Mihrshahi S, Cheng HL, Redfern J, Partridge SR. Adolescent participation in research, policies and guidelines for chronic disease prevention: a scoping review protocol. Int J Environ Res Public Health 2020 Nov 09;17(21):8257 [FREE Full text] [doi: 10.3390/ijerph17218257] [Medline: 33182256]

18. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. BMC Med Res Methodol 2018 Nov 19;18(1):143 [FREE Full text] [doi: 10.1186/s12874-018-0611-x] [Medline: 30453902]
19. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol 2005;8(1):19-32 [FREE Full text]
20. Aromataris E, Munn Z, editors. JBI Manual for Evidence Synthesis. Adelaide, Australia: JBI; 2020.
21. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018 Oct 02;169(7):467-473 [FREE Full text] [doi: 10.7326/M18-0850] [Medline: 30178033]
22. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implement Sci 2010 Sep 20;5:69 [FREE Full text] [doi: 10.1186/1748-5908-5-69] [Medline: 20854677]
23. Khalil H, Peters M, Godfrey CM, McInerney P, Soares CB, Parker D. An evidence-based approach to scoping reviews. Worldviews Evid Based Nurs 2016 Apr;13(2):118-123. [doi: 10.1111/wvn.12144] [Medline: 26821833]
24. Apply PCC. University of South Australia. 2022. URL: https://guides.library.unisa.edu.au/ScopingReviews/ApplyPCC [accessed 2022-01-17]
25. Society for Adolescent Health and Medicine. Young adult health and well-being: a position statement of the society for adolescent health and medicine. J Adolesc Health 2017 Jun;60(6):758-759. [doi: 10.1016/j.jadohealth.2017.03.021] [Medline: 28532650]
26. Changes in young adulthood. Young Adult Development Project. 2018. URL: https://hr.mit.edu/static/worklife/youngadult/changes.html#young [accessed 2021-02-11]
27. Co-designing with young people. Orygen: The National Youth Centre of Excellence in Youth Mental Health. 2019. URL: https://www.orygen.org.au/Training/Resources/Service-knowledge-and-development/Guidelines/Co-designing-with-young-people-The-fundamentals/Orygen-Co-designing-with-YP-the-fundamentals?ext= [accessed 2021-02-11]
28. Joanna Briggs Institute reviewers' manual; 2015 edition/supplement. The Joanna Briggs Institute. 2015. URL: https://nursing.lsuhsc.edu/JBI/docs/ReviewersManuals/Scoping-.pdf [accessed 2021-11-23]
29. Critical appraisal tools. JBI Global. URL: https://jbi.global/critical-appraisal-tools [accessed 2021-11-23]
30. Al-Jundi A, Sakka S. Critical appraisal of clinical research. J Clin Diagn Res 2017 May;11(5):JE01-JE05 [FREE Full text] [doi: 10.7860/JCDR/2017/26047.9942] [Medline: 28658805]
31. Casu L, Gillespie S, Nisbett N. Integrating nutrition and physical activity promotion: a scoping review. PLoS One 2020;15(6):e0233908 [FREE Full text] [doi: 10.1371/journal.pone.0233908] [Medline: 32502158]
32. Attribution 4.0 International (CC BY 4.0). Creative Commons. URL: https://creativecommons.org/licenses/by/4.0/ [accessed 2022-10-20]
33. Villegas N, Santisteban D, Cianelli R, Ferrer L, Ambrosia T, Peragallo N, et al. The development, feasibility and acceptability of an internet-based STI-HIV prevention intervention for young Chilean women. Int Nurs Rev 2014 Mar;61(1):55-63 [FREE Full text] [doi: 10.1111/inr.12080] [Medline: 24512261]
34. Rothgangel A, Braun S, Smeets R, Beurskens A. Design and development of a telerehabilitation platform for patients with phantom limb pain: a user-centered approach. JMIR Rehabil Assist Technol 2017 Feb 15;4(1):e2 [FREE Full text] [doi: 10.2196/rehab.6761] [Medline: 28582249]
35. Hides L, Dingle G, Quinn C, Stoyanov SR, Zelenko O, Tjondronegoro D, et al. Efficacy and outcomes of a music-based emotion regulation mobile app in distressed young people: randomized controlled trial. JMIR mHealth uHealth 2019 Jan 16;7(1):e11482 [FREE Full text] [doi: 10.2196/11482] [Medline: 30664457]

Abbreviations

FU: future user
JBI: Joanna Briggs Institute
PCC: participants, concept, context
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
ScR: scoping review
YA: young adult

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Protocol

Profiling of Learners in Medical Schools as a Move Toward Precision Education: Protocol for a Scoping Review

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Abstract

Background: Academic experiences seek to get the best out of learners, maximizing performance and developing the skills and competencies needed to foster lifelong learning. The more personalized and tailored the academic experience among learners, the better the outcome. Precision education is a novel approach to research and practice, which is concerned with identifying and tailoring education to the precise needs of the learner. An emerging area of precision education is using data to develop learner profiles for a better understanding of individual learners relative to the characteristics and competencies of lifelong learners.

Objective: This scoping review aims to identify literature that reports on profiling learners within medical schools. Our review, as described in this paper, will describe the characteristics being measured, the methods and data sources used to generate profiles, and the resulting profiles that emerge. This review aims to provide guidance to those supporting medical school learners on the current state of learner profiling.

Methods: This scoping review will use the Population, Concept, and Context framework, published by Joanna Briggs Institute, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews guidelines. The search strategy was developed in collaboration with a library specialist. An initial search was conducted in PubMed, ERIC, Google Scholar, Cochrane, CINAHL, and SCOPUS. Data will be extracted, and 2 authors will undertake the screening procedure using the Preferred Reporting Items for Systematic reviews and Meta-Analyses Extension for Scoping Reviews checklist.

Results: The database searches yielded 166 results, and title and abstract screening of 135 extracted articles is currently underway after eliminating 31 duplicates. We anticipate the scoping review to be completed in the first week of October 2022. The final scoping review will present the findings in a narrative and pictorial fashion**.**

Conclusions: This review will help guide scholars looking to understand the current state of learner profiling within medical schools.

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KEYWORDS

learners; medical students; medical undergraduates; medical graduates; profiling of learner; learner profile; medical education; medical universities; precision education; student record; graduate education; data extraction tool

Introduction

Background

Academic experiences must seek to get the best out of learners, maximizing performance and developing the skills and competencies needed to foster lifelong learning [1,2]. Lifelong learning is a concept involving the development of human potential through a continuously supportive process, beginning with self-directed activities that stimulate and empower individuals to acquire all the knowledge, values, skills, and understanding they will need throughout their lifetimes and to apply them with confidence, creativity, and enjoyment in all roles, situations, and contexts [3-7]. The more personalized and tailored the academic experience is to learners, the better the outcome [8,9]. Precision education is a novel approach to research and practice, which is concerned with identifying and tailoring education to the precise needs of the learner [10]. The fuel that powers precision education is data [11]. An emerging area of precision education is using data to develop learner profiles for a better understanding of individual learners relative to the characteristics and competencies of lifelong learners [12,13]. This can include dimensions such as motivation, metacognition, reflection, confidence, and regulation [13,14].

Learner Profiling

Recent studies have investigated how best to profile learners to understand their relationship with how they learn. For example, a study in Finland used latent profile analysis to develop learner profiles around learner epistemic beliefs [14]. An exploratory study in the United Kingdom used cluster analysis to develop learner groups, with further examination to explore the differences between these student profiles and the extent to which cultural background impacts these profiles [13].

Efforts to profile learners are varied and focus on profiling a variety of characteristics, such as conceptions of learning [14,15]; epistemic beliefs [14]; learning styles [16]; self-directed learning skills, attributes, and strategies [16-18]; recognition of prior learning [19]; learning difficulties [20]; motivation level [9,14,21]; lifelong learning trends [22]; digital readiness for collaborative learning [23]; cognitive, metacognitive, and motivational strategies [24]; educational backgrounds, students' study performance, and orientations [14,15]; situational reaction tendencies [25]; and coping styles, neuroticism, openness to experience, and agreeableness [26].

Learning strategies, approaches to learning, and perceptions of the learning environment as they relate to academic success are some areas that have been the focus of numerous studies generating the profiles of students pursuing higher education [13,27-30]. However, the focus has not been specific to medical students. Consolidating knowledge on this topic is crucial to facilitate teaching and drive future research and educational methods aimed at improving lifelong medical learners' attributes, skills, and competencies and their impact on academic performance. Considering that Arksey and O'Malley [31] state that the goal of a scoping review is to create a summative map of existing evidence and identify research gaps, this protocol describes our approach to conducting a scoping review on the practice of learner profiling in medical schools.

Aim and Objectives

This study aims to review the profiling of learners in medical schools. In addition, this review investigates distinct learner profiles based on abilities and characteristics of lifelong learning. Therefore, we intend to answer the following research questions: (1) How are learner profiles generated in medical schools? (2) What methodologies are used to characterize learners in medical schools? (3) What characteristics are being measured to develop learner profiles?

Methods

Key Considerations

This review will use the Joanna Briggs Institute's Population, Concept, and Context (PCC) methodology [32] for scoping reviews to determine the research subjects' suitability. In addition, the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) reporting guidelines and checklist [33] will be used at the reporting stage. Modifications of the approach, when needed, will be considered throughout the review process. The updated Joanna Briggs Institute (JBI) methodological guidelines for the conduct of scoping reviews [34] suggest breaking down the review process into 9 distinct steps, starting from defining and aligning the objectives and questions; developing and aligning the inclusion criteria with the objectives and questions; describing the planned approach to evidence searching, selection, data extraction, and presentation of the evidence; searching for the evidence; selecting the evidence; extracting the evidence; analysis of the evidence; presentation of the results; and summarizing the evidence in relation to the purpose of the review, making conclusions and noting any implications of the findings.

Eligibility Criteria

Sample

Previously published studies with the target population of medical students will be included.

Concept

All articles included will relate to learning profiling in a medical school context. This includes the characteristics being measured, the methods and data sources used to generate profiles, and the components of the final profiles themselves.

Context

Our scoping review will only include studies conducted in medical schools.

Types of Sources

This scoping review will include peer reviewed articles whose primary focus is on profiling medical learners. We will not include letters, comments, conference abstracts, editorials, doctoral theses, systematic reviews, non–peer-reviewed articles, and gray literature. Studies published in a language other than English will not be included. Table 1 provides a summary of the inclusion and exclusion criteria.

Table 1. Inclusion and exclusion criteria.

Criterion	Inclusion	Exclusion
Study type	Peer-reviewed articles	Letters, comments, conference abstracts, editorials, doctoral thesis, non–peer-reviewed studies, systematic reviews, and gray literature
Time period	Any	N/A[a]
Participants	Medical students	Other health care students including physiotherapists, nurses, postgraduates, physicians, social sciences students, and students in other higher education departments
Focus area	Key competencies areas addressed, data sources, tools and instruments, and statistical analysis for profiling learners	Studies without data sources will be excluded
Outcome	Generated profiles based on attributes and learning in medical schools	N/A
Language	English	Non-English

[a]N/A: not applicable.

Search Strategy

According to JBI, the bibliographic database search should be carried out in accordance with a step-by-step plan. In the first part of the limited search process, we looked through the PubMed and ERIC databases by analyzing the words in the titles and abstracts of the papers that have been retrieved, as well as an examination of the index keywords that have been used to characterize the publications. In the second step, we used all of the previously identified keywords and index terms to conduct a second search of the databases, including PubMed, ERIC, SCOPUS, Cochrane, CINAHL, and Google Scholar, to retrieve peer-reviewed research papers that are relevant to our objective. After screening, the final set of included studies were imported into the reference management software Zotero, where duplicates were removed. Coauthor ST, the information specialist, helped establish a comprehensive search strategy by ensuring that the search strings are inclusive, and the selected databases are relevant to our research. The used keywords and search strings are mentioned in Tables 2 and 3.

Table 2. Keywords and Medical Subject Headings (MeSH) terms for the Population, Concept and Context framework.

Population		Concept		Context	
MeSH	Keywords	MeSH	Keywords	MeSH	Keywords
Students, Medical	Medical student*		Learner profiling	Education, Medical, Undergraduate	Medical Education
	Learners		Profiling of learner*	Education, Medical	Medical School*
	Medical undergraduates		Learner profile*	Education, Medical, Graduate	

Table 3. Search strings.

Search strings	Database	Results, n
((((Students, Medical[MeSH Terms]) OR (Learners)) OR (Medical students)) OR (Medical undergraduates)) AND ((((Profiling of learner*) OR (Learner profile*) OR (learner profiling) AND ((((Education, Medical, Undergraduate[MeSH Terms]) OR (education, graduate[MeSH Terms])) OR (education, medical[MeSH Terms])) OR (Education, Medical, Graduate[MeSH Terms]))	PubMed	42
(“Medical student*”)) AND ((“ Profiling of learner”) OR (“Learner profile*”)) AND ((“Medical education”) OR (“Medical Universit*”))	Google Scholar	53
“Learner profile” AND “medical education”	ERIC	17
“Learner profile” AND “medical students” AND “Medical school”	CINAHL	19
“Learner profile” AND “medical students” AND “Medical school”	SCOPUS	28
“Learner profile” AND “medical students” AND “Medical school”	Cochrane	7

Study Selection and Screening

The web-based software platform Rayyan [35] will streamline the screening process. As recommended by Levac et al [36], titles and abstracts will be screened separately by 2 reviewers (HS and LP) to ensure that they are relevant to the review. A discussion of article selections and search strategies will occur at various points throughout the screening process. It is possible to uncover and integrate new keywords, sources, and search phrases into the search strategy. The reviewers will go through the complete text and apply the inclusion criteria mentioned in Table 1 for papers that were not disqualified on the basis of the title or abstract. A single arbitrator (NZ) will determine any disagreements among reviewers.

Per the PRISMA-ScR statement [33], the final review will be delivered in narrative and pictorial form. In addition, the final research will include an appendix with information on the eliminated papers after full-text review and validation.

Data Extraction

A data extraction tool will be developed to extract data from included publications. Textbox 1 displays the data to be extracted. The data extraction tool may be adjusted and amended during the process, and any changes will be documented in the final report. Relevant information on the population, topic, setting, research methodology, and significant results will be retrieved. Any disagreements between reviewers will be resolved through discussion or the involvement of an additional reviewer during the screening process [37]. Reviewers may also contact article authors to seek missing or extra information.

Textbox 1. Data extraction protocol.

Data to be extracted from articles

All study information will be extracted and processed using a data charting table. The data to be extracted and explained include the following:

General study information

General study specifics entail bibliographic information, purpose or objective, study design, and participants.

Related to profiling of learners

1. We will collect the characteristics measured in the study.
2. What instruments or tools were used to measure the scales?
3. What data sources are used to generate learner profiles?
4. What kinds of learner profiles were generated?
5. We will look for any associations of generated profiles with study approaches, learning strategies, academic success, and study exhaustion.
6. Collect information regarding the various statistical procedures used for data analysis.

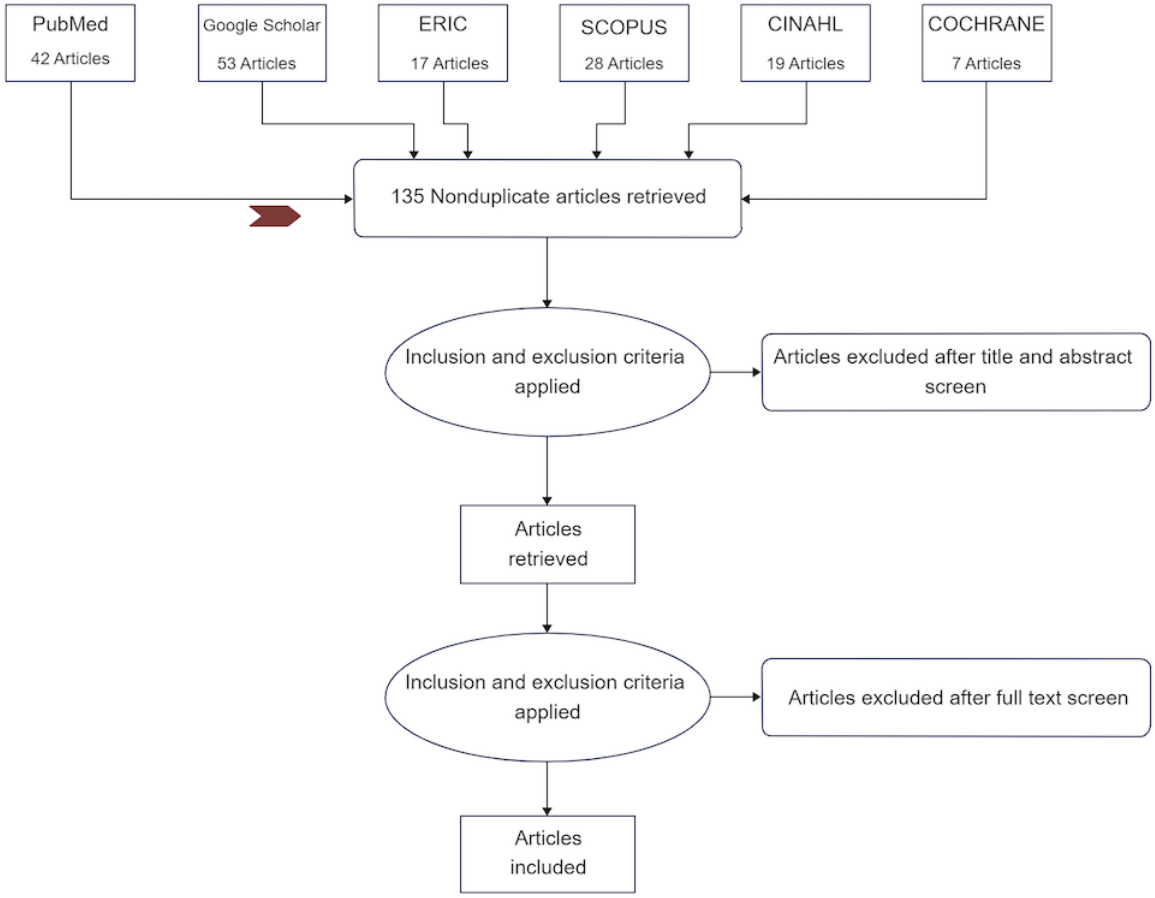
Data Analysis

Abstracted information from all the included articles will be compiled, and the results will be presented independently by two researchers (HS and LP) to capture the extent of the literature. Tables of the extracted data will be developed to provide an overview of the information from each paper. This overview will be followed by a narrative presentation of the synthesized mapping of the included literature and descriptive qualitative content analysis to identify or clarify concepts or definitions within a field and highlight qualities associated with a concept. In addition, the research team will analyze findings regarding the study's overall purpose and evaluate the implications for future research, practice, and policy.

Results

Initial database searches revealed 166 studies. The database searches were completed in August 2022, and title and abstract screening of 135 extracted articles is currently underway after the elimination of 31 duplicates; we anticipate the final results in the first week of October 2022. The extracted findings will be presented in accordance with the scoping review's goals and questions. In accordance with Peter et al [32], our findings will comprise 2 major components. The first component will include a PRISMA flowchart describing the research selection procedure (as shown in Figure 1). The most important data or findings pertinent to the scoping review's goals or queries are presented in the second part. Upon evaluation of the contents of the included evidence, this could be further refined throughout the review phase. The outcomes of a scoping review will be displayed as a map of the data gathered from the studies that were included, both in tabular form and in a descriptive format that is in line with the review's goals and scope. The components of the PCC inclusion criteria will help determine the most effective method for communicating the scoping review's findings to the audience.

Figure 1. Flowchart of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for the scoping review procedure. Small colored arrow represents the current status.



Discussion

Background

The essence of "precision" conveys the necessity of collecting complex and multidimensional data related to learners' characteristics, behavior, interactions, and performance, enabling educators to better understand learners' needs. Profiling learners from multiple perspectives and points of view can be a useful pathway to obtaining a good understanding. Learner profiling has been previously investigated in higher education; however, no review has been undertaken on learners in medical schools. This review will map the research in this field to better understand how learner profiles are being developed and are being used in medical education.

Profiling learners in medical schools can be a potentially helpful strategy for facilitating successful academic and lifelong learning outcomes [38]. By conducting this scoping review, we strive to harmonize distinct styles, strategies, and methods that might increase clarity in this domain. In addition, by reporting on the validated instruments, resources, and design and development strategies used to generate learner profiles in medical education, we will inform those seeking to develop learner profiles in their setting, potentially leading to an efficient, personalized learning process [39]. We intend to disseminate our results through publication in a peer-reviewed journal.

Limitations

First, the review methodology does not include gray literature such as book chapters, theses, short papers, editorials, non–peer-reviewed reports, and conference abstracts; second, we will only include studies written in English owing to the feasibility and limitation of resources. To mitigate the publication biases, adhering to the JBI's principles for scoping reviews will help to ensure a rigorous and logistical methodology in terms of the research framework, a search strategy including search strings and keywords, and searches of well-established academic databases. Lastly, it may not be possible to generate practice recommendations based on the outcomes of this scoping review since no evaluation of methodological quality or rating of evidence levels will be conducted. However, this study will identify further research gaps and the potential need for additional systematic reviews.

Conclusions

This scoping review will provide a foundational understanding of the current state of profiling learners in medical schools. The outcome of this scoping review can help further the field of precision education and potentially promote lifelong learning to help produce learners who have the attributes necessary to fulfill their individual and collective responsibilities to society and who are prepared to serve the fundamental purposes of medicine. This scoping review protocol describes the design for the review on medical school learner profiling and outlines the methodological challenges and steps taken to ensure

rationality. The latter can be applied and expanded on by researchers outside the medical field.

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Data Availability

All data relevant to the study will be provided in the scoping review.

Conflicts of Interest

None declared.

References

1. Schwartz S. Leaving college: rethinking the causes and cures of student attrition by Vincent Tinto. Academe 1987;73(6):46-47. [doi: 10.2307/40250027]
2. Maslov Kruzicevic S, Barisic KJ, Banozic A, Esteban CD, Sapunar D, Puljak L. Predictors of attrition and academic success of medical students: a 30-year retrospective study. PLoS One 2012 Jun 18;7(6):e39144 [FREE Full text] [doi: 10.1371/journal.pone.0039144] [Medline: 22737228]
3. Aspin D, Chapman J. Towards a philosophy of lifelong learning. In: International Handbook of Lifelong Learning. Dordrecht: Springer; 2001:3-33.
4. Davies WK, Longworth N. Lifelong learning. London: Routledge; 1996.
5. Hojat M, Nasca TJ, Erdmann JB, Frisby AJ, Veloski JJ, Gonnella JS. An operational measure of physician lifelong learning: its development, components and preliminary psychometric data. Med Teach 2003 Jul 03;25(4):433-437. [doi: 10.1080/0142159031000137463] [Medline: 12893557]
6. Longworth N. Learning communities for a learning century. In: International Handbook of Lifelong Learning. Dordrecht: Springer; 2001:591-617.
7. Odabasi F, Kuzu A, Gunuc S. Characteristics of lifelong learner. 2012 Presented at: Society for Information Technology & Teacher Education International Conference; March 5, 2012; Austin, TX.
8. Camacho DJ, Legare JM. Shifting gears in the classroom-movement toward personalized learning and competency-based education. Competency-based Education 2016 Dec 26;1(4):151-156. [doi: 10.1002/cbe2.1032]
9. Whalley B, France D, Park J, Mauchline A, Welsh K. Towards flexible personalized learning and the future educational system in the fourth industrial revolution in the wake of Covid-19. Higher Education Pedagogies 2021 Feb 25;6(1):79-99. [doi: 10.1080/23752696.2021.1883458]
10. Cook CR, Kilgus SP, Burns MK. Advancing the science and practice of precision education to enhance student outcomes. J Sch Psychol 2018 Feb;66:4-10. [doi: 10.1016/j.jsp.2017.11.004] [Medline: 29429494]
11. Hart SA. Precision education initiative: moving towards personalized education. Mind Brain Educ 2016 Dec 13;10(4):209-211 [FREE Full text] [doi: 10.1111/mbe.12109] [Medline: 28642807]
12. Ng B. Identifying the profile of a potential lifelong learner. New Waves Educational Research & Development 2019;22(1):1-13 [FREE Full text]
13. Cockrill A, Harris N. Learner Profiles at a UK University: An Exploratory Study. URL: http://repository.uwtsd.ac.uk/773/1/Academy%20of%20Marketing%202015%20rev.pdf [accessed 2022-10-12]
14. Lonka K, Ketonen E, Vermunt JD. University students' epistemic profiles, conceptions of learning, and academic performance. High Educ 2020 Jul 04;81(4):775-793. [doi: 10.1007/s10734-020-00575-6]
15. Vettori G, Vezzani C, Bigozzi L, Pinto G. Cluster profiles of university students' conceptions of learning according to gender, educational level, and academic disciplines. Learn Motiv 2020 May;70:101628. [doi: 10.1016/j.lmot.2020.101628]
16. Nokelainen P, Ruohotie P. Modeling Student's Motivational Profile for Learning in Vocational Higher Education. In: Theoretical Understandings for Learning in the Virtual University. Hämeenlinna, Finland: Elsevier; 2002:177-206.
17. Ning HK, Downing K. A latent profile analysis of university students' self-regulated learning strategies. Stud High Educ 2014 Apr 08;40(7):1328-1346. [doi: 10.1080/03075079.2014.880832]
18. Kell C. Undergraduates' learning profile development: what is happening to the men? Med Teach 2006 Feb 03;28(1):e16-e24. [doi: 10.1080/01421590600568462] [Medline: 16627315]
19. Snyman M, van den Berg G. The significance of the learner profile in recognition of prior learning. Adult Education Quarterly 2017 Sep 21;68(1):24-40. [doi: 10.1177/0741713617731809]
20. Heiman T, Precel K. Students with learning disabilities in higher education: academic strategies profile. J Learn Disabil 2003 Aug 18;36(3):248-258. [doi: 10.1177/002221940303600304] [Medline: 15515645]

21. Botejara-Antúnez M, Sánchez-Barroso G, González-Domínguez J, García-Sanz-Calcedo J. Determining the learning profile of engineering projects students from their characteristic motivational profile. Educ Sci 2022 Apr 03;12(4):256. [doi: 10.3390/educsci12040256]
22. Brown JN. Lifelong Learning Trends. A Profile of Continuing Higher Education. ERIC. 1990. URL: https://eric.ed.gov/?id=ED319961 [accessed 2022-05-11]
23. Blayone TJB, Mykhailenko O, Kavtaradze M, Kokhan M, vanOostveen R, Barber W. Profiling the digital readiness of higher education students for transformative online learning in the post-soviet nations of Georgia and Ukraine. Int J Educ Technol High Educ 2018 Oct 22;15(1). [doi: 10.1186/s41239-018-0119-9]
24. Heikkilä A, Lonka K, Nieminen J, Niemivirta M. Relations between teacher students' approaches to learning, cognitive and attributional strategies, well-being, and study success. High Educ 2012 Jan 24;64(4):455-471. [doi: 10.1007/s10734-012-9504-9]
25. Mäkinen J, Olkinuora E. University students' situational reaction tendencies: reflections on general study orientations, learning strategies, and study success. Scand J Educ Res 2004 Nov;48(5):477-491. [doi: 10.1080/0031380420002721 31]
26. Romosan R, Dehelean L, Enatescu V, Bredicean A, Papava I, Giurgi-Oncu C, et al. Profiling undergraduate students from a Romanian medical university. NDT 2018 Jul;Volume 14:1891-1899. [doi: 10.2147/ndt.s165797]
27. Rogiers A, Merchie E, Van Keer H. Learner profiles in secondary education: occurrence and relationship with performance and student characteristics. J Educ Res 2019 Mar 19;112(3):385-396. [doi: 10.1080/00220671.2018.1538093]
28. Alexander PA, Murphy PK. Learner profiles: valuing individual differences within classroom communities. In: Ackerman PL, Kyllonen PC, Roberts RD, editors. Learning and individual differences: process, trait, and content determinants. Washington, DC: American Psychological Association; 1999:413-436.
29. Skourlas C, Belsis P. Learner profiles and the process of learning in the higher educational context. IJIIM 2015. [doi: 10.15556/ijiim.02.01.003]
30. Kirchmeyer BC, Xethakis L. Learner profiles for EFL in Japanese higher education: incoming student beliefs, experiences, and expectations. SILC Journal 2021:20-37.
31. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol 2005 Feb 20;8(1):19-32 [FREE Full text] [doi: 10.1080/1364557032000119616]
32. Peters MDJ, Godfrey C, McInerney P, Munn Z, Tricco AC, Khalil H. Scoping reviews (2020 version). JBI Manual for Evidence Synthesis. 2020. URL: https://jbi-global-wiki.refined.site/space/MANUAL/4687342/Chapter+11%3A+Scoping+reviews [accessed 2022-10-12]
33. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018 Oct 02;169(7):467-473 [FREE Full text] [doi: 10.7326/M18-0850] [Medline: 30178033]
34. Peters MDJ, Marnie C, Tricco AC, Pollock D, Munn Z, Alexander L, et al. Updated methodological guidance for the conduct of scoping reviews. JBI Evid Synth 2020 Oct;18(10):2119-2126. [doi: 10.11124/JBIES-20-00167] [Medline: 33038124]
35. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016 Dec 05;5(1):210 [FREE Full text] [doi: 10.1186/s13643-016-0384-4] [Medline: 27919275]
36. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implement Sci 2010 Sep 20;5(1):69 [FREE Full text] [doi: 10.1186/1748-5908-5-69] [Medline: 20854677]
37. van Tulder M, Furlan A, Bombardier C, Bouter L. Updated method guidelines for systematic reviews in the Cochrane collaboration back review group. Spine 2003;28(12):1290-1299. [doi: 10.1097/01.brs.0000065484.95996.af]
38. Sternberg RJ. The concept of intelligence and its role in lifelong learning and success. American Psychologist 1997 Oct;52(10):1030-1037. [doi: 10.1037/0003-066x.52.10.1030]
39. Dabbagh N, Kitsantas A. Personal learning environments, social media, and self-regulated learning: a natural formula for connecting formal and informal learning. Internet High Educ 2012 Jan;15(1):3-8. [doi: 10.1016/j.iheduc.2011.06.002]

Abbreviations

JBI: Joanna Briggs Institute
PCC: Population, Concept, and Context
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Examining Emailed Feedback as Boosters After a College Drinking Intervention Among Fraternities and Sororities: Rationale and Protocol for a Remote Controlled Trial (Project Greek)

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Abstract

Background: College students involved in Greek life (ie, members of fraternities and sororities) tend to engage in more high-risk alcohol use and experience more negative consequences than those not involved in Greek life. Web-based alcohol interventions, such as Alcohol eCHECKUP TO GO, have been successful in reducing alcohol use and consequences among the general college student population, but interventions targeting alcohol reduction among those involved in Greek life have had limited success. Booster emails including personalized feedback regarding descriptive norms and protective behavioral strategies have shown potential in increasing the effectiveness of web-based interventions among college drinkers. Studies are needed to determine the efficacy of these boosters among those involved in Greek life.

Objective: The primary objective of this study is to assess the efficacy of booster emails sent to Greek life students who complete Alcohol eCHECKUP TO GO. Specifically, we expect that participants who receive the booster emails will reduce their alcohol consumption and related problems (primary aim 1), reduce perceived peer drinking, and increase the number of protective behavioral strategies they use over time (primary aim 2) relative to those who do not receive boosters. Contingent upon finding the emailed booster efficacious and sufficient enrollment of members from each organization, an exploratory aim is to examine social mechanisms of change (ie, through selection vs socialization).

Methods: This study is a remote, controlled intervention trial following participants for up to 6 months. Participants must be aged at least 18 years, undergraduate students, and members of a participating fraternity or sorority. Eligible participants complete a web-based baseline survey to assess their alcohol consumption behaviors and beliefs, including norms and protective behavioral strategies, and information about their social networks. After completing the baseline survey, they participate in the web-based intervention. Follow-up surveys are sent 1, 3, and 6 months after the intervention. Those in the booster condition also receive emails containing personalized feedback at 2 weeks and 14 weeks after the intervention. Latent growth models and R-Simulation Investigation for Empirical Network Analysis will be used to analyze the data.

Results: As of September 2022, we have enrolled 18 participants from 2 fraternities and 2 sororities, and they have completed the baseline survey. Overall, 72% (13/18) of participants have completed the 1-month follow-up. Enrollment will continue through December 2022.

Conclusions: This study aims to examine the effectiveness of personalized feedback booster emails sent after an alcohol intervention among members of college Greek life. A secondary, exploratory aim is to provide information about social mechanisms

of change (if possible). The current methodology targets whole network recruitment, with chapter presidents serving as gatekeepers and facilitators. Unique challenges of recruiting whole networks and working with campus administrators are discussed.

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KEYWORDS

college drinking; fraternities; sororities; web-based intervention; boosters

Introduction

Background

College drinking is prevalent and linked to numerous academic problems and physical consequences [1-6]. Moreover, members of fraternities and sororities tend to drink more and do not respond well to interventions designed to reduce drinking or related harm, as described in the following sections. Boosters are a promising way to strengthen and extend the effects of web-based interventions, while maintaining low cost and easy dissemination. This study examines whether a personalized feedback booster delivered via email after a web-based intervention enhances outcomes relative to the intervention alone among members of fraternities and sororities.

Drinking Among Members of Fraternities and Sororities

College students involved in Greek life (eg, members of fraternities or sororities) tend to consume more drinks [7-10] and report more negative alcohol-related consequences than non–Greek-involved students [7,9,11-13]. Not only do they consume more drinks but they are also more likely to engage in binge drinking [10-14] than their non-Greek counterparts. Rates of binge drinking among Greek-involved students range from 70.4% to 86% [13-15] and approximately two-thirds (64%) of members of fraternities engage in frequent binge drinking (defined as consuming ≥5 drinks on at least three occasions during the past 2 weeks) [15]. These high rates of heavy drinking suggest that students involved in Greek life represent a particularly high-risk group of drinkers.

Students involved in Greek life are highly socially connected, potentially influencing their heavy drinking behaviors. Previous studies have found that alcohol consumption is high among Greek-involved students who live in fraternity or sorority houses compared with those who are members but do not live in Greek housing [13,14,16], suggesting that fraternities and sororities are close-knit networks that tend to drink more together than apart. A longitudinal social network study of fraternity members revealed that members who “hang out” together tend to consume similar quantities of alcohol, and those who hang out with heavy drinkers tend to either drink heavily already or increase their alcohol consumption over time [17]. Moreover, a series of studies tracking drinking behaviors and Greek membership over time demonstrated that although heavy drinkers are more likely to join Greek organizations, there is also an immediate and sustained influence to increase and maintain heavy drinking over time via environmental influences [18,19]. Those who join Greek organizations demonstrate increased drinking, whereas those who disaffiliate demonstrate decreased drinking [18]. These findings suggest that the drinking behaviors of Greek-involved students, already an at-risk group for heavy drinking, are influenced by strong social connections with other Greek-involved students.

Interventions Among Members of Fraternities and Sororities

Given that student members of fraternities and sororities consume more alcohol and report more consequences than nonmembers, they have been a target for alcohol harm reduction interventions. However, a meta-analysis of 21 different alcohol interventions with this population revealed few significant reductions in alcohol consumption or related problems after the intervention relative to controls [20]. Interventions yielded limited success, with some reductions observed in the number of drinks consumed on specific occasions or frequency of drinking (small to medium effect sizes). In addition, interventions that were brief (<60 minutes) versus long (>60 minutes) yielded strong reductions in heavy drinking frequency. The limited intervention success in this population coupled with strong effects of brief interventions suggest that this population may be an ideal target for personalized feedback booster emails after a brief web-based intervention.

Alcohol eCHECKUP TO GO

Alcohol eCHECKUP TO GO is a brief web-based alcohol education program that asks questions about alcohol use, related perceptions, and risks and provides a personalized feedback report. It has strong empirical support and is listed as program of high effectiveness by the National Institute on Alcohol Abuse and Alcoholism College Alcohol Intervention Matrix [21]. The program has been shown to be efficacious in reducing alcohol use and related risks among incoming students [22-28] and samples of general college drinkers [29,30]. Reductions in alcohol use after administration of Alcohol eCHECKUP TO GO have also been demonstrated among specific high-risk college populations, such as heavy drinkers or frequent heavy drinkers [31-36], heavy or problematic drinkers [37,38], or students mandated to receive treatment [39-42]. Despite these strong successes with high-risk college populations, so far, no studies have examined the efficacy of Alcohol eCHECKUP TO GO specifically among students involved in Greek life.

Boosters for Web-Based College Drinking Interventions

Boosters refer to brief or delayed maintenance sessions aimed at increasing an intervention’s efficacy [43]. Using boosters as a technique to supplement programs or interventions has been

effective in a variety of fields for further promoting healthful behaviors or reducing problematic behaviors, such as by promoting physical activity [44], improving family functioning [45], and reducing harmful alcohol use [46]. Given that the effects of in-person college drinking interventions on peak drinking tend to decay by 27 weeks and that web-based college drinking intervention effects tend to decay by 14 weeks (refer to the paper by Carey et al [47] for a meta-analysis), it is important to use methods designed to increase the effects of college drinking interventions, such as boosters. Few studies have examined the long-term efficacy of boosters in reducing alcohol use among college students [48,49].

Emailed boosters (ie, follow-up emails after the intervention) [43,49] are an efficient and inexpensive delivery method. However, evidence is equivocal regarding the long-term efficacy of emailed boosters for web-based college drinking interventions [49,50]. The content of emailed boosters may prove to be key and may be informed by efficacious components of brief interventions. Effective methods of reducing college drinking include personalized normative feedback (ie, providing accurate information about peer drinking, often correcting normative misperceptions) [51] and promoting protective behavioral strategies (ie, engaging in techniques to reduce alcohol consumption, problems, or both) [52]. Importantly, despite the limited studies on boosters after college drinking, personalized normative feedback via boosters has been shown to prolong the effects of reduced drinking after the intervention [43,48,49,53]. In total, 2 studies using personalized feedback about both norms and protective behavioral strategies as content for emailed boosters observed a continuous reduction in reported alcohol use among college students at 4 weeks [43] and among legal drinking-aged college students for up to 9 months after the intervention [49], thus further demonstrating the potential effectiveness of emailed boosters in a college population.

Normative Perceptions and Protective Behavioral Strategy Use in Greek Life

Both descriptive drinking norms and protective behavioral strategy use, key components in the booster feedback deployed as part of this study, have strong links to drinking among members of fraternities and sororities. Descriptive drinking norms have been found to mediate associations between involvement in Greek life and alcohol use [7], with members of Greek life holding higher normative perceptions and greater norms being linked to greater consumption. There is conflicting evidence regarding whether fraternity and sorority members use greater or fewer protective behavioral strategies than students not involved in Greek life. Barry et al [54] found that Greek-involved students used few strategies, whereas Soule, Barnett, and Moorhouse [12] found that they used more. Regardless of whether members of Greek life use few versus many of these strategies, Barry et al [54] found when controlling for alcohol consumption, that using more protective behavioral strategies was linked to reporting fewer alcohol-related problems among fraternity and sorority members, suggesting that they are key to reducing harm. Taken together, personalized feedback regarding drinking norms and protective behavioral strategy use may be useful to be included in emailed boosters after college drinking interventions delivered to students involved in Greek life.

Study Objectives

Overview

Members of sororities and fraternities engage in heavier drinking than their non-Greek counterparts and often report more consequences [7,9,11-13]; furthermore, previous intervention efforts with this population have yielded limited success [20]. Therefore, this study aims to strengthen and extend alcohol intervention effects by using personalized feedback boosters sent via email. Moreover, given the close connections among members of fraternities and sororities, these may be closed peer networks that can facilitate the examination of how changes in drinking occur through social influence. In other words, we can potentially examine if change happens through *selection* (ie, transitioning into friendships with individuals who are similar), such that those who drink less after the intervention change who they drink with to peers who also drink less, or *socialization* (ie, becoming more similar to individuals who one spends time with), such that participants may drink less if their drinking buddies are drinking less after the intervention and booster. Thus, this study has 2 primary aims (to be examined regardless of study outcomes or participation rates) and 1 exploratory secondary aim (to be examined only if the booster is efficacious and most members of each enrolled organization complete the study).

Primary Aim 1

We will examine the efficacy of a personalized feedback booster emailed after Alcohol eCHECKUP TO GO is delivered to members of fraternities and sororities. We hypothesize initial postintervention drinking reductions for both study conditions, with individuals in the booster condition reporting further reductions at later follow-ups.

Primary Aim 2

Given the focus on perceived descriptive norms and protective behavioral strategies in the personalized feedback boosters, we will examine whether the booster affects changes in those constructs over time. We hypothesize that individuals in the booster condition will report further reductions in norms and increases in protective behavioral strategies at later follow-ups.

Exploratory Aim

If the emailed booster is efficacious and most members of each enrolled organization complete the study, we will examine social mechanisms of change (ie, through selection vs socialization).

In the following sections, we review the methodological approach currently used, challenges (eg, administrative red tape, gatekeepers in recruitment, change in health programing, and extended time lines), and protocol revisions executed in response to these challenges (eg, changing data collection sites and seeking additional approvals).

Methods

Project Overview and Design

Project Greek is an ongoing clinical trial of a personalized feedback booster emailed to members of fraternities and sororities after they complete Alcohol eCHECKUP TO GO, a web-based intervention designed to reduce college drinking. Study conditions include *intervention only* versus *intervention plus booster*. Participants are assigned to a condition at the organization level so that all members of an organization are in the same condition (ie, all enrolled members of the organization received a feedback booster email or all enrolled members of the organization did not). In both conditions, participants attend a virtual baseline session where they complete a survey and Alcohol eCHECKUP TO GO and are invited to complete follow-up surveys 1, 3, and 6 months later. Tailored feedback booster emails are sent 2 weeks after the intervention (known to be effective) [43,49] and 14 weeks after (known to be the window when web-based intervention effects wane based on meta-analysis) [47]. At each time point, participants complete a survey about their current alcohol-related behaviors, cognitions, and beliefs. They are also asked to name close network members at each time point to allow exploration of the influence of socialization versus selection via social network analysis.

Setting and Participant Selection

Eligibility criteria include being aged ≥18 years, an undergraduate student, and a member of a participating fraternity or sorority. Alcohol criteria were omitted because (1) we want to enroll as many members of participating organizations (fraternities and sororities) as possible to facilitate the social network examination involved in the secondary aim of the study and (2) given rates of alcohol use among members of Greek life (described previously), this seemed unnecessary.

Data collection was originally planned for the research team's host institution, a minority serving, large, public institution. It is a majority commuter campus, with only 20.1% of students living on campus in spring of 2019 (before the COVID-19 global pandemic). Moreover, 25% of students are affiliated with the military (including spouses and children of those active in the military). After forming a student advisory panel comprising undergraduate students in sororities or fraternities and consulting them on the study design, this plan was changed. We learned that many members of fraternities and sororities at this institution do not consider other members of the same organization to be close friends, and they often drink alcohol with individuals who are not in these organizations. If asked to list their top 5 closest friends, most of them would not include members of their Greek organization. This is because many students maintain connections with peers from before joining the institution (eg, they still live near childhood friends) and many have responsibilities outside college (eg, taking care of family or working at a job). This would be problematic for the secondary aim of the study, as we hoped to recruit closed social networks of drinkers by recruiting all members of a participating fraternity or sorority. Given how many close friends and drinking buddies are not in their social organization, recruiting through fraternities and sororities at the host institution would likely be insufficient for recruiting participants' close friends and drinking buddies.

Data collection now occurs at a nearby institution. Both schools are public, 4-year institutions that also offer advanced degrees. However, the new data collection site is a medium-sized university with a requirement that full-time students must live on campus during their first 2 years. This facilitates creating new social ties with fellow students at the institution over maintaining old ties with friends from high school. Moreover, there is a strong presence of Greek life, with 32% of undergraduate men and 36% of undergraduate women involved in fraternities or sororities and with 13 sorority and 16 fraternity chapters on campus. These conditions are more favorable for recruiting closed networks of drinkers via fraternities and sororities.

The student advisory panel provided suggestions for incentives, one of which was donating to the organization's charity of choice or philanthropy if a specific threshold of members of the organization participated in the study. However, this student-generated option was not approved by the institutional review board (IRB), with concerns that this form of incentive could lead to peer pressure to participate. As such, all incentives for participation are individual in nature. Participants receive a gift card worth US $20 for their baseline participation and a promotional item with their organization's Greek letters or crest on it (eg, sticker or keychain). Participants receive US $5 for each completed follow-up survey (for the 1-, 3-, and 6-month assessments). As an additional incentive, participants who complete all assessments will be given US $5 as bonus (yielding US $40 in total if all follow-ups are completed). All individual monetary compensation is provided via web-based gift card.

Ethics Approval

The study protocol was approved by the Old Dominion University IRB (protocol 1565916-7). As noted previously, approval was also secured by the William & Mary Protection of Human Subjects Committee (protocol PHSC-2021-12-31-15372) and the National Panhellenic Conference's research committee.

Study Procedures

Overview

We worked with the school administrators and chapter presidents to obtain member lists and recruit potential participants. Participants may schedule their baseline session at a time of their choice (completely web-based) and meet with a research assistant via web-based meeting platform. Follow-up emails are sent 1, 3, and 6 months after participation, with daily reminders sent for up to 30 days (or until the relevant survey is completed). We ask participants to opt in to alternative contact methods in the baseline assessment (ie, nonschool email addresses and phone numbers for texting) to facilitate high retention in the follow-up surveys. This study is registered in ClinicalTrials.gov (NCT05107284) and is funded by the National Institute on Alcohol Abuse and Alcoholism (refer to Multimedia Appendix 1 for the summary statement provided during grant peer review).

Recruitment

To obtain member lists for recruitment purposes, we asked the campus administrators to share information about who is involved in Greek life. Although they were amenable to this request, they required more protection than that required by the federal regulations or IRB. For instance, they required that we secure approval from the research committee of the National Panhellenic Conference (a national network with 26 sororities). Campus administrators also requested that the recruitment site's IRB review the proposal, even though we had an institutional agreement naming the host institution as the lead approving IRB. Approval was eventually obtained from the National Panhellenic Conference's research committee and the site IRB, but this created some project delays. After securing all relevant approvals, the campus administrators provided the names and institutional email addresses for presidents of local chapters of the 16 fraternities and 13 sororities.

We grouped chapters with similar membership sizes, and for our first round of selection, we randomly assigned one from each pair to each study condition. We will continue selecting and enrolling chapters until the target enrollment is reached. After selecting a round of chapters, we contacted the presidents of those chapters to explain the purpose and design of the study, share our approvals from the relevant IRBs and the National Panhellenic Conference's research committee, and share that we have a Certificate of Confidentiality from the National Institutes of Health. Presidents who opt in for their chapter's participation share membership lists (names and email addresses), help in selecting a promotional item for compensation purposes, and help in identifying optimal data collection windows (described in more detail in the Baseline section). Names on membership lists are used for social network assessment in each survey (described in more detail in the Measures section). Emails are sent to all members in the participating organizations. This email contains content similar to that of the email sent to chapter presidents (ie, study purpose and design, relevant approvals, and compensation structure). We also ask chapter presidents if we may attend a chapter meeting to describe the study in more detail and answer questions. Overall, 25% (1/4) of the enrolled organizations have chosen to do this so far. Undergraduate research assistants, who are also members of Greek life, make these visits. Recruitment emails include a link to schedule a web-based baseline session.

Baseline

The project staff work with each chapter president to identify times that may work well for most members (such as participating before or after a chapter meeting), but several other meeting times are also available to maximize the availability of participation. Participants schedule their participation time through a web-based time management system. They receive an email reminder from the time management system 24 hours before their assigned time slot. Regardless of the condition, participants complete a baseline session with research staff over a meeting platform, with cameras and microphones enabled. Upon signing in to the meeting, the research assistants provide participants with a link (using the chat function) to a web-based survey. Participants read and view videos of the study procedures on the first page of this website. After reviewing the videos, participants are provided with the informed consent document and have the opportunity to ask questions. After consenting to participate, the web page automatically loads the baseline survey (approximately 30-45 minutes), which assesses their behaviors over the past 30 days.

After completing the initial assessment, participants are directed to navigate through a web-based intervention program to address college drinking (Alcohol eCHECKUP TO GO) until it is completed (approximately 20-30 minutes). As participants navigate through the website, research assistants remain on the virtual meeting to ensure that the participants do not go off-task such as walking away from the computer screen or looking at their phone. However, they do not monitor the participants' progress or responses through the program. Baseline sessions can accommodate up to 20 participants per session, but typically, 1-2 participants participate per session.

Intervention

When we first contacted the campus administrators at the data collection institution, all incoming students were required to complete alcohol programing before arriving on campus for their first semester, specifically AlcoholEDU for College. This program has been empirically supported, with a recent meta-analysis revealing consistent reductions in overall and peak drinking after the intervention [55]. However, the institution changed midyear to another program that lacks empirical support. Moreover, after examining the content of the new program, we saw an absence of empirically supported components such as personalized normative feedback, an important component for effective interventions [51,56]. Although there is exposure to an alcohol education program before matriculation (either AlcoholEDU for College or another), Alcohol eCHECKUP TO GO is different, and therefore offers new information to Greek life participants.

Alcohol eCHECKUP TO GO is a web-based intervention customized to each institution using it, such as including local resources and institution-specific norms. The program asks students questions (such as expectations about drinking alcohol, individual risk factors, perceptions of peer use, student goals, etc), and then provides a personalized feedback report. Alcohol eCHECKUP TO GO has been repeatedly documented as efficacious, with several studies documenting its efficacy among college students, as noted in the Introduction section. It was tailored for this study, with normative information specific to the data collection institution.

Follow-up Sessions

Approximately 1, 3, and 6 months after the initial assessment, researchers send each participant an email inviting them to complete a follow-up assessment, which contains a link to the web-based survey. Daily reminders are sent for up to 30 days or until the relevant survey is completed. If participants opt in to provide additional ways to contact them (a second email address or a phone number to send SMS text message), these methods are also used to send the link to the follow-up surveys.

Booster

Personalized feedback emailed to participants at 2 and 14 weeks after the baseline session serve as a booster to the original intervention. Baseline data are used to provide students with normative information and reminders of protective behavioral strategies they can use to reduce drinking-related harm. The personalized normative feedback uses institution-specific data from previous studies by the research team. The feedback compares (1) their typical weekly consumption provided at baseline, (2) their normative perceptions (ie, what they think their close friends and other typical students at their university consume), (3) the average consumption of actual male and female students at their university, and (4) the percentage of gender-matched students at their university who drink less than them. This information is provided to participants with a colorful bar graph and accompanying text. The reminders of harm reduction strategies (eg, "Alternating alcoholic and nonalcoholic beverages when you are drinking") are presented separately for strategies participants report using versus strategies they may consider starting to use. A tracking image is included to record if and when each booster email is viewed.

Measures

Overview

All participants complete a computerized survey at the beginning of their baseline session that assesses alcohol use, alcohol-related problems, protective behavioral strategies for drinking and their perceived effectiveness, alcohol-related cognitions (motives, expectancies, and beliefs about alcohol use), cannabis and tobacco use, COVID-19 pandemic experiences, internalizing symptoms (symptoms of stress, anxiety, and depression), demographics, and social network (refer to Table 1 for list of all measures and citations). The social network assessment can be operationalized into network-level variables (eg, proportion of heavy drinkers in their network), but participants report who specifically they are friends with and whom they drink with, which will allow for the examination of the exploratory secondary aim about selection versus socialization. The primary outcomes of the study are alcohol use and related problems, as these are expected to reduce after the intervention and booster. Secondary outcomes include normative perceptions and protective behavioral strategies, given that they are directly addressed by the personalized booster feedback. Other constructs assessed are potential moderators (eg, alcohol-related cognitions and internalizing symptoms) or covariates (eg, pandemic experiences and demographics). Most constructs are assessed at all time points, but some are assessed only during the baseline session. Table 1 contains a complete list of the constructs assessed, measures used, and time points assessed for each.

Table 1. Constructs assessed in the study, including measure used and time points assessed.

Construct	Description	Measure	Time points assessed
Primary outcomes			
Alcohol use	Number of drinks consumed each day of a typical week for the past 30 days and number of hours lapsed while drinking	Daily Drinking Questionnaire [57]	All
Alcohol-related problems	Problems that participants report related to their alcohol use for the past 30 days	Brief Young Adult Alcohol Consequences Questionnaire [58]	All
Secondary outcomes			
Protective behavioral strategies	Unidimensional measure of strategies one can use to reduce drinking and related harms (past 30 days)	Protective Drinking Practices Scale [59]	All
Normative perceptions of peer drinking	Descriptive norms (perceptions of how much close friends and peers at the same institution drink) and injunctive norms (perceptions of close friends' approval of drinking)	Injunctive norms adapted from the study by Carey et al [60]	All
Social network	Assessment of behaviors of close friends in their organization and out of their organization (eg, drinking and social behaviors)	Adapted version [61] of the Brief Important People Interview [62]	All
Other measures			
Alcohol expectancies	Expectations about the effects of alcohol on an individual	Comprehensive Effects of Alcohol Questionnaire [63]	Baseline
Drinking motives	Why one engages in alcohol use	Drinking Motives Questionnaire–Revised [64]	Baseline
Alcohol beliefs	How salient alcohol use is to college life	College Life Alcohol Salience Scale [65]	Baseline
Cannabis and tobacco use	Current, past month, and lifetime use	Created by the researchers	All
Cannabis beliefs	How salient cannabis use is to college life	Perceived Importance of Marijuana to the College Experience Scale [66]	Baseline
Pandemic experiences	Questions about participants' experiences with the COVID-19 pandemic (eg, stressors)	Created by the researchers	Baseline
Depression	Measure of symptoms of depression in the past 30 days	Center for Epidemiologic Studies Depression Scale-10 [67]	Baseline
Anxiety	Measure of symptoms of general anxiety in the past 30 days	General Anxiety Disorder-7 [68]	Baseline
Stress	Measure of symptoms of perceived stress in the past 30 days (specifically the vulnerability subscale)	Perceived Stress Scale–Revised [69]	Baseline
Demographics	Information such as age, race, sex, GPA[a], class standing, athletic status, student status (full-time student vs part-time student), residential status, relationship status, and sexual identity	N/A[b]	Baseline

[a]GPA: grade point average.

[b]N/A: not applicable.

Attention Checks

Given the length of the surveys, each assessment contains several attention checks. These are items that are either directive in nature (eg, "For this item, select 'most of the time'") or have a clearly correct answer (eg, "Which is the highest number?"). They are included to detect inattention, such as if a participant is clicking through the survey without fully reading the items. Participants who are not fully providing their attention to the survey can introduce noise in the data and attenuate the study's power [70]. Given the investment in each participant in a study with this design (a longitudinal assessment of select individuals within specifically targeted organizations), it is not beneficial to exclude the data of inattentive individuals. Instead, live feedback is provided to direct them to focus their attention: "Your answer for this question is not correct. Your responses are very important to us. Please be sure to read questions thoroughly and answer carefully." Then, participants have to select the correct answer before moving on to the next question.

Data Analysis Plan

Before hypothesis testing, the data will be examined for normality and outliers. Histograms and values for skewness and kurtosis will be examined. Positively skewed variables will be natural log transformed, unless paired with an excessive number of zeroes. If there are an excess of zeroes in an outcome, the variable will be dichotomized if other values are not well represented or appropriate modeling techniques will be used

(eg, hurdle models) if other values are well represented. Boxplots and IQRs will be used to check for outliers. Extreme values will be winsorized (ie, cases are retained in the sample, but values are made less extreme). Cases with missing data will be compared with complete cases across major study variables to identify whether there are systematic differences in missingness. If significant associations are identified, these variables will be used as covariates in later analyses.

For primary aim 1, latent growth models will be used to examine the efficacy of the personalized feedback boosters sent via email. The model will specify 1 intercept and 2 slopes to capture initial postintervention change (with slope 1 loadings coded as 0 for baseline and 1 for each follow-up assessment) versus long-term impacts on alcohol use (slope 2 loadings coded as 0, 0, 2, and 5 to reflect months since the first follow-up). Multiple models will be conducted specifying different forms of the second slope (eg, linear vs quadratic change), with the best-fitting model serving as the final model. The intercept and both slopes will be regressed on study condition, with booster efficacy demonstrated as a significant, negative coefficient for the impact of study condition on slope 2. Separate models will be conducted for alcohol use versus alcohol-related problems (with time-varying covariates for alcohol use; eg, problems at month 1 will control for alcohol quantity at month 1). Sex will be controlled for in all models.

Given that the tailored feedback boosters address both descriptive drinking norms and protective behavioral strategies, these are considered as secondary outcomes. Models identical to the one described previously will be conducted (eg, latent growth models with 2 slopes, regressed on study condition), but with norms and protective behavioral strategies serving as the outcomes of interest rather than alcohol use or related problems (for addressing primary aim 2). All models will be conducted in Mplus (version 8; Mplus) [71] using maximum likelihood estimation. These analyses assume normally distributed outcomes; thus, for any outcome that demonstrates nonnormality, competing approaches will be explored (eg, variable transformation vs specifying a different distribution), and we will choose the best-fitting model for the data.

For the exploratory secondary aim, R-Simulation Investigation for Empirical Network Analysis will be used to conduct stochastic, actor-based models [72]. These will allow us to examine whether behavior change precedes network changes (ie, selection) or whether network changes precede behavior change (ie, socialization). These models will be conducted only if reductions in drinking or related problems are observed in the primary aim 1 examination (ie, there is behavior change over time) and if several members of each organization participate (so that network change can be examined over time).

Power Analysis

Power estimations were conducted using Monte Carlo simulation methods within a structural equation modeling framework [73]. Estimates of effect sizes, variances, and covariances were based on data from a preliminary study using a similar protocol (some participants received only the intervention, whereas others received the intervention and booster) among college drinkers [43]. A meta-analysis of randomized controlled trials assessing alcohol interventions for first-year college students indicated an average retention rate of 76% across studies [74]; therefore, this retention estimate was used for the power analysis. Monte Carlo simulation methods indicated that for the expected effect size (b=6.57; β=.537) and expected 24% attrition, total sample size of 180 students should yield power=0.82 to detect differences in the slope estimate across study conditions.

Results

The IRB approval was obtained in November 2021, with the amendment to switch data collection sites approved in February 2022. Approval was obtained from the research committee of the National Panhellenic conference in January 2022. As of September 2022, we have enrolled 18 participants from 2 fraternities and 2 sororities, and they have completed the baseline survey. Of the 18 participants, 13 (72%) participants have completed the 1-month follow-up. We expect to complete enrollment by the end of 2022. Analysis has not yet begun, but is expected to begin immediately following the completion of the last follow-up assessment (ie, July 2023).

Discussion

Overview

This study addresses alcohol use and related problems among members of sororities and fraternities, an at-risk population that often engages in heavier drinking than their non-Greek counterparts, typically reporting more consequences [9,11-13]. As members of Greek life are a group that has not responded to previous intervention efforts [20], they are in need of efforts to strengthen and extend intervention effects. Personalized feedback boosters sent via email have led to further drinking reductions among select college drinkers [43,49], suggesting that they may be a promising tool for reducing drinking among members of fraternities and sororities. This study examines the efficacy of personalized boosters emailed after interventions to address alcohol use and related problems (primary aim 1) and normative perceptions and protective behavioral strategies (primary aim 2). We hypothesize initial postintervention drinking reductions for both study conditions, with individuals in the booster condition reporting further reductions at later follow-ups. We also hypothesize that individuals in the booster condition will report further reductions in norms and increases in protective behavioral strategies at later follow-ups.

Given the close connections among members of fraternities and sororities, these may be closed peer networks that can facilitate the examination of how changes in drinking occur through social influence. Thus, this study has an exploratory secondary aim to examine social mechanisms of change (ie, through selection vs socialization). This aim will be examined only if the booster is efficacious and if several members of each organization participate.

Methodological Challenges and Consideration

This study has presented several unexpected challenges, leading to revisions in the protocol. After learning from the study advisory panel about the nature of Greek life at the host institution, a new data collection site was identified. Campus

administrators also requested additional approvals beyond those required by federal guidelines. Finally, the data collection institution changed the programs addressing college drinking among their student body. To control for previous exposure to other programs, the project staff examined the new program and how comparable it was with the old program. Each of these challenges caused delay of a month or more, and collectively, they had a major impact on the study time line and therefore the study budget. By the time data collection was launched, the institution had begun its spring break. After returning from the spring break, students were focused on the final exams and end of the semester, thus hindering data collection.

Another major challenge is our attempt to recruit whole networks, because of which we cannot use typical data collection methods such as sending emails to the entire student body, posting student announcements, hanging flyers around the campus, and so on. To try to enroll entire organizations, we focus our recruitment efforts on chapter presidents, and then solicit their help with recruitment of their members (obtain member lists and email addresses, help in selecting promotional item, obtain access to chapter meetings for recruitment purposes, etc). This means that the president serves as a gatekeeper to their organization, and if they are not interested, are wary of unsolicited email, or do not keep up with their email, it prevents their entire organization from participating. We send recruitment emails from members of the research team both within and outside the data collection institution and at different times of the day to increase the probability of having any individual chapter president read the recruitment emails. This challenge was compounded by an institutional transition to a new student email provider, which resulted in a change in student email addresses. This occurred midyear, and there was confusion among students, who may not have been good at monitoring the new email address during this time.

Providing adequate compensation was also a challenge. As we are recruiting full networks, we needed to not only consider compensation for the individual participants but also for the group as a whole to incentivize participation. Owing to concerns of coercion or peer pressure (ie, providing an incentive if a specific percentage of the organization participated in the baseline survey), the compensation method suggested by the study advisory board was not approved.

Institutional Administration

This study relies strongly on institutional administration to facilitate the study protocol (ie, providing information about existing alcohol harm reduction programs and connecting project staff with chapter presidents of fraternities and sororities). At the home institution, we have strong ties with the administrators who provide critical help to facilitate studies in launching quickly and running smoothly. These include individuals at the highest levels who strongly believe in the purpose of our research to help college students make healthy, responsible choices. It would have been beneficial to cultivate these connections at the data collection site also. When we had to change the recruitment site, we directly contacted the offices that can provide the information we needed and did not engage the high-level administrators. Although we provided ample information about the study purpose and the steps taken to secure participant confidentiality, we experienced delays and additional approval requirements. The process may have been fast and smooth if we had first cultivated a relationship with high-positioned administration officials who could have made these requests on our behalf, possibly with better results.

Fully Remote Data Collection

We planned for fully remote data collection because of pandemic-related restrictions on in-person data collection at the host institution. Although these restrictions were being eased as we prepared to launch the study, we worried that they could be reintroduced if case counts rise. This was helpful, as we changed to data collection at another institution. The institution is nearby, but still approximately an hour away; we did not want this travel time as a requirement for the participants or research assistants. Remote data collection has been both an advantage and disadvantage. The student advisory panel indicated a strong preference for remote data collection via virtual meetings, rather than face-to-face meetings. This may be much more convenient for participants, as they do not have to travel to a specific location (or allow for travel time in their schedule). Volunteer research assistants have shared that they appreciate the convenience of this data collection method, and it allows for web-based students to obtain research experience, which is often a challenge. However, enrollment within an organization might be high if we could attend a chapter meeting in person with laptops or other devices to facilitate baseline session participation. It also presented some early challenges in terms of identifying a web-based scheduling system, creating meetings that will allow research assistants from different institutions to be the host, and so on, but all these challenges were resolved fairly easily.

Informational Videos

Given the complexities of this study, we thought that it was of critical importance for participants to understand the protocol. Moreover, we have a large team of research assistants who are ready to help with data collection. As such, we created informational videos that provide all the information they need for the study (in addition to reading the informed consent document). The videos are created in a program that uses clip art–style images, allowing race, gender, and other identities to not be present in the videos, unlike if the researchers created videos of themselves presenting the information. Overall, 3 videos were created. The first video reviewed the purpose of the study and provided information about confidentiality to participants. The second video explained the steps involved in the baseline session and related compensation. The third video provided information about the long-term steps of the study (follow-up surveys and feedback emails) and related compensation. Using the videos to provide this information, rather than a research assistant, allows for participants who are late to the session to still receive the necessary information, without the research assistant needing to repeat themselves or distract participants who already began the survey (ie, lets participants go through the information at their own pace). In addition, it allows for a standardized way for participants to receive important information about the study. In other words,

everyone hears and reads the same information, regardless of who is leading the session that day, thus providing guaranteed fidelity.

Recommendations and Future Directions

Given the challenges we experienced, we list several recommendations for researchers. Cultivating a relationship with high-ranking administration officials can potentially help future researchers to either prevent or better address potential challenges. We may not have been required to secure additional approvals, may have received our requested information fast, and may have learned about upcoming changes early (for email and alcohol programming transitions). Our student advisory panel was incredibly helpful in forming the design of the study, and we recommend their use to other researchers moving into a new method or population. We recommend against study protocols that include single gatekeepers (in our case, chapter presidents); we suggest identifying other methods when possible. If gatekeepers are required, better methods should be identified to secure buy-in and promote group participation (such as our prohibited charity donation). We also recommend being proactive in addressing data quality, such as informational videos to ensure fidelity of information transfer to participants, and methods to detect survey inattention that can provide live feedback, such as attention check items.

Study Implications and Potential Impact

Project Greek assesses the utility of an email-delivered personalized feedback booster after a web-based intervention with Greek-involved college students. This population typically drinks more heavily than their peers and is often resistant to intervention, making them an ideal population for this approach. Alcohol eCHECKUP TO GO was selected as the intervention owing to its empirical support and low cost. In addition, both the booster and intervention use mobile technology that allows for remote delivery. The results of this study may reveal a path for reducing drinking in this high-risk group, which does not require many resources and is both cost-effective and easy to disseminate. In summary, Project Greek will provide information about the efficacy of personalized feedback boosters after a web-based intervention to address risky drinking among members of Greek life. This is a promising avenue of research toward the goal of helping college students to make healthy, responsible choices about their drinking.

Conclusions

Project Greek has great potential to address the high-risk drinking patterns documented repeatedly among members of Greek life. The protocol described here assesses the utility of personalized normative feedback delivered via email after a web-based intervention for members of fraternities and sororities, using the same automated technology and remote delivery as the original intervention. However, there were numerous challenges in launching the study, resulting in several updates to the protocol. These included changing the data collection institution and securing additional approvals to work with administrative offices on campus, among others. Persistent limitations include the use of a recruitment method that includes gatekeepers for access to other participants (ie, chapter presidents) and the inability to provide group-level incentives. Using a student advisory panel was a helpful approach for obtaining feedback about the protocol before launching it, and we recommend its use to other researchers.

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Data Availability

Data will be available from the principal investigator upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report by Epidemiology, Prevention and Behavior Research Review Subcommittee - National Institute on Alcohol Abuse and Alcoholism (AA-2) Initial Review Group - National Institute on Alcohol Abuse and Alcoholism (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 162 KB - resprot_v11i10e42535_app1.pdf]

References

1. Bolin RM, Pate M, McClintock J. The impact of alcohol and marijuana use on academic achievement among college students. Soc Sci J 2017;54(4):430-437. [doi: 10.1016/j.soscij.2017.08.003]
2. Conway JM, DiPlacido J. The indirect effect of alcohol use on GPA in first-semester college students: the mediating role of academic effort. J Coll Stud Ret 2015 Mar 16;17(3):303-318. [doi: 10.1177/1521025115575705]

3. Hingson R, Zha W, Smyth D. Magnitude and trends in heavy episodic drinking, alcohol-impaired driving, and alcohol-related mortality and overdose hospitalizations among emerging adults of college ages 18-24 in the United States, 1998-2014. J Stud Alcohol Drugs 2017 Jul;78(4):540-548 [FREE Full text] [doi: 10.15288/jsad.2017.78.540] [Medline: 28728636]
4. Patrick ME, Terry-McElrath YM, Evans-Polce RJ, Schulenberg JE. Negative alcohol-related consequences experienced by young adults in the past 12 months: differences by college attendance, living situation, binge drinking, and sex. Addict Behav 2020 Jun;105:106320 [FREE Full text] [doi: 10.1016/j.addbeh.2020.106320] [Medline: 32007832]
5. Table 2.28B: Binge Alcohol Use in Past Month: Among People Aged 12 or Older; by Age Group and Demographic Characteristics, Percentages, 2019 and 2020. Substance Abuse and Mental Health Services Administration. 2019 National Survey on Drug Use and Health (NSDUH). 2019. URL: https://www.samhsa.gov/data/report/2020-nsduh-detailed-tables [accessed 2022-10-07]
6. Testa M, Hoffman JH. Naturally occurring changes in women's drinking from high school to college and implications for sexual victimization. J Stud Alcohol Drugs 2012 Jan;73(1):26-33 [FREE Full text] [doi: 10.15288/jsad.2012.73.26] [Medline: 22152659]
7. Capone C, Wood MD, Borsari B, Laird RD. Fraternity and sorority involvement, social influences, and alcohol use among college students: a prospective examination. Psychol Addict Behav 2007 Sep;21(3):316-327 [FREE Full text] [doi: 10.1037/0893-164X.21.3.316] [Medline: 17874882]
8. Glassman TJ, Dodd VJ, Sheu JJ, Rienzo BA, Wagenaar AC. Extreme ritualistic alcohol consumption among college students on game day. J Am Coll Health 2010;58(5):413-423. [doi: 10.1080/07448480903540473] [Medline: 20304753]
9. Huchting K, Lac A, LaBrie JW. An application of the Theory of Planned Behavior to sorority alcohol consumption. Addict Behav 2008 Apr;33(4):538-551 [FREE Full text] [doi: 10.1016/j.addbeh.2007.11.002] [Medline: 18055130]
10. Scott-Sheldon LA, Carey KB, Carey MP. Health behavior and college students: does Greek affiliation matter? J Behav Med 2008 Feb;31(1):61-70 [FREE Full text] [doi: 10.1007/s10865-007-9136-1] [Medline: 17999173]
11. Ragsdale K, Porter JR, Mathews R, White A, Gore-Felton C, McGarvey EL. “Liquor before beer, you're in the clear”: binge drinking and other risk behaviours among fraternity/sorority members and their non-Greek peers. J Subst Use 2012;17(4):323-339. [doi: 10.3109/14659891.2011.583312]
12. Soule EK, Barnett TE, Moorhouse MD. Protective behavioral strategies and negative alcohol-related consequences among US college fraternity and sorority members. J Subst Use 2015;20(1):16-21. [doi: 10.3109/14659891.2013.858783]
13. Wechsler H, Kuh G, Davenport AE. Fraternities, sororities and binge drinking: results from a national study of American colleges. NASPA J 2009 Oct 20;46(3):395-416. [doi: 10.2202/1949-6605.5017]
14. Sidani JE, Shensa A, Primack BA. Substance and hookah use and living arrangement among fraternity and sorority members at US colleges and universities. J Community Health 2013 Apr;38(2):238-245 [FREE Full text] [doi: 10.1007/s10900-012-9605-5] [Medline: 22903805]
15. Caudill BD, Crosse SB, Campbell B, Howard J, Luckey B, Blane HT. High-risk drinking among college fraternity members: a national perspective. J Am Coll Health 2006;55(3):141-155. [doi: 10.3200/JACH.55.3.141-155] [Medline: 17175900]
16. Rodriguez LM, Young CM, Tomkins MM, DiBello AM, Krieger H, Neighbors C. Friends in low places: the impact of locations and companions on 21st birthday drinking. Addict Behav 2016 Jan;52:52-57 [FREE Full text] [doi: 10.1016/j.addbeh.2015.08.009] [Medline: 26363304]
17. Phua J. The influence of peer norms and popularity on smoking and drinking behavior among college fraternity members: a social network analysis. Soc Influ 2011 Jul;6(3):153-168. [doi: 10.1080/15534510.2011.584445]
18. Park A, Sher KJ, Krull JL. Risky drinking in college changes as fraternity/sorority affiliation changes: a person-environment perspective. Psychol Addict Behav 2008 Jun;22(2):219-229 [FREE Full text] [doi: 10.1037/0893-164X.22.2.219] [Medline: 18540719]
19. Park A, Sher KJ, Krull JL. Selection and socialization of risky drinking during the college transition: the importance of microenvironments associated with specific living units. Psychol Addict Behav 2009 Sep;23(3):404-414 [FREE Full text] [doi: 10.1037/a0016293] [Medline: 19769425]
20. Scott-Sheldon LA, Carey KB, Kaiser TS, Knight JM, Carey MP. Alcohol interventions for Greek letter organizations: a systematic review and meta-analysis, 1987 to 2014. Health Psychol 2016 May 16;35(7):670-684 [FREE Full text] [doi: 10.1037/hea0000357] [Medline: 27183305]
21. CollegeAIM Alcohol Intervention Matrix: Individual-Level Strategies. National Institute on Alcohol Abuse and Alcoholism. Bethesda, MD, USA: U.S. Department of Health and Human Services; 2019. URL: https://www.collegedrinkingprevention.gov/CollegeAIM/IndividualStrategies/default.aspx [accessed 2022-10-07]
22. Alfonso J. The role of social norms in personalized alcohol feedback: a dismantling study with emerging adults. J Child Adolesc Subst Abuse 2015 Jun 25;24(6):379-386. [doi: 10.1080/1067828x.2013.872064]
23. Doumas DM, Andersen LL. Reducing alcohol use in first-year university students: evaluation of a Web-based personalized feedback program. J Coll Couns 2009;12(1):18-32. [doi: 10.1002/j.2161-1882.2009.tb00037.x]
24. Doumas DM, Kane CM, Navarro TB, Roman J. Decreasing heavy drinking in first-year students: evaluation of a web-based personalized feedback program administered during orientation. J Coll Couns 2011;14(1):5-20. [doi: 10.1002/j.2161-1882.2011.tb00060.x]

25. Doumas DM, Nelson K, DeYoung A, Renteria CC. Alcohol-related consequences among first-year university students: effectiveness of a web-based personalized feedback program. J Coll Couns 2014 Jul 01;17(2):150-162. [doi: 10.1002/j.2161-1882.2014.00054.x]
26. Hustad JT, Barnett NP, Borsari B, Jackson KM. Web-based alcohol prevention for incoming college students: a randomized controlled trial. Addict Behav 2010 Mar;35(3):183-189 [FREE Full text] [doi: 10.1016/j.addbeh.2009.10.012] [Medline: 19900763]
27. Lane DJ, Lindemann DF, Schmidt JA. A comparison of computer-assisted and self-management programs for reducing alcohol use among students in first year experience courses. J Drug Educ 2012;42(2):119-135. [doi: 10.2190/DE.42.2.a] [Medline: 23185834]
28. Walters ST, Vader AM, Harris TR. A controlled trial of web-based feedback for heavy drinking college students. Prev Sci 2007 Mar;8(1):83-88. [doi: 10.1007/s11121-006-0059-9] [Medline: 17136461]
29. Braitman AL, Strowger M, Lau-Barraco C, Shipley JL, Kelley ML, Carey KB. Examining the added value of harm reduction strategies to emailed boosters to extend the effects of online interventions for college drinkers. Psychol Addict Behav 2022 Sep;36(6):635-647. [doi: 10.1037/adb0000755] [Medline: 34081487]
30. Ganz T, Braun M, Laging M, Schermelleh-Engel K, Michalak J, Heidenreich T. Effects of a stand-alone web-based electronic screening and brief intervention targeting alcohol use in university students of legal drinking age: a randomized controlled trial. Addict Behav 2018 Feb;77:81-88. [doi: 10.1016/j.addbeh.2017.09.017] [Medline: 28985586]
31. Chavez K, Palfai TP. Reducing heavy episodic drinking among college students using a combined web and interactive text messaging intervention. Alcohol Treat Q 2021;39(1):82-95. [doi: 10.1080/07347324.2020.1784067]
32. Fazzino TL, Rose GL, Helzer JE. An experimental test of assessment reactivity within a web-based brief alcohol intervention study for college students. Addict Behav 2016 Jan;52:66-74 [FREE Full text] [doi: 10.1016/j.addbeh.2015.08.011] [Medline: 26363306]
33. Jouriles EN, Brown AS, Rosenfield D, McDonald R, Croft K, Leahy MM, et al. Improving the effectiveness of computer-delivered personalized drinking feedback interventions for college students. Psychol Addict Behav 2010 Dec;24(4):592-599. [doi: 10.1037/a0020830] [Medline: 21198222]
34. Murphy JG, Dennhardt AA, Skidmore JR, Martens MP, McDevitt-Murphy ME. Computerized versus motivational interviewing alcohol interventions: impact on discrepancy, motivation, and drinking. Psychol Addict Behav 2010 Dec;24(4):628-639 [FREE Full text] [doi: 10.1037/a0021347] [Medline: 21198224]
35. Murphy JG, Dennhardt AA, Yurasek AM, Skidmore JR, Martens MP, MacKillop J, et al. Behavioral economic predictors of brief alcohol intervention outcomes. J Consult Clin Psychol 2015 Dec;83(6):1033-1043 [FREE Full text] [doi: 10.1037/ccp0000032] [Medline: 26167945]
36. Walters ST, Vader AM, Harris TR, Field CA, Jouriles EN. Dismantling motivational interviewing and feedback for college drinkers: a randomized clinical trial. J Consult Clin Psychol 2009 Feb;77(1):64-73 [FREE Full text] [doi: 10.1037/a0014472] [Medline: 19170454]
37. Tahaney KD, Palfai TP. Text messaging as an adjunct to a web-based intervention for college student alcohol use: a preliminary study. Addict Behav 2017 Oct;73:63-66. [doi: 10.1016/j.addbeh.2017.04.018] [Medline: 28478315]
38. Welter TL, Rossmann PD, Hines HE. A health risk assessment and early alcohol intervention program for non-mandated students. J Am Coll Health 2022 Jul;70(5):1508-1517. [doi: 10.1080/07448481.2020.1808661] [Medline: 32877615]
39. Alfonso J, Hall TV, Dunn ME. Feedback-based alcohol interventions for mandated students: an effectiveness study of three modalities. Clin Psychol Psychother 2013;20(5):411-423. [doi: 10.1002/cpp.1786] [Medline: 22362618]
40. Bernstein MH, Baird GL, Yusufov M, Mastroleo NR, Carey KB, Graney DD, et al. A novel approach for streamlining delivery of brief motivational interventions to mandated college students: using group and individual sessions matched to level of risk. Subst Use Misuse 2017 Dec 06;52(14):1883-1891 [FREE Full text] [doi: 10.1080/10826084.2017.1318148] [Medline: 28812420]
41. Doumas DM, Workman CR, Navarro A, Smith D. Evaluation of web-based and counselor-delivered feedback interventions for mandated students. J Addict Offender Couns 2011;32(1-2):16-28. [doi: 10.1002/j.2161-1874.2011.tb00204.x]
42. Doumas DM, Workman C, Smith D, Navarro A. Reducing high-risk drinking in mandated college students: evaluation of two personalized normative feedback interventions. J Subst Abuse Treat 2011 Jun;40(4):376-385. [doi: 10.1016/j.jsat.2010.12.006] [Medline: 21295938]
43. Braitman AL, Henson JM. Personalized boosters for a computerized intervention targeting college drinking: the influence of protective behavioral strategies. J Am Coll Health 2016 Oct;64(7):509-519 [FREE Full text] [doi: 10.1080/07448481.2016.1185725] [Medline: 27148633]
44. Müller-Riemenschneider F, Reinhold T, Nocon M, Willich SN. Long-term effectiveness of interventions promoting physical activity: a systematic review. Prev Med 2008 Oct;47(4):354-368. [doi: 10.1016/j.ypmed.2008.07.006] [Medline: 18675845]
45. Tolan PH, Gorman-Smith D, Henry D, Schoeny M. The benefits of booster interventions: evidence from a family-focused prevention program. Prev Sci 2009 Dec;10(4):287-297. [doi: 10.1007/s11121-009-0139-8] [Medline: 19513845]
46. Longabaugh R, Woolard RE, Nirenberg TD, Minugh AP, Becker B, Clifford PR, Licsw, et al. Evaluating the effects of a brief motivational intervention for injured drinkers in the emergency department. J Stud Alcohol 2001 Nov;62(6):806-816. [doi: 10.15288/jsa.2001.62.806] [Medline: 11838918]

47. Carey KB, Scott-Sheldon LA, Elliott JC, Garey L, Carey MP. Face-to-face versus computer-delivered alcohol interventions for college drinkers: a meta-analytic review, 1998 to 2010. Clin Psychol Rev 2012 Dec;32(8):690-703 [FREE Full text] [doi: 10.1016/j.cpr.2012.08.001] [Medline: 23022767]
48. Neighbors C, Lewis MA, Atkins DC, Jensen MM, Walter T, Fossos N, et al. Efficacy of web-based personalized normative feedback: a two-year randomized controlled trial. J Consult Clin Psychol 2010 Dec;78(6):898-911 [FREE Full text] [doi: 10.1037/a0020766] [Medline: 20873892]
49. Braitman AL, Lau-Barraco C. Personalized boosters after a computerized intervention targeting college drinking: a randomized controlled trial. Alcohol Clin Exp Res 2018 Sep;42(9):1735-1747 [FREE Full text] [doi: 10.1111/acer.13815] [Medline: 29995326]
50. Carey KB, Walsh JL, Merrill JE, Lust SA, Reid AE, Scott-Sheldon LA, et al. Using e-mail boosters to maintain change after brief alcohol interventions for mandated college students: a randomized controlled trial. J Consult Clin Psychol 2018 Sep;86(9):787-798 [FREE Full text] [doi: 10.1037/ccp0000339] [Medline: 30138017]
51. Lewis MA, Neighbors C. Social norms approaches using descriptive drinking norms education: a review of the research on personalized normative feedback. J Am Coll Health 2006;54(4):213-218 [FREE Full text] [doi: 10.3200/JACH.54.4.213-218] [Medline: 16450845]
52. Peterson R, Kramer MP, Pinto D, De Leon AN, Leary AV, Marin AA, et al. A comprehensive review of measures of protective behavioral strategies across various risk factors and associated PBS-related interventions. Exp Clin Psychopharmacol 2021 Jun;29(3):236-250. [doi: 10.1037/pha0000498] [Medline: 34264735]
53. Braitman AL, Lau-Barraco C. Descriptive norms but not harm reduction strategies as a mediator of personalized boosters after a computerized college drinking intervention. Alcohol Clin Exp Res 2020 Jan;44(1):284-296 [FREE Full text] [doi: 10.1111/acer.14248] [Medline: 31758564]
54. Barry A, Madson M, Moorer K, Christman K. Predicting use of protective behavioral strategies: does fraternity/sorority affiliation matter? J Stud Aff Res Pract 2016 Jun 24;53(3):294-304. [doi: 10.1080/19496591.2016.1165107]
55. Hennessy EA, Tanner-Smith EE, Mavridis D, Grant SP. Comparative effectiveness of brief alcohol interventions for college students: results from a network meta-analysis. Prev Sci 2019 Jul;20(5):715-740 [FREE Full text] [doi: 10.1007/s11121-018-0960-z] [Medline: 30604290]
56. Dotson KB, Dunn ME, Bowers CA. Stand-alone personalized normative feedback for college student drinkers: a meta-analytic review, 2004 to 2014. PLoS One 2015 Oct 8;10(10):e0139518 [FREE Full text] [doi: 10.1371/journal.pone.0139518] [Medline: 26447792]
57. Collins RL, Parks GA, Marlatt GA. Social determinants of alcohol consumption: the effects of social interaction and model status on the self-administration of alcohol. J Consult Clin Psychol 1985 Apr;53(2):189-200. [doi: 10.1037//0022-006x.53.2.189] [Medline: 3998247]
58. Kahler CW, Strong DR, Read JP. Toward efficient and comprehensive measurement of the alcohol problems continuum in college students: the brief young adult alcohol consequences questionnaire. Alcohol Clin Exp Res 2005 Jul;29(7):1180-1189. [doi: 10.1097/01.alc.0000171940.95813.a5] [Medline: 16046873]
59. Martin JL, Colvin KF, Madson MB, Zamboanga BL, Pazienza R. Optimal assessment of protective behavioral strategies among college drinkers: an item response theory analysis. Psychol Assess 2020 Apr;32(4):394-406 [FREE Full text] [doi: 10.1037/pas0000799] [Medline: 31999144]
60. Carey KB, Henson JM, Carey MP, Maisto SA. Perceived norms mediate effects of a brief motivational intervention for sanctioned college drinkers. Clin Psychol (New York) 2010 Mar;17(1):58-71 [FREE Full text] [doi: 10.1111/j.1468-2850.2009.01194.x] [Medline: 22238504]
61. DeMartini KS, Prince MA, Carey KB. Identification of trajectories of social network composition change and the relationship to alcohol consumption and norms. Drug Alcohol Depend 2013 Sep 01;132(1-2):309-315 [FREE Full text] [doi: 10.1016/j.drugalcdep.2013.02.020] [Medline: 23523132]
62. Zywiak W, Longabaugh R. The Brief Important People Interview Manual. Providence, RI, USA: Center for Alcohol and Addiction Studies; 2002.
63. Fromme K, Stroot EA, Kaplan D. Comprehensive effects of alcohol: development and psychometric assessment of a new expectancy questionnaire. Psychol Assess 1993 Mar;5(1):19-26. [doi: 10.1037/1040-3590.5.1.19]
64. Cooper ML. Motivations for alcohol use among adolescents: development and validation of a four-factor model. Psychological Assessment 1994 Jun;6(2):117-128. [doi: 10.1037/1040-3590.6.2.117]
65. Osberg TM, Atkins L, Buchholz L, Shirshova V, Swiantek A, Whitley J, et al. Development and validation of the College Life Alcohol Salience Scale: a measure of beliefs about the role of alcohol in college life. Psychol Addict Behav 2010 Mar;24(1):1-12. [doi: 10.1037/a0018197] [Medline: 20307107]
66. Pearson MR, Kholodkov T, Gray MJ, Marijuana Outcomes Study Team. Perceived Importance of Marijuana to the College Experience Scale (PIMCES): initial development and validation. J Stud Alcohol Drugs 2017 Mar;78(2):319-324 [FREE Full text] [doi: 10.15288/jsad.2017.78.319] [Medline: 28317514]
67. Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). Am J Prev Med 1994;10(2):77-84. [doi: 10.1016/s0749-3797(18)30622-6] [Medline: 8037935]

68. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006 May 22;166(10):1092-1097. [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
69. Wickrama KA, Ralston PA, O'Neal CW, Ilich JZ, Harris CM, Coccia C, et al. Linking life dissatisfaction to health behaviors of older African Americans through psychological competency and vulnerability. Res Aging 2012 Jun 13;35(5):591-611. [doi: 10.1177/0164027512449473]
70. Oppenheimer DM, Meyvis T, Davidenko N. Instructional manipulation checks: detecting satisficing to increase statistical power. J Exp Soc Psychol 2009 Jul;45(4):867-872. [doi: 10.1016/j.jesp.2009.03.009]
71. Muthén LK, Muthén BO. Mplus User's Guide. Version 8.4. 1998-2019. Los Angeles, CA, USA: Muthén & Muthén; 2019.
72. Ripley R, Snijders TA, Boda Z, Vörös A, Preciado P. Manual for SIENA. Version 4.0. Oxford, UK: University of Oxford, Department of Statistics; 2017.
73. Muthén LK, Muthén BO. How to use a Monte Carlo study to decide on sample size and determine power. Struct Equ Modeling 2002 Oct;9(4):599-620. [doi: 10.1207/S15328007SEM0904_8]
74. Scott-Sheldon LA, Carey KB, Elliott JC, Garey L, Carey MP. Efficacy of alcohol interventions for first-year college students: a meta-analytic review of randomized controlled trials. J Consult Clin Psychol 2014 Apr;82(2):177-188 [FREE Full text] [doi: 10.1037/a0035192] [Medline: 24447002]

Abbreviations

IRB: institutional review board

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Protocol

Leveraging Social Media to Increase Access to an Evidence-Based Diabetes Intervention Among Low-Income Chinese Immigrants: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Type 2 diabetes (T2D) in Chinese Americans is a rising public health concern for the US health care system. The majority of Chinese Americans with T2D are foreign-born older immigrants and report limited English proficiency and health literacy. Multiple social determinants of health limit access to evidence-based diabetes interventions for underserved Chinese immigrants. A social media–based diabetes intervention may be feasible to reach this community.

Objective: The purpose of the Chinese American Research and Education (CARE) study was to examine the potential efficacy of a social media–based intervention on glycemic control in Chinese Americans with T2D. Additionally, the study aimed to explore the potential effects of the intervention on psychosocial and behavioral factors involved in successful T2D management. In this report, we describe the design and protocol of the CARE trial.

Methods: CARE was a pilot randomized controlled trial (RCT; n=60) of a 3-month intervention. Participants were randomized to one of two arms (n=30 each): wait-list control or CARE intervention. Each week, CARE intervention participants received two culturally and linguistically tailored diabetes self-management videos for a total of 12 weeks. Video links were delivered to participants via WeChat, a free and popular social media app among Chinese immigrants. In addition, CARE intervention participants received biweekly phone calls from the study's community health workers to set goals related to T2D self-management and work on addressing goal-achievement barriers. Hemoglobin A_{1c} (HbA_{1c}), self-efficacy, diabetes self-management behaviors, dietary intake, and physical activity were measured at baseline, 3 months, and 6 months. Piecewise linear mixed-effects modeling will be performed to examine intergroup differences in HbA_{1c} and psychosocial and behavioral outcomes.

Results: This pilot RCT study was approved by the Institutional Review Board at NYU Grossman School of Medicine in March 2021. The first participant was enrolled in March 2021, and the recruitment goal (n=60) was met in March 2022. All data collection is expected to conclude by November 2022, with data analysis and study results ready for reporting by December 2023. Findings from this pilot RCT will further guide the team in planning a future large-scale study.

Conclusions: This study will serve as an important first step in exploring scalable interventions to increase access to evidence-based diabetes interventions among underserved, low-income, immigrant populations. This has significant implications for chronic care in other high-risk immigrant groups, such as low-income Hispanic immigrants, who also bear a high T2D burden, face similar barriers to accessing diabetes programs, and report frequent social media use (eg, WhatsApp).

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International Registered Report Identifier (IRRID): DERR1-10.2196/42554

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KEYWORDS

diabetes; health equity; immigrant health; mobile health; social media; messaging app; health education; education video; diabetes education; self-management

Introduction

Type 2 diabetes (T2D), which accounts for 90% to 95% of diabetes cases in the United States [1], is a persistent public health issue and results in significant economic costs [2]. According to the latest statistics, diabetes affects 37.3 million Americans [3] and remains the seventh-leading cause of death in the nation [4]. T2D disproportionately affects racial and ethnic minorities, including Asian Americans [5,6]. Compared to non-Hispanic White people, Asian Americans bear a higher T2D burden [5,7]. Indeed, one report found that about one in two Chinese Americans in New York City (NYC) has diabetes or prediabetes [8]. Many of these individuals are low-income, foreign-born Chinese immigrants who speak little or no English [8].

Diabetes self-management education and support (DSMES) programs have been widely recognized as effective strategies to promote diabetes self-management and improve glycemic control [9,10]. Traditionally, DSMES involves multiple in-person office visits (eg, 6 to 12 1-hour-long group sessions) with a certified diabetes educator or health coach, who provides important education and counseling about diabetes self-management and lifestyle changes [9,10]. These programs are, however, difficult to access for Chinese immigrants with T2D because of the barriers related to social determinants of health. First, our prior studies showed that 80% of Chinese immigrants with T2D reported limited English proficiency [11,12], which has been shown to correlate with health care discrimination and miscommunication [13]. Previous studies also found that even with translation services, individuals who report Chinese to be their preferred language know less about diabetes and have higher hemoglobin A_{1c} (HbA_{1c}) levels than those who prefer to speak English [14]. Second, the lack of cultural tailoring of existing evidence-based programs is another major barrier [15,16]. Most DSMES curricula are based on a western diet and culture, and dietary recommendations are often inconsistent with the dietary preferences of Chinese immigrants. Within such programs, Chinese immigrants find it difficult to initiate healthier dietary practices [15,17]. Third, these programs require traveling to a centralized location where counseling is delivered via multiple in-person sessions. Attending such programs can be challenging for low-income immigrants who face transportation barriers or have little-or-no sick leave [18]. Given the high T2D burden and the numerous barriers to accessing the DSMES programs, there is a pressing need to develop and test culturally tailored strategies to increase access to DSMES interventions for Chinese immigrants.

A social media–based strategy may be a viable solution to address the barriers mentioned above [19,20]. In earlier work, we found that in a sample of 91 older Chinese immigrants (mean age 70 years), most participants had smartphones and used a free social media app called WeChat to stay connected with family and friends in Mainland China or other parts of the United States [11]. The majority reported strong interest in receiving WeChat-based DSMES [11]. Building on these pilot data, we developed a 12-week culturally and linguistically tailored DSMES video program, consisting of two brief videos (5-10 minutes) per week sent to participants with T2D via WeChat, with biweekly phone calls to discuss the content and answer any questions they may have had [12]. Feasibility and acceptability of the intervention were assessed in a single-group pilot study (n=30), which demonstrated that over 90% of the videos were viewed, and 100% of participants were retained through the 12-week intervention period [12]. We also observed a reduction in HbA_{1c} and improvements in dietary behaviors and physical activity [12]. However, this was a single group pre- and posttest study design. To rigorously test this approach and control for potential confounders, we are conducting a pilot randomized controlled trial (RCT) to examine whether we can still observe the positive trends in improving health outcomes in Chinese immigrants with T2D.

The purpose of the Chinese American Research and Education (CARE) trial is to pilot-test the intervention in an RCT among Chinese Americans with T2D living in NYC. The main objective is to examine the potential efficacy of the CARE intervention for improving glycemic control. The secondary objective is to explore the potential effects of the CARE intervention on psychological and behavioral factors related to glycemic control. In this report, we describe the CARE trial study protocol.

Methods

Study Design

The CARE trial is a pilot RCT (n=60) with a 6-month duration. Participants were randomized to one of two arms (n=30 each): (1) wait-list control or (2) CARE intervention. HbA_{1c} levels, self-efficacy, diabetes self-management behaviors, dietary intake, and physical activity will be measured at baseline, 3 months, and 6 months.

Ethics Approval

This study was approved by the NYU Grossman School of Medicine Institutional Review Board (protocol s18-00609) and was registered at ClinicalTrials.gov (NCT03557697).

Eligibility Criteria

To be eligible for the study, participants must meet the following inclusion criteria:

1. Self-identify as a Chinese immigrant or Chinese American.
2. Be 18 to 70 years old.
3. Be able to speak and understand Mandarin.
4. Self-report a diagnosis of T2D.
5. Have a baseline HbA_{1c} of 7% or greater.
6. Have experience using WeChat or text messages.

7. Be willing to receive WeChat or text messages regarding T2D management.
8. Express willingness and confidence in their ability to watch two diabetes videos each week for a total of 12 weeks.
9. Express motivation to make lifestyle changes to control their diabetes.
10. Be willing to wear an ActiGraph accelerometer for 8 days.

Individuals are excluded from participation if they do any of the following:

1. Are unable or unwilling to provide verbal consent.
2. Are unable to participate meaningfully in the intervention (eg, uncorrected sight and hearing impairment).
3. Are unwilling to accept their randomization assignment.
4. Are pregnant or plan to become pregnant in the next 6 months, or become pregnant during the study.
5. Are breastfeeding.
6. Live in a facility or other health care setting where they have no control over diabetes self-management.

Recruitment

Overview

The study employed multipronged recruitment strategies within several NYC health care facilities, including the Charles B. Wang Community Health Center (CBWCHC), private primary care providers (PCPs), and NYU Langone Health (NYULH) and affiliated practices.

CBWCHC is a federally qualified health center with locations in both Manhattan's Chinatown and Queens Flushing's Chinatown. CBWCHC is one of the largest and leading community centers in NYC, having established a trusting relationship with the Chinese American community. Given that many Chinese immigrants seek diabetes care from their PCPs, we also worked with several PCP offices to recruit. In addition, NYU Langone Brooklyn Family Health Center is also a federally qualified health center and serves a large number of low-income Chinese and Hispanic immigrants in the Brooklyn Sunset Park area. We recruited participants from these clinic partners using three methods: posters, direct referral by providers, and electronic medical record Epic search and DataCore.

Posters

Posters were placed in the mentioned health care facilities' waiting and examination rooms. Posters listed a contact telephone number that patients can call if interested in enrolling. Patients who self-referred were screened for eligibility.

Direct Referral by Providers

CBWCHC, NYU Langone Brooklyn site providers, and private practice PCPs approached patients who were potentially eligible for the study and solicited their interest in the study. When patients expressed verbal interest in study participation, health care providers shared the patient's contact information with the study staff, or patients were advised to self-refer using the information provided on the study poster. A study staff member called the patient and, with the patient's verbal consent, the staff member conducted a telephone screening to confirm eligibility prior to study enrollment.

Electronic Medical Record Epic Search and DataCore

We worked through the NYULH DataCore—a resource that provides the NYULH research community with clinical data from the NYULH electronic medical record system and ancillary clinical systems—to recruit participants from NYU Langone Manhattan, Brooklyn, and Long Island campuses. The Epic electronic medical record was queried to identify and generate a report of potentially eligible patients, including their name, sex, date of birth, address, phone number, weight, height, BMI, name of PCP, and the date and result of their most recent HbA_{1c} test. Potentially eligible individuals were sent a letter via US postal mail describing the study and were provided with directions for opting out of future recruitment calls. Study staff contacted those not opting out to describe the study and, if interested, screened them for eligibility.

Overview of the Intervention

We are leveraging the DSMES intervention used in the Enhancing Adherence in Type 2 Diabetes (ENHANCE) trial, which has been shown to be effective for decreasing HbA_{1c} levels in a highly educated, predominately non-Hispanic White population [21]. Similar to the ENHANCE intervention, the CARE intervention is based on the widely used Social Cognitive Theory (SCT), which posits that self-efficacy is an important determinant of the performance of behavior and is affected by four major sources of information: mastery experiences, social modeling, verbal persuasion, and physiological states [22,23]. To promote mastery experience, intervention videos focused on encouraging participants to set incremental, easily achievable goals, and self-evaluate progress toward goals. Participants were counseled about the use of self-reward for goal achievement. Videos also involved training in problem-solving around common barriers to self-management. We operationalized social modeling with videos showing a Chinese patient sharing a similar immigration background who has been successful in managing T2D. We used verbal persuasion to support behavior change. We guided participants to recognize the physiologic benefits they would experience as a result of dietary changes and increased physical activity (eg, better sleep and better glucose control). In addition to the SCT-based content, we delivered educational videos about medication adherence, glucose monitoring, stress management, healthy eating and cooking, and tips to engage in physical activity.

The intervention adaptation was guided by the Cultural Adaptation Model [24] and the Ecological Validity Model (EVM) [25]. According to these models, the target community should be actively engaged throughout the adaptation process. During the first 2 years, we conducted extensive formative work to culturally adapt the ENHANCE intervention for Chinese immigrants. For example, we convened a community advisory board, which consisted of a primary care doctor, a diabetes educator, a nurse, and a patient with T2D, all of whom were Chinese immigrants or Chinese Americans and understood Chinese culture. We shared the outline of the intervention content and specific aspects of cultural adaptation (Table 1). Video prototypes were reviewed by members of the community advisory board for necessary modifications prior to their implementation.

The EVM adaptation model suggests considering the following eight domains for adaptation: language, person, metaphors, content, concepts, goal, method, and context [25]. For *language*, we translated the intervention materials into Mandarin Chinese. Whereas there are other dialects spoken by Chinese individuals, Mandarin is the official language of China and is understood by most people [26]. With regard to the *person* domain, all CARE team members are bilingual and bicultural members of the Chinese community. For the *metaphors* domain, we incorporated culturally relevant metaphors into the intervention content as appropriate. For the *content* and *concepts* domains, we tailored the T2D-related content and concepts based on Chinese culture and norms. For instance, we provided recommendations for healthy eating during traditional Chinese festivals. We also created a video demonstration of healthy grocery shopping at Chinese supermarkets. In the *goal* and *method* domains, the EVM advises delivering interventions using methods that are mutually agreeable and culturally acceptable. For example, rather than dictating study goals, patients were encouraged to set their own goals for participation. In addition, we used WeChat to deliver our intervention, a platform with which many Chinese immigrants are familiar. Lastly, with regard to the *context*, we provided information on local health care resources and Chinese grocery stores.

Table 1. Intervention content and cultural adaptation.

Week	Intervention component (educational + behavioral content)	Cultural adaptation
1	Overview of diabetes, self-management, and goals for life	T2D[a] risks in the context of Chinese culture and norms
2	T2D diet, healthy eating, and portion control (part 1); setting goals	T2D diet in the context of Chinese culture and norms
3	T2D diet, healthy eating, and portion control (part 2); self-reward	T2D diet in the context of Chinese culture and norms
4	Medication management; social support	Common barriers to taking medication among Chinese patients with T2D and strategies
5	Glucose self-monitoring; problem-solving model; problem-solving: barriers and setbacks	Local resources for obtaining free testing supplies
6	Exercise and diabetes; problem-solving: behavioral triggers	Misconceptions about exercise in Chinese culture and exercise examples popular in Chinese culture (eg, Tai Chi)
7	Building muscles with strength training; problem-solving: emotional eating	Misconceptions about strength training in Chinese culture and tips for starting strength training
8	Grocery shopping at a Chinese supermarket; problem-solving: cravings for white rice	A grocery shopping video at a Chinese supermarket in Chinatown
9	Stress and T2D; problem-solving: eliminating negative self-talk	Common causes of stress among Chinese patients with T2D and ways to cope
10	Chinese holidays and dining out; problem-solving: anticipating high-risk situations	Tips for healthy eating during Chinese festivals
11	Attending doctor appointments; problem-solving: lapses and relapse	Common barriers to seeking care among Chinese patients with T2D; local resources for low-income Chinese patients with T2D
12	Navigating the US health care system; problem-solving: coping with lapses and setting new goals	Local resources for low-income Chinese patients with T2D

[a]T2D: type 2 diabetes.

Randomization and Intervention Groups

Overview

The study's bilingual community health workers (CHWs) called patients and provided more details about the study. If the patient expressed interest in participation, the study CHW administered several screening questions. After eligibility was determined and verbal consent was obtained, a baseline survey was administrated over the phone, after which participants were randomized via a computer-generated randomization scheme with equal allocation to one of the two groups: wait-list control or CARE intervention.

Wait-list Control Group

Control group participants continued to receive the standard of care for T2D from their providers during our study. At the end of the study, all study videos will be offered to participants in the control group via WeChat links.

CARE Intervention

Participants in the intervention group received the standard of care, plus brief prerecorded videos, which included both educational and SCT-based behavioral content. Two culturally and linguistically tailored video links were sent each week via WeChat or regular text messages for a total of 12 weeks. Videos were 5 to 10 minutes in duration. WeChat and text messages were used only for video delivery. All other communication occurred via regular phone calls made from an NYULH-provided study phone. In particular, video delivery was supplemented by biweekly phone calls from the study CHW to review the video content, clarify questions, guide participants in setting goals, review progress toward goal achievement, and problem-solve any barriers or problems they encountered.

Procedures

The study involves measurements at baseline, 3 months, and 6 months. Participants will be paid US $30 for each completed measurement. Due to COVID-19, all data will be collected via telephone. To offset data plan expenditures incurred from watching intervention videos using their mobile phones, participants from both groups will be paid US $5 per week for a maximum total payment of US $60.

Measures

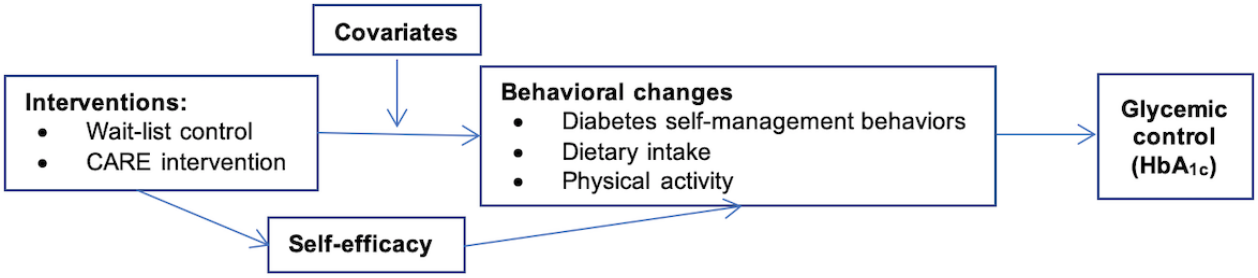
Primary Outcome

HbA_{1c} level is the primary outcome. As part of usual care, patients with T2D receive an HbA_{1c} blood test at their doctors' offices every 3 to 6 months. To minimize participant burden and possible COVID-19 exposure, no additional laboratory tests are required. Rather, HbA_{1c} results will be extracted from participants' electronic medical records.

Secondary Outcomes

Consistent with our conceptual model (Figure 1), we will measure self-efficacy, diabetes self-management behaviors, dietary intake, and physical activity at each time point (ie, baseline, 3 months, and 6 months).

Figure 1. Conceptual model. CARE: Chinese American Research and Education; HbA_{1c}: hemoglobin A_{1c}.



Self-efficacy

We used the Stanford Diabetes Self-Efficacy Scale [27] to measure participants' confidence in managing T2D. This instrument contains eight items and asks participants to rate their confidence level in performing specific self-management behaviors, using a 10-point Likert scale ranging from 1 (not at all confident) to 10 (totally confident).

Diabetes Self-Management Behaviors

We administered the Summary of Diabetes Self-Care Activities measure [28] to assess participants' adherence to diabetes self-management behaviors. This scale consists of 13 items and asks participants to describe their diabetes self-care activities over the past 7 days. It assesses participants' adherence to several key diabetes self-management behaviors, including diet, exercise, self-monitoring of blood glucose, foot care, and medication adherence.

Dietary Intake

Informed by a previous study among Chinese Americans [29], we used the adapted Mediterranean Dietary Screener [30] to estimate participants' dietary intake behaviors at baseline, 3 months, and 6 months. This questionnaire asks for participants' daily average intake of fruit, vegetables, refined grains, whole grains, sugary drinks, and potatoes over the past 30 days.

Physical Activity

We used the International Physical Activity Questionnaire [31] short version to assess the frequency and duration of various physical activities undertaken by adults over the past 7 days. This questionnaire will provide an estimate of the number of minutes per week participants engage in each category of physical activity (eg, vigorous, moderate, and mild intensity, as well as sedentary activity). We also used ActiGraph activity monitors to objectively measure physical activity and sleep. We mailed the device to participants once they were eligible for the study. Participants wore the ActiGraph for 8 days and returned it to the investigators using a prepaid envelope.

Covariates: Sociodemographic and Health Characteristics

A sociodemographic questionnaire was used to collect basic information about the participant, such as age, gender, education, income, duration of residence in the United States, health insurance, duration of T2D, and medical history.

Data Analysis

An intention-to-treat approach will be employed. We will also conduct a detailed descriptive analysis of all the data collected in the study. To establish the proof of concept regarding the efficacy of the CARE intervention for glycemic control among Chinese immigrants with T2D, we will test whether the two groups are comparable on baseline sociodemographic and health characteristics. If significant differences are found, we will include the variables as covariates in the models. We will fit the longitudinally collected HbA_{1c} measurement using piecewise linear mixed-effects models to compare the group difference in the HbA_{1c} level's changing trend over different periods, adjusting for the covariates as needed.

To explore the potential effects of the CARE intervention on psychosocial and behavioral factors in glycemic control, we will analyze the collected secondary outcomes. For continuous secondary outcome variables (ie, self-efficacy, adherence to diabetes self-management behaviors, physical activity, and dietary intake), piecewise linear mixed-effects modeling will be used to examine the group difference in each outcome's

changing trend from baseline to 3 months and from 3 to 6 months.

Sample Size Justification

According to Whitehead et al [32], to detect a small, standardized effect size of 0.2 in the primary outcome of HbA_{1c} with 80% power at a 5% significance level, a sample size of 50 is needed for a pilot RCT. Given the data from prior studies among Chinese Americans [33-35], we estimated an attrition rate of 15%. Thus, we planned to recruit a total of 60 participants, with 30 in each group, for this pilot RCT. With regard to secondary outcomes, given the pilot nature of this trial, we are not adequately powered to detect significant differences in self-efficacy, adherence to diabetes management behaviors, dietary intake, or physical activity.

Results

This pilot RCT is part of a 5-year career development K99/R00 award funded by the National Institutes of Health (NIH) from 2018 to 2023. The first 2 years of this career award (K99 phase) were devoted to formative research, including a qualitative study to understand barriers faced by Chinese immigrants with T2D and a single-group study to develop and test the feasibility of the social media–based CARE intervention [12]. The R00 phase started in June 2020, and the goal is to conduct a pilot RCT to examine the potential efficacy of the CARE intervention. This pilot RCT was launched in March 2021, with the first participant enrollment in March 2021. A total of 60 participants have been enrolled and were computer-randomized into two groups in March 2022. The 3-month assessment for all participants has been completed. Data collection for the 6-month assessment is expected to conclude in November 2022. Data analysis and final study results are expected to be reported by December 2023.

Discussion

Overview

This report describes the protocol and design of a pilot RCT of a social media–based diabetes intervention among Chinese immigrants with T2D. We hypothesize that this social media–based strategy is a promising medium to increase Chinese immigrants' self-efficacy and knowledge about their T2D, improve their dietary and physical activity behaviors, and ultimately improve their glycemic control. Participants in the intervention group are anticipated to have a greater reduction in HbA_{1c}, to be more confident in managing their diabetes, to consume healthier diets, and to be more active in physical activities than those in the control group.

It is well documented that T2D disproportionately affects racial and ethnic minorities [36], who face many barriers to accessing evidence-based diabetes interventions, barriers that are related to social determinants of health; these interventions are usually delivered with multiple in-person sessions [37,38]. Leveraging a social media platform that the underserved communities are familiar with is a convenient and scalable approach to enhancing their access to DSMES [11,12]. If ultimately found to be effective, CARE could easily be delivered to patients with T2D residing in other US locations that have large Chinese populations. CARE may also serve as a program model for reducing disparities in other high-risk populations that also bear a high T2D burden and face many social and health-related barriers to care, including African, Native, and Hispanic Americans and adults living in rural areas [37,39].

Strengths, Limitations, and Future Directions

CARE is a proof-of-concept randomized trial, the sample size is relatively small, and we are not adequately powered to detect statistical significances between groups for the secondary outcomes. However, informed by the NIH Stage Model for Behavioral Intervention Development [40], large investments in full-scale RCTs should be informed by pilot studies. Lessons learned in this pilot trial will also help us to plan the larger trial with regard to recruitment strategies, intervention videos, and survey questions. In addition, given the limited resources, we were only able to develop 24 videos in Mandarin Chinese. Therefore, for those who can only understand Cantonese or other dialects, they are not eligible to join the program. Yet, based on the most recent data, many Chinese immigrants who speak a different dialect are still able to understand Mandarin Chinese [26]. In addition, the study participants were only recruited from the NYC metropolitan area, and results may not be generalizable to the Chinese populations living in the Midwest where access to culturally tailored care may be even more limited.

Nonetheless, this study represents an initial step to exploring potential scalable strategies to increase access to evidence-based interventions among underserved, low-income, minority populations. If the results are promising, this may serve as an important milestone in considering how to deliver culturally and linguistically tailored interventions in underserved immigrant populations. Findings from this study will also serve as the foundation for a large full-scale RCT to test the program in a broad population.

Dissemination Plan

We will disseminate research findings through presentations at regional (eg, the Annual Health Disparity Symposium at NYU and the NYU Asian American Pacific Islander Health conference), national (eg, the American Diabetes Association Annual Symposium), and international meetings and conferences (eg, the International Conference on Behavioral Medicine). We will also publish findings in peer-reviewed journals. In addition, we will work closely with our partners to identify strategies to disseminate study findings to the Chinese American community. This can include patient forums held at community locations (eg, parks and community centers), newsletters mailed to study participants, or a one-page brief summary of research findings. We will also post study findings via social media platforms (eg, Twitter and WeChat).

Acknowledgments

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Data Availability

The data sets generated or analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

LH, NI, HL, and MAS were responsible for conceptualization and design of the study. LH, YZ, YS, and MAS wrote, reviewed, and edited the manuscript. NI, HL, and CW reviewed and edited the manuscript. We have complied with the authors' guidelines. LH is the guarantor for this manuscript.

Conflicts of Interest

LH reports holding stock in Tencent Holdings Limited.

Multimedia Appendix 1
Peer-review report reviewed by: National Institute on Minority Health and Health Disparities Special Emphasis Panel - NIH Pathway to Independence Award (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 134 KB - resprot_v11i10e42554_app1.pdf]

References

1. Type 2 diabetes. Centers for Disease Control and Prevention. URL: https://www.cdc.gov/diabetes/basics/type2.html [accessed 2022-06-13]
2. American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. Diabetes Care 2018 May;41(5):917-928 [FREE Full text] [doi: 10.2337/dci18-0007] [Medline: 29567642]
3. National Diabetes Statistics Report. Centers for Disease Control and Prevention. URL: https://www.cdc.gov/diabetes/data/statistics-report/index.html [accessed 2022-07-05]
4. Heron M. Deaths: Leading causes for 2019. Natl Vital Stat Rep 2021 Jul;70(9):1-114 [FREE Full text] [Medline: 34520342]
5. Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and trends in diabetes among adults in the United States, 1988-2012. JAMA 2015 Sep 08;314(10):1021-1029. [doi: 10.1001/jama.2015.10029] [Medline: 26348752]
6. Cheng YJ, Kanaya AM, Araneta MRG, Saydah SH, Kahn HS, Gregg EW, et al. Prevalence of diabetes by race and ethnicity in the United States, 2011-2016. JAMA 2019 Dec 24;322(24):2389-2398 [FREE Full text] [doi: 10.1001/jama.2019.19365] [Medline: 31860047]
7. Thorpe LE, Upadhyay UD, Chamany S, Garg R, Mandel-Ricci J, Kellerman S, et al. Prevalence and control of diabetes and impaired fasting glucose in New York City. Diabetes Care 2009 Jan;32(1):57-62 [FREE Full text] [doi: 10.2337/dc08-0727] [Medline: 19114627]
8. Rajpathak SN, Wylie-Rosett J. High prevalence of diabetes and impaired fasting glucose among Chinese immigrants in New York City. J Immigr Minor Health 2011 Feb;13(1):181-183 [FREE Full text] [doi: 10.1007/s10903-010-9356-2] [Medline: 20533090]
9. Davis J, Fischl A, Beck J, Browning L, Carter A, Condon J, et al. 2022 National Standards for Diabetes Self-Management Education and Support. Diabetes Care 2022 Feb 01;45(2):484-494. [doi: 10.2337/dc21-2396] [Medline: 35050365]
10. Powers M, Bardsley J, Cypress M, Funnell M, Harms D, Hess-Fischl A, et al. Diabetes Care 2020 Jul;43(7):1636-1649. [doi: 10.2337/dci20-0023] [Medline: 32513817]
11. Hu L, Trinh-Shevrin C, Islam N, Wu B, Cao S, Freeman J, et al. Mobile device ownership, current use, and interest in mobile health interventions among low-income older Chinese immigrants with type 2 diabetes: Cross-sectional survey study. JMIR Aging 2022 Feb 02;5(1):e27355 [FREE Full text] [doi: 10.2196/27355] [Medline: 35107426]
12. Hu L, Islam N, Trinh-Shevrin C, Wu B, Feldman N, Tamura K, et al. A social media-based diabetes intervention for low-income Mandarin-speaking Chinese immigrants in the United States: Feasibility study. JMIR Form Res 2022 May 11;6(5):e37737 [FREE Full text] [doi: 10.2196/37737] [Medline: 35544298]
13. Ho EY, Chesla CA, Chun KM. Health communication with Chinese Americans about type 2 diabetes. Diabetes Educ 2012;38(1):67-76. [doi: 10.1177/0145721711428774] [Medline: 22127677]

14. Hsu W, Cheung S, Ong E, Wong K, Lin S, Leon K, et al. Identification of linguistic barriers to diabetes knowledge and glycemic control in Chinese Americans with diabetes. Diabetes Care 2006 Feb;29(2):415-416. [doi: 10.2337/diacare.29.02.06.dc05-1915] [Medline: 16443897]
15. Ho EY, Tran H, Chesla CA. Assessing the cultural in culturally sensitive printed patient-education materials for Chinese Americans with type 2 diabetes. Health Commun 2015;30(1):39-49 [FREE Full text] [doi: 10.1080/10410236.2013.835216] [Medline: 24446839]
16. Chun KM, Chesla CA. Cultural issues in disease management for Chinese Americans with type 2 diabetes. Psychol Health 2004 Dec;19(6):767-785. [doi: 10.1080/08870440410001722958]
17. Chesla C, Chun K, Kwan C. Cultural and family challenges to managing type 2 diabetes in immigrant Chinese Americans. Diabetes Care 2009 Oct;32(10):1812-1816 [FREE Full text] [doi: 10.2337/dc09-0278] [Medline: 19628812]
18. Yeh M, Heo M, Suchday S, Wong A, Poon E, Liu G, et al. Translation of the Diabetes Prevention Program for diabetes risk reduction in Chinese immigrants in New York City. Diabet Med 2016 Apr;33(4):547-551 [FREE Full text] [doi: 10.1111/dme.12848] [Medline: 26179569]
19. Gabarron E, Årsand E, Wynn R. Social media use in interventions for diabetes: Rapid evidence-based review. J Med Internet Res 2018 Aug 10;20(8):e10303 [FREE Full text] [doi: 10.2196/10303] [Medline: 30097421]
20. Hong Y, Juon HS, Chou WYS. Social media apps used by immigrants in the United States: Challenges and opportunities for public health research and practice. Mhealth 2021;7:52 [FREE Full text] [doi: 10.21037/mhealth-20-133] [Medline: 34805383]
21. Sevick MA, Korytkowski M, Stone RA, Piraino B, Ren D, Sereika S, et al. Biophysiologic outcomes of the Enhancing Adherence in Type 2 Diabetes (ENHANCE) trial. J Acad Nutr Diet 2012 Aug;112(8):1147-1157 [FREE Full text] [doi: 10.1016/j.jand.2012.05.008] [Medline: 22818724]
22. Bandura A. Social cognitive theory: An agentic perspective. Annu Rev Psychol 2001;52:1-26. [doi: 10.1146/annurev.psych.52.1.1] [Medline: 11148297]
23. Bandura A. Health promotion from the perspective of social cognitive theory. Psychol Health 1998 Jul;13(4):623-649. [doi: 10.1080/08870449808407422]
24. Domenech Rodríguez MM, Baumann A, Schwartz A. Cultural adaptation of an evidence based intervention: From theory to practice in a Latino/a community context. Am J Community Psychol 2011 Mar;47(1-2):170-186. [doi: 10.1007/s10464-010-9371-4] [Medline: 21116707]
25. Bernal G, Bonilla J, Bellido C. Ecological validity and cultural sensitivity for outcome research: Issues for the cultural adaptation and development of psychosocial treatments with Hispanics. J Abnorm Child Psychol 1995 Feb;23(1):67-82. [doi: 10.1007/BF01447045] [Medline: 7759675]
26. Semple K. In Chinatown, sound of the future is Mandarin. The New York Times. 2009 Oct 21. URL: https://www.nytimes.com/2009/10/22/nyregion/22chinese.html [accessed 2022-10-11]
27. Lorig K, Ritter PL, Villa FJ, Armas J. Community-based peer-led diabetes self-management: A randomized trial. Diabetes Educ 2009;35(4):641-651. [doi: 10.1177/0145721709335006] [Medline: 19407333]
28. Toobert D, Hampson S, Glasgow R. The summary of diabetes self-care activities measure: Results from 7 studies and a revised scale. Diabetes Care 2000 Jul;23(7):943-950. [doi: 10.2337/diacare.23.7.943] [Medline: 10895844]
29. Ho EY, Pak S, Leung G, Xu S, Yu CK, Hecht FM, et al. Pilot cluster randomized controlled trial of integrative nutritional counseling versus standard diabetes self-management education for Chinese Americans with type 2 diabetes. Health Equity 2020;4(1):410-420 [FREE Full text] [doi: 10.1089/heq.2020.0002] [Medline: 33111026]
30. Panagiotakos D, Pitsavos C, Stefanadis C. Dietary patterns: A Mediterranean diet score and its relation to clinical and biological markers of cardiovascular disease risk. Nutr Metab Cardiovasc Dis 2006 Dec;16(8):559-568. [doi: 10.1016/j.numecd.2005.08.006] [Medline: 17126772]
31. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003 Aug;35(8):1381-1395. [doi: 10.1249/01.MSS.0000078924.61453.FB] [Medline: 12900694]
32. Whitehead AL, Julious SA, Cooper CL, Campbell MJ. Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. Stat Methods Med Res 2016 Jun;25(3):1057-1073 [FREE Full text] [doi: 10.1177/0962280215588241] [Medline: 26092476]
33. Chesla CA, Chun KM, Kwan CM, Mullan JT, Kwong Y, Hsu L, et al. Testing the efficacy of culturally adapted coping skills training for Chinese American immigrants with type 2 diabetes using community-based participatory research. Res Nurs Health 2013 Apr 19;36(4):359-372. [doi: 10.1002/nur.21543]
34. Chesla C, Chun K, Kwong Y, Gay C, Chi H, Gu Y, et al. Cultural adaptation of the Group Lifestyle Balance Program for Chinese Americans. Diabetes Educ 2016 Dec;42(6):686-696. [doi: 10.1177/0145721716666679] [Medline: 27624905]
35. Sun AC, Tsoh JY, Saw A, Chan JL, Cheng JW. Effectiveness of a culturally tailored diabetes self-management program for Chinese Americans. Diabetes Educ 2012;38(5):685-694 [FREE Full text] [doi: 10.1177/0145721712450922] [Medline: 22722610]

36. Zhu Y, Sidell MA, Arterburn D, Daley MF, Desai J, Fitzpatrick SL, et al. Racial/ethnic disparities in the prevalence of diabetes and prediabetes by BMI: Patient Outcomes Research To Advance Learning (PORTAL) multisite cohort of adults in the U.S. Diabetes Care 2019 Dec;42(12):2211-2219 [FREE Full text] [doi: 10.2337/dc19-0532] [Medline: 31537541]
37. Hill-Briggs F, Adler N, Berkowitz S, Chin M, Gary-Webb T, Navas-Acien A, et al. Social determinants of health and diabetes: A scientific review. Diabetes Care 2020 Nov 02;44(1):79 [FREE Full text] [doi: 10.2337/dci20-0053] [Medline: 33139407]
38. Canedo JR, Miller ST, Schlundt D, Fadden MK, Sanderson M. Racial/ethnic disparities in diabetes quality of care: The role of healthcare access and socioeconomic status. J Racial Ethn Health Disparities 2018 Feb;5(1):7-14 [FREE Full text] [doi: 10.1007/s40615-016-0335-8] [Medline: 28078660]
39. Diabetes Self-Management Education Barrier Study. Augusta, ME: Maine Department of Health and Human Services; 2006 Sep. URL: https://www.maine.gov/dhhs/mecdc/phdata/non-dhp-pdf-doc/diabetes-self-managment-education-barrier-study-september-.pdf [accessed 2022-10-11]
40. Onken LS, Carroll KM, Shoham V, Cuthbert BN, Riddle M. Reenvisioning clinical science: Unifying the discipline to improve the public health. Clin Psychol Sci 2014 Jan 01;2(1):22-34 [FREE Full text] [doi: 10.1177/2167702613497932] [Medline: 25821658]

Abbreviations

CARE: Chinese American Research and Education
CBWCHC: Charles B. Wang Community Health Center
CHW: community health worker
DSMES: diabetes self-management education and support
ENHANCE: Enhancing Adherence in Type 2 Diabetes
EVM: Ecological Validity Model
HbA_{1c}: hemoglobin A_{1c}
NIH: National Institutes of Health
NYC: New York City
NYULH: NYU Langone Health
PCP: primary care provider
RCT: randomized controlled trial
SCT: Social Cognitive Theory
T2D: type 2 diabetes

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Protocol

Incentives and Reminders to Improve Long-term Medication Adherence (INMIND): Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Nonadherence to antiretroviral therapy (ART) among people living with HIV is a crucial barrier to attaining viral suppression globally. Existing behavioral interventions have successfully increased ART adherence, but typically show only short-term impact that dissipates after the interventions are withdrawn.

Objective: This study aims to test the feasibility, acceptability, and preliminary efficacy of a novel intervention that uses SMS text messages and conditional incentives to support ART initiators in establishing pill-taking habits.

Methods: A sample of 150 participants aged ≥18 years who have initiated ART in the preceding 3 months will be recruited from Mildmay Uganda in Kampala, Uganda. All (150/150, 100%) participants will be educated on the anchoring strategy and will choose an existing routine to pair with their daily ART adherence from a set of 3 suggested routines: getting dressed in the morning, eating breakfast, or eating dinner. Then, participants will be randomized to receive either usual care (control group: 50/150, 33.3%) or 1 of the 2 interventions delivered over 3 months: daily SMS text message reminders to follow their chosen anchoring plan (*messages* group; treatment group 1: 50/150, 33.3%) or daily SMS text messages and incentives conditional on taking their ART medication around the time of their chosen anchor (*incentives* group; treatment group 2: 50/150, 33.3%). Long-term ART adherence will be evaluated for 6 months after the intervention, and survey assessments will be conducted at baseline, 3 months, and 9 months. Outcomes include feasibility and acceptability measures and intervention efficacy outcomes defined by electronically measured mean medication adherence during the intervention and during the 6 months after the intervention, along with a measure of routine ART adherence based on taking medications around the time of participants' anchor during the intervention and during the 6 months after intervention.

Results: As of February 18, 2022, recruitment was completed. A total of 150 participants were recruited, and data collection is expected to end in December of 2022. Final results are expected to be submitted for publication by April 2023.

Conclusions: This study is the first to use behavioral economics–based interventions in combination with the anchoring strategy to improve long-term ART adherence among treatment initiators. We hypothesize that the combination of SMS text message reminders and incentives will increase participants' use of their anchoring strategy, and thus medication adherence will be better maintained after the intervention ends in our intervention groups relative to the control group that uses only the anchoring strategy. Results of this pilot study will help to refine this combined intervention approach for testing at scale and broaden our understanding of the habit formation process.

Trial Registration: ClinicalTrials.gov NCT05131165; https://clinicaltrials.gov/ct2/show/NCT05131165

International Registered Report Identifier (IRRID): DERR1-10.2196/42216

(JMIR Res Protoc 2022;11(10):e42216) doi:10.2196/42216

KEYWORDS

medication adherence; HIV; antiretroviral therapy; habit formation; routines; behavioral economics

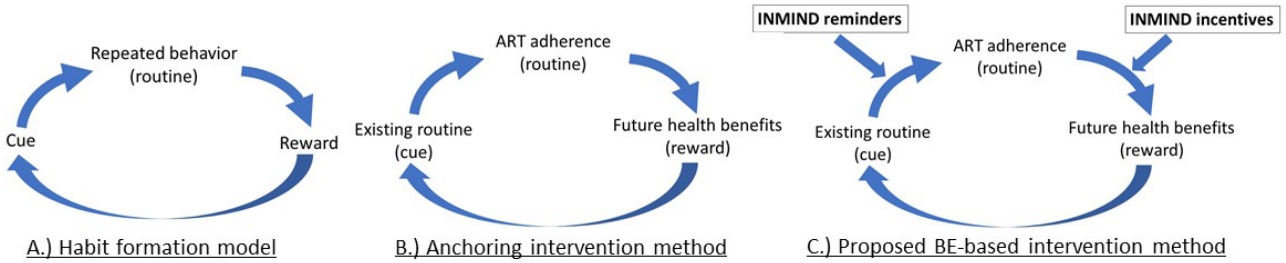
Introduction

Background

Antiretroviral therapy (ART) has transformed an HIV infection from a likely death sentence to a manageable chronic condition [1], but the efficacy of ART hinges on maintaining high (at least 80%-85%) mean medication adherence [2-4]. Globally, approximately 53% of people living with HIV have access to ART, but only 44% of people living with HIV are virally suppressed [5]. In sub-Saharan Africa, only one-fourth of people living with HIV are virally suppressed [5], which results in avoidable cases of drug resistance [6] and death [7]. Structural (eg, drug availability), social (eg, stigma), and economic (eg, distance to clinic and clinic fees) ART adherence barriers have been documented in the literature [8-10], but patient behavior has been identified as a key factor determining the lack of viral suppression [11]. Recent studies have shown that mean ART adherence ranges from 60% to 80% in Uganda, and only 30% to 60% of patients achieve 85% adherence [12-14]. Thus, novel behavioral interventions are needed to help establish and maintain high ART adherence habits among people living with HIV in Uganda.

Daily habits (or routines) are a commonly reported strategy for maintaining high medication adherence among patients who successfully manage chronic diseases [15,16], but forming new routines is often difficult for patients to do on their own. According to recent psychology research, it takes approximately 3 months of repeatedly performing a daily behavior in response to the same contextual cue [17-20], as outlined in the Habit Formation Model in Figure 1A [21], before the behavior becomes routinized. Once routinized, the cognitive processes that govern the behavior move to neurological systems that operate nonconsciously [22-25]. In addition, behaviors that are routinized no longer require high intrinsic motivation to be performed, and thus can enable even the most vulnerable ART treatment initiators, such as those with limited motivation, to maintain high long-term adherence.

Figure 1. Depiction of the habit formation model by Duhigg [21] that underlies the anchoring intervention strategy, which we propose to enhance in Incentives and Reminders to Improve Long-term Medication Adherence (INMIND) through incentives and reminders to successfully routinize antiretroviral therapy (ART) adherence among patients with HIV. BE: behavioral economics.



A common intervention method for establishing new routines is to anchor the targeted behavior to an existing routine that acts as the contextual cue. For example, taking ART medication after brushing one's teeth in the morning or after completing evening prayers. This method is often called anchoring (Figure 1B) and has been shown to be an effective intervention for promoting physical activity routines [26], improving dietary routines [27], and maintaining smoking cessation [28]. However, these existing studies typically enrolled participants with high intrinsic motivation for the targeted behavior [29-33], and therefore have little potential for real-life clinical situations where there is no extra support for individuals with low intrinsic motivation (as is typical for many patients in HIV care [34]). Moreover, less than half of the participants in these existing studies successfully used their anchor and maintained the desired behavior in the long term [35].

Behavioral economic theory demonstrates the need for ongoing support during the time it takes to complete the routinization process and provides proven intervention methods for delivering such support to enhance existing anchoring interventions. The behavioral economic biases of lack of salience of ART adherence (eg, over time, more pressing needs of daily life dominate one's attention and focus) and present bias (eg, excessively undervaluing the future health benefits of one's actions) help to explain why many people have trouble adhering to their healthy intentions [36,37]. Fortunately, behavioral economics also suggests 2 methods for countering these biases: (1) SMS text messages that can be used to reinforce the information provided at recruitment and to increase the salience of the anchoring routinization strategy and (2) small behavioral economics–based incentives that have successfully changed a range of health behaviors by countering present bias [38-41]. Therefore, this study will test whether incentives for linking daily pill taking to the timing of an existing routine behavior can establish and maintain high ART adherence routines in a feasible and scalable manner.

In addition, this intervention is being targeted to treatment initiators to leverage the *fresh start* effect [42], a period of heightened motivation and attention. ART adherence instructions are initially salient for treatment initiators; however, over time, they fade from attention. Among adults with HIV in sub-Saharan Africa, forgetfulness is the most frequently reported barrier to maintaining high long-term adherence [43,44]. Therefore, treatment initiators may need subsequent support for adhering

to the ART medication protocol until the behavior has been successfully routinized, which will be provided in the form of SMS text messages and incentives.

Objective

We propose to test the intervention, *Incentives and Reminders to Improve Long-term Medication Adherence* (INMIND), in a pilot, parallel group randomized controlled trial (RCT) at the Mildmay Uganda HIV clinic in Kampala, Uganda, with 2 intervention groups and 1 control group, using an even allocation ratio of 1:1:1 among the 3 study groups. All (150/150, 100%) participants (including those in the control group) will receive information about the importance of behavioral routines, as it is a part of the standard adherence counseling for treatment initiators at Mildmay Uganda, and will create personalized ART adherence anchoring strategies. The first intervention group will additionally receive SMS text message reminders of their anchoring strategy, and the second intervention group will receive both SMS text message reminders and small incentives conditional on taking ART pills within a time window that corresponds to participants' personalized anchoring strategy. We hypothesize that the SMS text message reminders and incentives will increase participants' use of their anchoring strategy, and thus, medication adherence will be better maintained after the intervention ends in both the intervention groups relative to the control group. We also expect to see stronger maintenance in the intervention group receiving both reminder messages and incentives than that in the intervention group receiving only reminder messages.

Methods

Ethics Approval

This pilot RCT has been funded by the National Institute of Mental Health in the United States (R34MH122331) and approved by the RAND Corporation's Human Subjects Protection Committee (2020-N0632), Mildmay Uganda Research Ethics Committee (0701-2021), and Uganda National Council for Science and Technology (HS128ES).

Study Design

This study will use a 3-armed RCT (2 intervention groups and 1 control group) with randomization at the individual level. Refer to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist for a guide to the key items reported in this protocol (Figure 2). The interventions will be administered for a period of 3 months from the baseline survey. During the intervention period, medication event monitoring system (MEMS) data readings will be collected monthly, wherein prize drawings for eligible participants in the *incentives* group will be conducted. As the population of interest is treatment initiators, the monthly study visits are expected to coincide with the monthly clinic visits as mandated for newly diagnosed clients who are becoming accustomed to ART treatment. During the postintervention period, the team will follow participants and continue MEMS data collection during the participants' regular clinic visits (expected to be every month for the first 6 months after treatment initiation and every 1-3 months thereafter) for a period of 6 months, thus bringing the total study period to 9 months.

Figure 2. Schedule of enrollment, interventions, and assessments (SPIRIT [Standard Protocol Items: Recommendations for Interventional Trials] figure). MEMS: medication event monitoring system; T1: treatment group 1; T2: treatment group 2.

			Months								
	Enrollment	Allocation	After allocation			After the intervention or closeout					
Timepoint	–1	0	1	2	3	4	5	6	7	8	9
Enrollment											
Eligibility screen	✓										
Informed consent	✓										
MEMS cap given	✓										
Allocation		✓									
Interventions											
T1, Messages		✓	♦—	—	—♦						
T2, Incentives		✓	♦—	—	—♦						
Assessments											
Adherence measured using MEMS-cap		✓	♦—	—	—	—	—	—	—	—	—♦
Participant surveys		✓			✓						✓
Viral load		✓			✓						✓

As the long-term goal of the study is viral suppression, viral load data will also be collected during the routine assessment. Viral load tests for treatment initiators are conducted after the first 6 months of ART initiation and then changed to 12-month periods as per the clinic and Ugandan Ministry of Health guidelines. Survey assessments will be administered at baseline, 3 months, and 9 months for all (150/150, 100%) participants.

It is important to note that the pilot study is being preceded by a formative phase and succeeded by an adaptation phase, both of which are designed to collect qualitative data pertaining to the overall design, feasibility, and acceptability of the interventions. The results of the formative phase will be used to adapt the pilot intervention materials and timeline before intervention administration. The adaptation phase is expected to provide feedback on several critical parameters of the interventions, which will be used to mold the intervention in preparation for a full-scale RCT. Figure 2 shows the timing of the study activities.

Study Sites

The study will be performed at Mildmay, Uganda, an HIV clinic in Kampala, Uganda. This clinic specializes in providing comprehensive HIV and AIDS prevention, care, and treatment services to >105,000 patients with HIV. It offers integrated health services to a diverse population base; of the 15,000 patients served at the main site in Lweeza, 11% are children younger than 18 years, 65% are women, and 100% of the patients are on ART. Mildmay also has well-established electronic medical records infrastructure, making it one of the growing number of facilities using electronic medical record systems in Uganda.

Apart from the patient-facing work, Mildmay also provides technical assistance to organizations and governments, hosting training and educational courses for >1500 professionals per year. Furthermore, the Mildmay Uganda laboratory is accredited by the South African National Accreditation System under International Organization for Standardization 15,189:2012 and specializes in virology and other tests. Mildmay also has numerous ongoing research projects involving international researchers. It has a standing community advisory board comprising church leaders, elected councilmen, health care providers (external to Mildmay), and advocates of clients with HIV.

Sampling Strategy

The objective of this study is to establish preliminary efficacy, acceptability, and feasibility of the interventions. Consequently, 150 participants will be recruited from Mildmay's main site for the pilot study. The sample will be representative of the patient population at Mildmay, with an approximately 70:30 ratio of female to male clients.

Electronic medical records and the hospital electronic database will be used to screen the client population for initial eligibility based on age and ART initiation period, as noted in the eligibility criteria in the following sections. For this step, the hospital staff (and not the study coordinator) will mine the electronic database for this information to create a master list of eligible clients. Given the focus on treatment initiators, this process will be conducted weekly to identify newly diagnosed clients who are eligible to participate in the study.

A daily list of expected clients will be generated from the master list for the study coordinators to identify those deemed eligible and who are due for a clinic visit. Once a client is identified, a prebaseline visit will be initiated, with the study coordinator approaching the client and inquiring about their interest in participating in an ongoing study. On confirming interest, clients will be taken to a separate study room to verify their eligibility and to obtain their consent to participate. Consented participants will be given a MEMS cap and instructed to store one of their HIV medications in a pill bottle with the MEMS cap attached. In addition, they will be given a study appointment approximately 1 month after this initial visit for adherence data retrieval and baseline survey administration. The first month of adherence data will be used as a baseline, and the intervention will not begin before this follow-up visit.

Inclusion Criteria

The study sample will consist of male and female clients aged ≥18 years who have started ART at Mildmay within the preceding 3 months. Treatment initiation is an important eligibility criterion given the conceptual framework of the pilot study, which suggests that habit formation during initiation is a key driver for sustained ART adherence over time. On the basis of electronic records data from Mildmay, each month, at least 100 to 150 clients with these characteristics begin treatment at the hospital (a total of 1758 clients in 2018); therefore, a large pool of potentially eligible clients will be available for recruitment. Given the nature of the intervention, inclusion will also require participants to own or have access to a phone for at least 5 days per week throughout the duration of the intervention and be willing to receive SMS text messages throughout the intervention period.

Exclusion Criteria

Children aged <18 years were excluded for 2 reasons: (1) the pediatric clinic is separate from the main recruitment site (which primarily caters to adult clients) and (2) the intervention may require alteration to account for the specific needs of children and adolescents. In addition, clients who are not mentally fit to understand the consenting or study procedures and clients who speak neither English nor Luganda (the local language spoken by most people in and around Kampala) were excluded. As both intervention groups rely on receiving SMS text messages, clients who do not own a mobile phone or have access to one will also be excluded.

Participation in another adherence study and inability or nondesire to use MEMS caps regularly throughout the course of the study will also be a basis for exclusion. Consequently, if the baseline MEMS reading suggests that participants opened their pill bottle <30% of the days and if that was not a consequence of low adherence, the participant will be given a transport refund and be unenrolled from the study. Finally, clients who come outside regular clinic working hours will be excluded.

Randomization and Allocation

Participants will be randomly assigned to either 1 of the treatment arms (treatment group 1 [T1]=*messages*; treatment group 2 [T2]=*incentives*) or the control arm after consenting but will only be informed of their assignment after the baseline survey is over to minimize any potential influence of the assignment on the baseline survey responses. The distribution ratios for the randomization will be 1:1:1, and the assignment will be conducted through a computer-generated randomization component built into the baseline survey administration software called Questionnaire Development System. The random assignment (to either the control arm or 1 of the 2 intervention arms) will be revealed at the end of the baseline survey to both the participant and study coordinator, who will not know the respondent's treatment assignment during the survey. Given the nature of the intervention, neither the interviewers nor the participants can be blinded to the treatment status. However, the data analyst who will conduct the impact analysis will be blinded to treatment assignment.

Procedures

Interventions

The pilot study will include a control arm, along with 2 intervention arms—*messages* (T1) and *incentives* (T2).

Control Group: Usual Care

Participants assigned to this arm will receive care as usual, including the adherence support mechanisms that are part of usual care practices. At recruitment, participants will be educated about the importance of pill taking using a leaflet that provides information on how to establish healthy pill-taking routines. Then, participants will be asked to select 1 of the following 3 pill-taking anchors: getting dressed in the morning, eating a meal (breakfast) in the morning, or eating dinner in the evening, which will also be described in a habit leaflet, and they will be asked to specify the time at which their anchor typically occurs. Once selected, participants will be asked to continue using their MEMS caps and bring them during the next visit.

During each of the subsequent study visits, scheduled approximately 1 month apart during the intervention period and 1 to 3 months apart subsequently, participants will be asked to complete a short questionnaire inquiring about changes in their ART adherence behavior, including any changes in location, times, and social activities surrounding their pill-taking behavior and ART adherence habit strength. They will also be asked about any clinical changes in their ART regimen and about their daily MEMS cap use. This is because pill pocketing (dispensing >1 dose in a given bottle opening event) is a common phenomenon among the population, with 15% of a previous study sample reporting pocketing [45]. If participants indicate pocketing, the study coordinator will work with the participant to find another solution to avoid pocketing and continue using their MEMS cap, and we will adjust for their pocketing in our assessment of their adherence outcomes. Finally, participants will be asked about any changes in their contact information or addresses, and updates will be noted in the contacts data.

Then, the study coordinator will download the readings from the MEMS cap, inquire about the participants' next visit, and remind them to continue taking their pills on time. This procedure will be conducted throughout the intervention and postintervention periods.

T1—Messages Group

Participants assigned to this arm will receive daily SMS text messages in addition to care as usual during the 3-month intervention period. When the participant is informed about their treatment assignment, they will be educated using the same habit leaflet as all other study groups and asked to pick an anchor and share the time of the day the anchor typically occurs. In addition, the study coordinator will register the participant's mobile phone number along with their language preference for SMS text messages (English or Luganda) on a web-based SMS text messaging system, Twilio. The system will include programmed SMS text messages that will be sent to all (50/50, 100%) participants at 2 PM local time every day for the 3-month intervention period. Textbox 1 shows some example SMS text messages, each of which would be sent on a specific day of the week. Once registered, the study coordinator will send the participant a test message to confirm registration. If, for any reason, the participant is unable to confirm receipt of the test message (eg, if their primary number is owned by another person whom they live with), the study coordinator will try registration again. If the registration is still not confirmed, the participant will be unenrolled from the study.

During each subsequent intervention-period study visit for the enrolled participants, they will be asked about the SMS text messages in addition to the questions asked to the participants in the control group. Specifically, participants will be asked whether they have been receiving the SMS text messages and whether they read them. MEMS data will also be downloaded during each subsequent clinic visit.

Textbox 1. Example SMS text messages for the messages and incentives groups in the Incentives and Reminders to Improve Long-term Medication Adherence (INMIND) intervention.

Sample messages

- Hello, this is INMIND. Take your vitamins together with your existing routine for good health!
- Hello, this is INMIND. Forming routines requires effort now but will pay off in the end!
- Hello, this is INMIND. Don't forget to take your vitamins every day at the same time!
- Hello, this is INMIND. Remember to stick with your healthy plans!

T2—Incentives Group

Participants assigned to this arm will receive monetary incentives in addition to daily SMS text messages (similar to the *messages* arm) and care as usual during the 3-month intervention period. Upon revealing their group assignment, participants will be registered on the Twilio platform following the same procedures outlined for the *messages* arm. Participants will also be informed that if, at their next visit, they have taken their medication on ≥70% of the past 30 days within –1 to +1 hour of their chosen anchor time, they will be eligible to participate in a lottery to win mobile airtime. The study coordinator will explain that they will receive 3 opportunities to participate in the lottery (ie, at each study visit over the next 3 months, if they are eligible). To ensure that participants understand the process, the study coordinator will conduct a mock prize drawing, wherein participants will choose 1 of 3 cards listing an airtime prize amount. The chosen card and corresponding prize will be revealed to the participant, and the amount listed on the card will be sent to the participant's phone number (via Reloadly) in the form of a mobile top-up balance.

During each subsequent study visit, the study coordinator will check the client's MEMS cap data and fill a form that asks questions about adherence behaviors (similar to the control group) and SMS text messages (similar to the messages group). The study coordinator will also ask about pill pocketing to assess prize eligibility. To avoid unfairly punishing participants who pocket doses (resulting in an underreporting of MEMS data in the software), participants will be asked about an estimated number of doses pocketed and will be allowed to enter a wild card prize drawing when they did not reach the adherence threshold. They will be specifically informed that this will be a 1-time exception. After the 3-month intervention, participants will follow the same procedures as the control and messages groups.

MEMS Cap Procedures

The MEMS caps will be used to assess the primary outcome measures—mean monthly adherence during the intervention and postintervention periods and a novel adherence measure assessing the timeliness of adherence during the intervention and postintervention periods. The caps will be distributed to all (50/50, 100%) participants, regardless of their group assignment to avoid any spurious intervention effects associated with cap use. The data captured by these caps will be downloaded at each clinic visit using a MEMS cap reader that will be connected to a study computer, and we will use these data to construct our participant-day-level measures of ART medication adherence.

The study coordinator will assist the patient in dispensing their medication into a bottle that we provide with an attached MEMS cap, or, if preferred by the patient, they can put the MEMS cap on the medication bottle provided by the clinic. We will monitor adherence to only 1 daily dose of antiretroviral medication, as studies show that rates of adherence do not differ significantly across medications taken by an individual patient [46]. All (150/150, 100%) participants will be asked to use their MEMS cap continuously throughout the study and return with the cap and pill bottle for each clinic visit. Participants will be informed that the cap records when the bottle is opened. They will also be informed that these data will not be shared with clinicians.

Study Timeline

Recruitment

The recruitment visit (or prebaseline visit) will be used as an opportunity to screen the clients. Once the client is found to meet the initial eligibility criteria, they will be given a MEMS cap, which will be used to track baseline adherence and study eligibility for approximately 1 month. If their clinic visit does not coincide with the expected study visit, participants will be provided a study visit appointment and will be told that they will receive travel compensation for making the additional trip. Clients will also be asked to consent to participate during this initial recruitment visit.

Visits Between Month 1 and Month 3

During the 3-month intervention period, participants will be scheduled for monthly clinic appointments, and the study coordinators will (1) collect information on changes or degradations of existing routine behaviors, (2) conduct prize drawings with the *incentive* group, and (3) update contact information if phone numbers or addresses have changed. After the first 3 months, this information will be collected during the participants' regular clinic visits. When participants report degradation of their selected behavioral anchor, a new daily routine will be identified for the anchoring strategy from the suggested list of 3 common routine behaviors.

Postintervention Surveys

Follow-up surveys will be administered at month 3 (ie, at the end of the intervention) and month 9 (ie, 6 months after the end of the intervention) to evaluate behavioral persistence. These surveys will be designed to evaluate how the intervention affects both primary and secondary outcomes and cognitive and motivational factors that may be influenced by the intervention. Intervention effects over the 9-month study period will also be assessed, as these effects may be most pronounced in the first months when the pill-taking routine is first established but taper as the novelty of the intervention fades or anchoring routines are changed. The postintervention assessment will happen during a scheduled hospital visit to avoid participants having to make costly additional hospital visits specifically for interviews.

Data Collection Methods

Surveys

The baseline survey contains questions pertaining to the following:

1. *Demographics and socioeconomic status*, including age, sex, education, relationship status, employment type and status, income, preferred language, housing, economic shocks, food insecurity, and household composition
2. *Attitudes and beliefs about HIV medication*, including adherence behaviors, perceived benefits, and community perceptions around pill taking
3. *Sources of motivation* for medication adherence; for example, reduction in HIV transmission, maintenance of

good health and ability to look after family, or maintenance of good physical appearance

4. *Habits* associated with regular pill taking, including pill-taking routines, missed doses and reasoning (to assess any perceptual and structural barriers to pill taking), and costs associated with prescription fills. This will be assessed using the Self-Reported Behavioral Automaticity Index [47], which is a validated subset of the Self-Reported Habit Index [48] that measures the automaticity of performing a specific routine behavior based on responses to 4 questions (eg, "taking my medication is something I do without thinking") on a 7-point Likert scale ranging from "strongly disagree" to "strongly agree."
5. *Health care information*, including perceptions about health since initiating ART and over the past month

In addition, a measure developed by Falk et al [49] will be used to assess risk and time preferences, altruism, trust, and positive and negative reciprocity on a scale from 0 to 10, where 0 means "completely unwilling to take risks" and 10 means "very willing to take risks." In addition, the Intrinsic Motivation Inventory will be used to examine participants' subjective motivation for taking medications [50]. The 3-month and 9-month surveys will additionally include questions assessing comfort with using the MEMS caps, acceptability of the SMS text messages and prize drawings, and overall study satisfaction. Upon completing each survey, participants will be given USh 30,000 (approximately US $8.25) as travel compensation.

MEMS Data and Access Forms

The MEMS data will be automatically downloaded and stored electronically using the MEMS cap software that will be installed on a tablet accessible by the study coordinator. Other study data, including participants' survey responses, monthly visit reports, and other information about study dropout, will be recorded by study personnel in Microsoft Access templates designed by the research team. These electronic data will be safely stored at Mildmay and securely transferred to the research team in the United States periodically during the study period and at the end of the 9-month study.

Chart Abstraction

Participant's viral load will be used as a complementary measure to the MEMS data for the assessment of ART adherence. They are now a part of routine clinical care at Mildmay, with tests conducted when someone receives a positive HIV test result, after 6 and 12 months from the initial diagnosis, and every 12 months thereafter. Consequently, the results of the viral load test will be collected from electronic medical records, and the data abstraction will be timed with the routine tests for the participants.

Participant Tracking

Extensive tracking information will be collected at recruitment and will be verified at each study visit. This will include the participants' mobile phone numbers, home addresses, and email addresses and contact information of 2 individuals who live in the same community and whom the participant is comfortable and familiar with. These additional contacts are collected to ensure that the participant can be located if their contact information changes. These procedures have limited attrition in the researchers' previous studies to approximately 5% [45,51].

If a participant in either treatment group loses, breaks, or cannot use their mobile phone, they will no longer be able to receive SMS text messages as part of the intervention. To address this possibility, the study coordinator will record the functionality of participants' mobile phones at each monthly visit, and those with missing or broken mobile phones will be noted. In addition, all active phone numbers of the participants (as it is not unusual for Ugandan people to use >1 SIM card or phone) will be recorded to ensure that an alternative means of delivering the messages exists, when available. In addition, participants will be given a handout at the start of the study, explaining that they should give the study team a call if they change phones or phone numbers at any point during the first 3 months of the study and that they will be rewarded with USh 3000 (US $0.78) for notifying the study coordinators of such a change.

Outcomes

The study will assess the following outcomes.

Feasibility and Acceptability

The feasibility and acceptability of the INMIND intervention will be assessed using the study retention rate, attendance rate for scheduled clinic visits, and survey responses collected at the end of the 3-month intervention and following the 6-month postintervention period. These survey measures ask participants about their ability to understand all the intervention materials and their perceived value of the intervention. We will also conduct focus groups with a sample of study participants after the postintervention survey to collect additional information about the study's feasibility and acceptability.

Preliminary Efficacy

Primary Outcome 1: Electronically Measured Mean Medication Adherence During the Intervention

MEMS data will be collected continuously over the course of the 3-month intervention period, allowing for mean adherence assessment during the intervention period. Specifically, the number of pill bottle openings detected by the MEMS cap will be used as a measure of each participant's pills taken per day. Then, mean adherence will be calculated as the number of pills taken per day during the intervention period divided by the number of pills prescribed during the intervention for a given participant (ie, number of actual bottle openings/number of prescribed bottle openings). This mean adherence measure will be capped at 100%, meaning that any pill bottle openings beyond the participants' number of prescribed daily pills will be ignored. In this way, the mean adherence measure will range from 0 to 100 and will be calculated for each participant on each day of the intervention period. Only one of the daily ART medication doses will be used to calculate the primary mean adherence variable. Both mean adherence over the 3-month intervention and monthly measure of mean adherence will be calculated and analyzed.

Primary Outcome 2: Electronically Measured Mean Medication Adherence After the Intervention

After the intervention, MEMS data will be collected continuously for 6 months to investigate postintervention mean ART adherence (*persistence*). The calculation of this outcome is the same as that of *outcome 1*, except for the timeline over which the data will be collected and analyzed.

Primary Outcome 3: Routinization of ART Adherence During the Intervention

In addition to *outcomes 1 and 2*, a novel measure of routine adherence will be assessed during the intervention period. The novelty of the measure is that it is explicitly based on the temporal pattern of pill taking. The measure will be calculated as the fraction of scheduled pills taken within a 2-hour window (–1 to +1 hour) around the typical time that participants report completing their existing routine behavior that anchors their pill taking. This measure provides an objective way for determining the behavioral automaticity of pill taking and will be calculated as the mean of all prescribed pills taken around the participants' anchor time over the 3-month intervention.

Primary Outcome 4: Routinization of ART Adherence After the Intervention

The fourth outcome will be calculated using the same procedures as that for *outcome 3*. However, the data from which the measure will be assessed will be collected during the postintervention period.

The team will also assess 2 secondary efficacy measures, as described in the following sections.

Secondary Outcome 1: Retention in Care

Retention in care is an important metric of treatment adherence. Failure to remain in care is a commonly observed problem for treatment initiators. To assess how well participants will continue to remain in care, Mildmay electronic records will be used to evaluate the number of study participants who fail to attend their regularly scheduled clinic visits. Participants who do not make any clinic visits for ≥6 months will be considered lost to follow-up. The study coordinator will call them using the tracking information collected for the study to inquire about their reason for stopping care at the Mildmay clinic. This outcome will be measured as an indicator of whether the participants are still active clients at the clinic at the end of the 9-month study.

Secondary Outcome 2: Viral Suppression

HIV RNA (viral load) is our final outcome measure. According to the AIDS Clinical Trials Group, virological failure is defined as a confirmed viral load >200 copies/mL. Below this level, the viral load is considered undetectable. Importantly, this is a reliable biological measure of ART adherence, as strong adherence leads to low viral load. Given the intervention design, viral load will be an important complementary measure of adherence. The analysis will examine the intervention's effects on the likelihood of being virally suppressed at the end of the 9-month study period.

Data Analysis

Statistical Methods and Analyses

Feasibility and acceptability will be analyzed using summary statistics derived directly from our self-reported measures. To estimate preliminary efficacy, statistical analyses comparing group-level differences in the secondary and tertiary outcome measures will be performed. An analysis of covariance framework will be used to test for group differences in each secondary and tertiary outcome, controlling for the participant characteristics that are found to differentiate the groups at baseline. For analyses of dichotomous variables, such as viral suppression, nonparametric McNemar test and analogous multiple logistic regression will be used to control for covariates to assess group differences. In addition to static comparisons of group means for each outcome at 3-month intervals, the longitudinal nature of the data will be leveraged by using repeated measures and time series techniques. Specifically, a linear mixed model with repeated observations will be fit using maximum likelihood through *xtmixed* in the software package, Stata, to study group-level temporal dynamics in daily measures of the primary and secondary outcomes.

Sample and Effect Size Estimation

We will recruit a total of 150 participants and will assume a 90% retention rate throughout the 9-month study period. This is a conservative estimate of attrition, as previous studies in the same clinic and with a similar population observed only 6% attrition over 12-month study periods [45,51]. Given the study objectives of establishing acceptability, feasibility, and preliminary effectiveness, the targeted sample size may not have the power to detect many of the effects that would be clinically significant. Nonetheless, effect size calculations associated with 80% power (2-tailed *t* test) regarding the primary outcomes at month 9 have been performed. A recent study conducted at Mildmay suggested that mean ART adherence rates are approximately 75% (SD 20%), as measured by MEMS caps [51]. Using these parameters as estimates of adherence for the control group and 10% attrition at month 9, a sample size of 150 will provide sufficient power to detect 9% difference in mean adherence between the pooled intervention groups and the control group (effect size=0.47) and approximately 11% difference in mean adherence between the 2 intervention groups. This translates to the study being able to detect medium effect sizes.

Qualitative Analysis

Qualitative analysis will be primarily performed through semistructured interviews and focus groups with clients, providers, and clinic administrators during the initiation and adaptation phases. The interviews administered during the initiation phase will primarily focus on perceptions of ART pill taking as an activity of daily life and investigate the range of existing behaviors that can be used as cues (such as eating, daily prayers, or brushing teeth) to understand how INMIND can best support ART adherence routinization. During the adaptation phase, 8 focus groups (n=4, 50% among participants in the *messages* group and n=4, 50% among the participants in the *incentives* group) will be organized to elicit additional qualitative

information about areas of program improvements that may not be captured in the surveys.

All qualitative data will be digitally recorded; translated into English; and uploaded to Dedoose, an analytic software package. In total, 2 qualitative researchers will independently read the text and identify all topics covered. A codebook that describes the inclusion and exclusion criteria, along with typical exemplars for each topic or theme will be developed. Intercoder reliability (evidenced by Cronbach $\alpha \geq .70$) will be established; discussion will be conducted until the coders converge on a single, agreed-upon meaning for the thematic area. For each topic, they will identify the range of themes, with attention to the most commonly discussed (ie, key themes) and least frequently discussed (ie, outliers) themes. They will produce research reports on specific topics describing the range, central tendency, and distribution of each theme.

Data Management

All data collected during the course of the study will have only the existing clinic identifiers as the unique participant identifiers. All other identifiable information will be stored separately. Data collection and storage hardware (ie, tablets and computers) will be password-protected, and physical storage spaces will have a locking mechanism for security. All physical storage spaces will be located at the Mildmay RAND office in Kampala, with access granted only to key personnel and the principal investigator. These physical storage spaces will be used to store the consent forms and other physical tracking documentation.

All data collection and on-ground study activities will be conducted by the study team in Uganda. This team will include a team leader, 2 lead interviewers, and 3 supporting team members. The design of the data collection instruments and protocols, quality monitoring of the qualitative and quantitative data, and data analysis will be conducted by the study team based in the United States. Data collected on the ground will be transferred to the US team on a weekly basis through a secure web portal (Kiteworks).

Published material will not contain any personally identifying information. There is no data monitoring committee because the trial was deemed to have minimal risk. The study team in the United States will still perform data monitoring and quality assurance exercises weekly during the 9-month study period.

Handling Missing Data and Attrition

Missing data for some variables will be imputed if a participant remained enrolled in the study. When participants drop out, multiple logistic regression models will be fit to assess whether this dropout is random. If it is not, *nonresponse* weights using logistic regression will be developed to adjust for dropout. All analyses will reflect these design effects in the calculation of SEs and statistical tests of significance.

Results

Recruitment was completed as of February 18, 2022. A total of 150 participants were recruited, and data collection is expected to end in December of 2022. Final results are expected to be submitted for publication by April 2023.

Discussion

Expected Outcomes

We hypothesize that our 2 intervention groups will display high mean medication adherence and high routinized medication adherence (ie, pill taking within –1 to +1 hour of participants' chosen anchor) during the 3-month intervention relative to the control group. After using their anchoring strategy more frequently, we hypothesize that our 2 intervention groups will better maintain their mean medication adherence and routinized medication adherence over the 6 months after the intervention is withdrawn. Finally, we hypothesize that our second treatment group, which receives both SMS text message reminders and small incentives for using their anchor during the 3-month intervention, will more strongly maintain their mean medication adherence and routinized medication adherence during the 6-month postintervention period.

Comparison With Previous Studies

INMIND has a strong scientific premise that addresses a critical knowledge gap in the literature around the design of interventions for establishing and maintaining long-term behavior change. A growing body of literature in the field of psychology targets long-term behavior change [18,52]; however, most intervention methods are one-off interventions that do not support participants during the approximately 3-month routinization process [17,20,53,54]. Behavioral economics–based interventions have also had limited efficacy in maintaining long-term behavior change. For example, incentives have successfully changed a range of health behaviors by countering present bias [38-41], including improved ART adherence [55], but these interventions typically show only short-term impact that dissipates after the incentives are withdrawn [38,52]. In our own previous studies, we also found that incentives did not have persistent effects, and only participants who showed timely adherence (an indicator that they potentially anchored pill taking to an existing routine) maintained high adherence after the incentives were withdrawn [51].

Our combined intervention approach attempts to leverage the successful components of these existing psychology-based and behavioral economics–based interventions to better maintain ART adherence. If successful, this intervention will help to expand the understanding of the habit formation process and common psychological barriers to successfully adhering to new health behaviors. The study also addresses biological variables such as age and sex appropriately and incorporates them in both the impact analysis and when testing for age and sex differences in behavioral biases and intrinsic motivation. Such analyses will be especially useful in designing a large-scale intervention that can assist all treatment initiators in establishing and maintaining long-term ART adherence.

Limitations

The study has some limitations. First, the study will recruit the sample from 1 clinic in Uganda, limiting the generalizability of our results. Second, the small sample size limits the team's ability to detect clinically meaningful effect sizes. Although

this is not the intended aim of this feasibility and acceptability study, the small sample size is still a limitation to the statistical analyses. Third, ART adherence will only be measured over 9 months; therefore, future studies will be needed to assess ART adherence over long durations. Fourth, ART adherence will be measured using MEMS caps, which is currently one of the most accurate ways to measure medication adherence, but conscious manipulation of the pill bottle openings by the participants is still a possibility that may lead to an overestimation of the study's adherence outcomes for participants in the *incentives* group, who may use deception to increase their chances of a prize drawing.

Dissemination and Future Directions

The team will use peer-reviewed publications and conference presentations as the primary means of disseminating results. The findings will be relevant to those interested in the behavioral mechanisms that underlie successful long-term ART adherence and, more broadly, the mechanisms underlying long-term behavior change. In addition, the findings will be used in the design of a large-scale RCT that we will use to rigorously assess the effectiveness of the INMIND intervention for establishing long-term ART adherence habits. In addition to future RCTs, we plan to use detailed MEMS data on the timing of daily pill taking to inform statistical models of the habit formation process, which will guide new intervention designs for promoting ART adherence habits.

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Data Availability

Deidentified research data will be made available, along with the survey instruments, to interested external researchers through collaborative agreements with the principal investigator and coinvestigators, as required by the National Institutes of Health's data sharing policies.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report from the HIV/AIDS Intra- and Inter-personal Determinants and Behavioral Interventions Study Section, AIDS and Related Research Integrated Review Group, Center for Scientific Review (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 153 KB - resprot_v11i10e42216_app1.pdf]

References

1. Palella Jr FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med 1998 Mar 26;338(13):853-860. [doi: 10.1056/NEJM199803263381301] [Medline: 9516219]
2. Parienti JJ, Ragland K, Lucht F, de la Blanchardière A, Dargère S, Yazdanpanah Y, ESPOIR and REACH study groups. Average adherence to boosted protease inhibitor therapy, rather than the pattern of missed doses, as a predictor of HIV RNA replication. Clin Infect Dis 2010 Apr 15;50(8):1192-1197 [FREE Full text] [doi: 10.1086/651419] [Medline: 20210643]
3. Kobin AB, Sheth NU. Levels of adherence required for virologic suppression among newer antiretroviral medications. Ann Pharmacother 2011 Mar;45(3):372-379. [doi: 10.1345/aph.1P587] [Medline: 21386024]
4. Pasternak AO, de Bruin M, Jurriaans S, Bakker M, Berkhout B, Prins JM, et al. Modest nonadherence to antiretroviral therapy promotes residual HIV-1 replication in the absence of virological rebound in plasma. J Infect Dis 2012 Nov;206(9):1443-1452. [doi: 10.1093/infdis/jis502] [Medline: 22927449]
5. AIDSinfo. Joint United Nations Programme on HIV/AIDS. 2017. URL: https://aidsinfo.unaids.org/ [accessed 2019-11-06]
6. Nachega JB, Marconi VC, van Zyl GU, Gardner EM, Preiser W, Hong SY, et al. HIV treatment adherence, drug resistance, virologic failure: evolving concepts. Infect Disord Drug Targets 2011 Apr;11(2):167-174 [FREE Full text] [doi: 10.2174/187152611795589663] [Medline: 21406048]
7. May MT, Gompels M, Delpech V, Porter K, Orkin C, Kegg S, UK Collaborative HIV Cohort (UK CHIC) Study. Impact on life expectancy of HIV-1 positive individuals of CD4+ cell count and viral load response to antiretroviral therapy. AIDS 2014 May 15;28(8):1193-1202 [FREE Full text] [doi: 10.1097/QAD.0000000000000243] [Medline: 24556869]

8. Hardon AP, Akurut D, Comoro C, Ekezie C, Irunde HF, Gerrits T, et al. Hunger, waiting time and transport costs: time to confront challenges to ART adherence in Africa. AIDS Care 2007 May;19(5):658-665. [doi: 10.1080/09540120701244943] [Medline: 17505927]
9. Tuller DM, Bangsberg DR, Senkungu J, Ware NC, Emenyonu N, Weiser SD. Transportation costs impede sustained adherence and access to HAART in a clinic population in southwestern Uganda: a qualitative study. AIDS Behav 2010 Aug;14(4):778-784 [FREE Full text] [doi: 10.1007/s10461-009-9533-2] [Medline: 19283464]
10. Byakika-Tusiime J, Oyugi JH, Tumwikirize WA, Katabira ET, Mugyenyi PN, Bangsberg DR. Adherence to HIV antiretroviral therapy in HIV+ Ugandan patients purchasing therapy. Int J STD AIDS 2005 Jan;16(1):38-41. [doi: 10.1258/0956462052932548] [Medline: 15705271]
11. Gallant JE. Strategies for long-term success in the treatment of HIV infection. JAMA 2000 Mar 08;283(10):1329-1334. [doi: 10.1001/jama.283.10.1329] [Medline: 10714734]
12. Shuter J, Sarlo JA, Stubbs RO, Rode RA, Zingman BS. Sequential antiretroviral adherence measurement using electronic bottle cap monitors in a cohort of HIV-infected adults. J Int Assoc Physicians AIDS Care (Chic) 2012;11(2):94-97. [doi: 10.1177/1545109711420498] [Medline: 22223595]
13. Ortego C, Huedo-Medina TB, Llorca J, Sevilla L, Santos P, Rodríguez E, et al. Adherence to highly active antiretroviral therapy (HAART): a meta-analysis. AIDS Behav 2011 Oct;15(7):1381-1396. [doi: 10.1007/s10461-011-9942-x] [Medline: 21468660]
14. Gardner EM, McLees MP, Steiner JF, Del Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. Clin Infect Dis 2011 Mar 15;52(6):793-800 [FREE Full text] [doi: 10.1093/cid/ciq243] [Medline: 21367734]
15. Alison Phillips L, Leventhal H, Leventhal EA. Assessing theoretical predictors of long-term medication adherence: patients' treatment-related beliefs, experiential feedback and habit development. Psychol Health 2013;28(10):1135-1151. [doi: 10.1080/08870446.2013.793798] [Medline: 23627524]
16. Brooks TL, Leventhal H, Wolf MS, O'Conor R, Morillo J, Martynenko M, et al. Strategies used by older adults with asthma for adherence to inhaled corticosteroids. J Gen Intern Med 2014 Nov;29(11):1506-1512 [FREE Full text] [doi: 10.1007/s11606-014-2940-8] [Medline: 25092003]
17. Wood W, Neal DT. A new look at habits and the habit-goal interface. Psychol Rev 2007 Oct;114(4):843-863. [doi: 10.1037/0033-295X.114.4.843] [Medline: 17907866]
18. Lally P, Gardner B. Promoting habit formation. Health Psychol Rev 2013 May;7(sup1):S137-S158. [doi: 10.1080/17437199.2011.603640]
19. Rothman AJ, Sheeran P, Wood W. Reflective and automatic processes in the initiation and maintenance of dietary change. Ann Behav Med 2009 Dec;38 Suppl 1:S4-17. [doi: 10.1007/s12160-009-9118-3] [Medline: 19787308]
20. Redish AD, Jensen S, Johnson A. Addiction as vulnerabilities in the decision process. Behav Brain Sci 2008 Jul 29;31(4):461-487 [FREE Full text] [doi: 10.1017/S0140525X08004986]
21. Duhigg C. The Power of Habit: Why We Do What We Do, and How to Change. New York, NY, USA: Random House; 2013.
22. Pfeffer I, Strobach T. Behavioural automaticity moderates and mediates the relationship of trait self-control and physical activity behaviour. Psychol Health 2018 Jul;33(7):925-940. [doi: 10.1080/08870446.2018.1436176] [Medline: 29431514]
23. Gardner B. A review and analysis of the use of 'habit' in understanding, predicting and influencing health-related behaviour. Health Psychol Rev 2015;9(3):277-295 [FREE Full text] [doi: 10.1080/17437199.2013.876238] [Medline: 25207647]
24. Rothman AJ, Gollwitzer PM, Grant AM, Neal DT, Sheeran P, Wood W. Hale and hearty policies: how psychological science can create and maintain healthy habits. Perspect Psychol Sci 2015 Nov;10(6):701-705. [doi: 10.1177/1745691615598515] [Medline: 26581721]
25. Park DC, Kidder DP. Prospective memory and medication adherence. In: Brandimonte M, Einstein GO, McDaniel MA, editors. Prospective Memory: Theory and Applications. New York, NY, USA: Lawrence Erlbaum Associates; 1996:369-390.
26. Prestwich A, Lawton R, Conner M. The use of implementation intentions and the decision balance sheet in promoting exercise behaviour. Psychol Health 2003 Dec;18(6):707-721. [doi: 10.1080/08870440310001594493]
27. Achtziger A, Gollwitzer PM, Sheeran P. Implementation intentions and shielding goal striving from unwanted thoughts and feelings. Pers Soc Psychol Bull 2008 Mar;34(3):381-393. [doi: 10.1177/0146167207311201] [Medline: 18272806]
28. Armitage CJ, Arden MA. How useful are the stages of change for targeting interventions? Randomized test of a brief intervention to reduce smoking. Health Psychol 2008 Nov;27(6):789-798. [doi: 10.1037/0278-6133.27.6.789] [Medline: 19025275]
29. Sheeran P, Orbell S. Implementation intentions and repeated behaviour: augmenting the predictive validity of the theory of planned behaviour. Eur J Soc Psychol 1999 Mar;29(2-3):349-369. [doi: 10.1002/(sici)1099-0992(199903/05)29:2/3<349::aid-ejsp931>3.0.co;2-y]
30. Lally P, Chipperfield A, Wardle J. Healthy habits: efficacy of simple advice on weight control based on a habit-formation model. Int J Obes (Lond) 2008 Apr;32(4):700-707. [doi: 10.1038/sj.ijo.0803771] [Medline: 18071344]

31. Gardner B, de Bruijn GJ, Lally P. A systematic review and meta-analysis of applications of the Self-Report Habit Index to nutrition and physical activity behaviours. Ann Behav Med 2011 Oct;42(2):174-187. [doi: 10.1007/s12160-011-9282-0] [Medline: 21626256]
32. Verplanken B, Faes S. Good intentions, bad habits, and effects of forming implementation intentions on healthy eating. Eur J Soc Psychol 1999 Aug;29(5-6):591-604. [doi: 10.1002/(sici)1099-0992(199908/09)29:5/6<591::aid-ejsp948>3.0.co;2-h]
33. Beeken RJ, Croker H, Morris S, Leurent B, Omar R, Nazareth I, et al. Study protocol for the 10 Top Tips (10TT) trial: randomised controlled trial of habit-based advice for weight control in general practice. BMC Public Health 2012 Aug 16;12:667 [FREE Full text] [doi: 10.1186/1471-2458-12-667] [Medline: 22898059]
34. Enriquez M, McKinsey DS. Strategies to improve HIV treatment adherence in developed countries: clinical management at the individual level. HIV AIDS (Auckl) 2011;3:45-51 [FREE Full text] [doi: 10.2147/HIV.S8993] [Medline: 22096406]
35. Gardner B, Sheals K, Wardle J, McGowan L. Putting habit into practice, and practice into habit: a process evaluation and exploration of the acceptability of a habit-based dietary behaviour change intervention. Int J Behav Nutr Phys Act 2014 Oct 30;11:135 [FREE Full text] [doi: 10.1186/s12966-014-0135-7] [Medline: 25359007]
36. O'Donoghue T, Rabin M. Present bias: lessons learned and to be learned. Am Econ Rev 2015 May 01;105(5):273-279. [doi: 10.1257/aer.p20151085]
37. Chetty R, Looney A, Kroft K. Salience and taxation: theory and evidence. Am Econ Rev 2009 Aug 01;99(4):1145-1177. [doi: 10.1257/aer.99.4.1145]
38. Mantzari E, Vogt F, Shemilt I, Wei Y, Higgins JP, Marteau TM. Personal financial incentives for changing habitual health-related behaviors: a systematic review and meta-analysis. Prev Med 2015 Jun;75:75-85 [FREE Full text] [doi: 10.1016/j.ypmed.2015.03.001] [Medline: 25843244]
39. Volpp KG, John LK, Troxel AB, Norton L, Fassbender J, Loewenstein G. Financial incentive-based approaches for weight loss: a randomized trial. JAMA 2008 Dec 10;300(22):2631-2637 [FREE Full text] [doi: 10.1001/jama.2008.804] [Medline: 19066383]
40. Volpp KG, Loewenstein G, Troxel AB, Doshi J, Price M, Laskin M, et al. A test of financial incentives to improve warfarin adherence. BMC Health Serv Res 2008 Dec 23;8:272 [FREE Full text] [doi: 10.1186/1472-6963-8-272] [Medline: 19102784]
41. Charness G, Gneezy U. Incentives to exercise. Econometrica 2009;77(3):909-931. [doi: 10.3982/ecta7416]
42. Dai H, Milkman KL, Riis J. The fresh start effect: temporal landmarks motivate aspirational behavior. Manag Sci 2014 Oct;60(10):2563-2582. [doi: 10.1287/mnsc.2014.1901]
43. Hodgson I, Plummer ML, Konopka SN, Colvin CJ, Jonas E, Albertini J, et al. A systematic review of individual and contextual factors affecting ART initiation, adherence, and retention for HIV-infected pregnant and postpartum women. PLoS One 2014 Nov 5;9(11):e111421 [FREE Full text] [doi: 10.1371/journal.pone.0111421] [Medline: 25372479]
44. Buscher A, Hartman C, Kallen MA, Giordano TP. Impact of antiretroviral dosing frequency and pill burden on adherence among newly diagnosed, antiretroviral-naive HIV patients. Int J STD AIDS 2012 May;23(5):351-355 [FREE Full text] [doi: 10.1258/ijsa.2011.011292] [Medline: 22648890]
45. Linnemayr S, Stecher C, Mukasa B. Behavioral economic incentives to improve adherence to antiretroviral medication. AIDS 2017 Mar 13;31(5):719-726 [FREE Full text] [doi: 10.1097/QAD.0000000000001387] [Medline: 28225450]
46. Cramer J, Vachon L, Desforges C, Sussman NM. Dose frequency and dose interval compliance with multiple antiepileptic medications during a controlled clinical trial. Epilepsia 1995 Nov;36(11):1111-1117. [doi: 10.1111/j.1528-1157.1995.tb00469.x] [Medline: 7588455]
47. Gardner B, Abraham C, Lally P, de Bruijn GJ. Towards parsimony in habit measurement: testing the convergent and predictive validity of an automaticity subscale of the Self-Report Habit Index. Int J Behav Nutr Phys Act 2012 Aug 30;9:102 [FREE Full text] [doi: 10.1186/1479-5868-9-102] [Medline: 22935297]
48. Verplanken B, Orbell S. Reflections on past behavior: a self-report index of habit strength. J Appl Soc Psychol 2003 Jun;33(6):1313-1330. [doi: 10.1111/j.1559-1816.2003.tb01951.x]
49. Falk A, Becker A, Dohmen T, Enke B, Huffman D, Sunde U. Global evidence on economic preferences. Q J Econ 2018 Nov;133(4):1645-1692. [doi: 10.1093/qje/qjy013]
50. Deci EL, Ryan RM. Intrinsic motivation. In: Weiner IB, Craighead WE, editors. The Corsini Encyclopedia of Psychology. Hoboken, NJ, USA: Wiley Online Library; 2010.
51. Stecher C, Mukasa B, Linnemayr S. Uncovering a behavioral strategy for establishing new habits: evidence from incentives for medication adherence in Uganda. J Health Econ 2021 May;77:102443 [FREE Full text] [doi: 10.1016/j.jhealeco.2021.102443] [Medline: 33831632]
52. Wood W, Neal DT. Healthy through habit: interventions for initiating and maintaining health behavior change. Behav Sci Policy 2016;2(1):71-83. [doi: 10.1353/bsp.2016.0008]
53. Galla BM, Duckworth AL. More than resisting temptation: beneficial habits mediate the relationship between self-control and positive life outcomes. J Pers Soc Psychol 2015 Sep;109(3):508-525 [FREE Full text] [doi: 10.1037/pspp0000026] [Medline: 25643222]
54. Sheeran P. Intention—behavior relations: a conceptual and empirical review. Eur Rev Soc Psychol 2002 Jan;12(1):1-36. [doi: 10.1080/14792772143000003]

55. Linnemayr S. Behavioral economics and HIV: a review of existing studies and potential future research areas. In: Hanoch Y, Barnes AJ, Rice T, editors. Behavioral Economics and Healthy Behaviors: Key Concepts and Current Research. London, UK: Routledge; 2017:141-156.

Abbreviations

ART: antiretroviral therapy
INMIND: Incentives and Reminders to Improve Long-term Medication Adherence
MEMS: medication event monitoring system
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
T1: treatment group 1
T2: treatment group 2

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